TABLE 1.

CLASSIFICATION OF PERIODONTAL AND PERI-IMPLANT DISEASES AND CONDITIONS 2017

Periodontal Diseases and Conditions

Periodontal Health, Gingival Diseases and Conditions

Chapple, Mealey, et al. 2018 Consensus Rept link

Trombelli et al. 2018 Case Definitions link

- Periodontal Health and Gingival Health
- Gingivitis: Dental Biofilm-Induced
- Gingival Diseases: Non-Dental Biofilm-Induced

Periodontitis

Papapanou, Sanz et al. 2018 Consensus Rept link

Jepsen, Caton et al. 2018 Consensus Rept link

Tonetti, Greenwell, Kornman. 2018 Case Definitions link

- Necrotizing Periodontal Diseases
- Periodontitis
- Periodontitis as a Manifestation of Systemic Disease

Other Conditions Affecting the Periodontium

Jepsen, Caton et al. 2018 Consensus Rept link

Papapanou, Sanz et al. 2018 Consensus Rept link

- Systemic diseases or conditions affecting the periodontal supporting tissues
- Periodontal Abscesses and Endodontic-Periodontal Lesions
- Mucogingival Deformities and Conditions
- Traumatic Occlusal Forces
- Tooth and Prosthesis Related Factors

Peri-Implant Diseases and Conditions

Berglundh, Armitage et al. 2018 Consensus Rept link

- Peri-Implant Health
- Peri-Implant Mucositis
- Peri-Implantitis
- Peri-Implant Soft and Hard Tissue Deficiencies

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2017 WORLD WORKSHOP

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A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

A classification scheme for periodontal and peri-implant diseases and conditions is necessary for clinicians to properly diagnose and treat patients as well as for scientists to investigate etiology, pathogenesis, natural history, and treatment of the diseases and conditions. This paper summarizes the proceedings of the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions. The workshop was co-sponsored by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) and included expert participants from all over the world. Planning for the conference, which was held in Chicago on November 9 to 11, 2017, began in early 2015.

An organizing committee from the AAP and EFP commissioned 19 review papers and four consensus reports covering relevant areas in periodontology and implant dentistry. The authors were charged with updating the 1999 classification of periodontal diseases and conditions[1] and developing a similar scheme for peri-implant diseases and conditions. Reviewers and workgroups were also asked to establish pertinent case definitions and to provide diagnostic criteria to aid clinicians in the use

of the new classification. All findings and recommendations of the workshop were agreed to by consensus.

This introductory paper presents an overview for the new classification of periodontal and peri-implant diseases and conditions, along with a condensed scheme for each of four workgroup sections, but readers are directed to the pertinent consensus reports and review papers for a thorough discussion of the rationale, criteria, and interpretation of the proposed classification. Changes to the 1999 classification are highlighted and discussed. Although the intent of the workshop was to base classification on the strongest available scientific evidence, lower level evidence and expert opinion were inevitably used whenever sufficient research data were unavailable.

The scope of this workshop was to align and update the classification scheme to the current understanding of periodontal and peri-implant diseases and conditions. This introductory overview presents the schematic tables for the new classification of periodontal and peri-implant diseases and conditions and briefly highlights changes made to the 1999 classification.[1] It cannot present the wealth of information included in the reviews, case definition papers, and consensus reports that has guided the development of the new classification, and reference to the consensus and case definition papers is necessary to provide a thorough understanding of its use for either case management or scientific investigation. Therefore, it is strongly recommended that the reader use this overview as an introduction to these subjects. Accessing this publication online will allow the reader to use the links in this overview and the tables to view the source papers (Table 1).

KEYWORDS
classification, gingivitis, peri-implant mucositis, peri-implantitis, periodontal diseases, periodontitis

TABLE 1.

CLASSIFICATION OF PERIODONTAL AND PERI-IMPLANT DISEASES AND CONDITIONS 2017

Periodontal Diseases and Conditions

Periodontal Health, Gingival Diseases and Conditions	Periodontitis	Other Conditions Affecting the Periodontium
Chapple, Mealey, et al. 2018 Consensus Rept link	Papapanou, Sanz et al. 2018 Consensus Rept link	Jepsen, Caton et al. 2018 Consensus Rept link
Trombelli et al. 2018 Case Definitions link	Jepsen, Caton et al. 2018 Consensus Rept link	Papapanou, Sanz et al. 2018 Consensus Rept link
	Tonetti, Greenwell, Kornman. 2018 Case Definitions link	

Periodontal Health and Gingival Health	Gingivitis: Dental Biofilm-Induced	Gingival Diseases: Non-Dental Biofilm-Induced	Necrotizing Periodontal Diseases	Periodontitis	Periodontitis as a Manifestation of Systemic Disease	Systemic diseases or conditions affecting the periodontal supporting tissues	Periodontal Abscesses and Endodontic-Periodontal Lesions	Mucogingival Deformities and Conditions	Traumatic Occlusal Forces	Tooth and Prosthesis Related Factors

Peri-Implant Diseases and Conditions

Berglundh, Armitage et al. 2018 Consensus Rept link

Peri-Implant Health	Peri-Implant Mucositis	Peri-Implantitis	Peri-Implant Soft and Hard Tissue Deficiencies

PERIODONTAL HEALTH, GINGIVITIS, AND GINGIVAL CONDITIONS[2-6]

The workshop addressed unresolved issues with the previous classification by identifying the difference between presence of gingival inflammation at one or more sites and the definition of a gingivitis case. It agreed that bleeding on probing should be the primary parameter to set thresholds for gingivitis.[2,5] The workshop also characterized periodontal health and gingival inflammation in a reduced periodontium after completion of successful treatment of a patient with periodontitis. Specific definitions were agreed to with regard to cases of gingival health or inflammation after completion of periodontitis treatment based on bleeding on probing and depth of the residual sulcus/pocket. This distinction was made to emphasize the need for a more comprehensive maintenance and surveillance of the successfully treated patient with periodontitis. It was accepted that a patient with gingivitis can revert to a state of health, but a periodontitis patient remains a periodontitis patient for life, even following successful therapy, and requires life-long supportive care to prevent recurrence of disease.[6] The workshop also reorganized the broad spectrum of non-plaque induced gingival diseases and conditions based on primary etiology (Table 2).[4]

A NEW CLASSIFICATION OF PERIODONTITIS

The 1989 workshop recognized that periodontitis had several distinct clinical presentations, different ages of onset and rates of progression.[7,8] Based on these variables the workshop categorized periodontitis as prepubertal, juvenile (localized and generalized), adult, and rapidly progressive. The 1993 European Workshop determined that the classification should be simplified and proposed grouping of periodontitis into two major headings: adult and early onset periodontitis.[9] The 1996 workshop participants determined that there was insufficient new evidence to change the classification.[10] Major changes were made in the 1999 classification of periodontitis,[11–13] which has been in use for the last 19 years. Periodontitis was reclassified as chronic, aggressive (localized and generalized), necrotizing and as a manifestation of systemic disease.

TABLE 2

Periodontal Health and Gingivitis: Consensus Report
Chapple, Mealey, et al. 2018
Active link to consensus report

Gingival Diseases: Case Definitions and Diagnostic Considerations
Trombelli, Tatakis, et al. 2018
Active link to case definitions

PERIODONTAL HEALTH, GINGIVAL DISEASES/CONDITIONS

1. **Periodontal health and gingival health**
   Lang & Bartold 2018 link
   a. Clinical gingival health on an intact periodontium
   b. Clinical gingival health on a reduced periodontium
      i. Stable periodontitis patient
      ii. Non-periodontitis patient

2. **Gingivitis – dental biofilm-induced**
   Murakami et al. 2018 link
   a. Associated with dental biofilm alone
   b. Mediated by systemic or local risk factors
   c. Drug-influenced gingival enlargement

3. **Gingival diseases – non-dental biofilm induced**
   Holmstrup et al. 2018 link
   a. Genetic/developmental disorders
   b. Specific infections
   c. Inflammatory and immune conditions
   d. Reactive processes
   e. Neoplasms
   f. Endocrine, nutritional & metabolic diseases
   g. Traumatic lesions
   h. Gingival pigmentation

Since the 1999 workshop, substantial new information has emerged from population studies, basic science investigations, and the evidence from prospective studies evaluating environmental and systemic risk factors. The analysis of this evidence has prompted the 2017 workshop to develop a new classification framework for periodontitis.[14]

In the last 30 years, the classification of periodontitis has been repeatedly modified in an attempt to align it with emerging scientific evidence. The workshop agreed that, consistent with current knowledge on pathophysiology, three forms of periodontitis can be identified: *necrotizing periodontitis*,[15] *periodontitis as a manifestation of systemic disease*,[16] and the forms of the disease previously recognized as "chronic" or "aggressive", now grouped under a single category, "periodontitis".[14,17–20] In revising the classification, the workshop agreed on a classification framework for periodontitis further characterized based on a multidimensional staging and grading system that could be adapted over time as new evidence emerges.[20]

Staging is largely dependent upon the severity of disease at presentation as well as on the complexity of disease management, while grading provides supplemental information about biological features of the disease, including a history based analysis of the rate of disease progression, assessment of the risk for further progression, anticipated poor outcomes of treatment, and assessment of the risk that the disease or its treatment may negatively affect the general health of the patient.[14,20] Staging involves four categories (stages 1 through 4) and is determined after considering several variables including clinical attachment loss, amount and percentage of bone loss, probing depth, presence and extent of angular bony defects and furcation involvement, tooth mobility, and tooth loss due to periodontitis. Grading includes three levels (grade A – low risk, grade B – moderate risk, grade C – high risk for progression) and encompasses, in addition to aspects related to periodontitis progression, general health status, and other exposures such as smoking or level of metabolic control in diabetes. Thus, grading allows the clinician to incorporate individual patient factors into the diagnosis, which are crucial to comprehensive case management (Table 3). For a complete description of the new classification scheme for periodontitis, the reader is directed to the consensus report on periodontitis[14] and the case definition paper on periodontitis.[20]

SYSTEMIC DISEASES ASSOCIATED WITH LOSS OF PERIODONTAL SUPPORTING TISSUES[16,21]

The new classification of periodontal diseases and conditions also includes systemic diseases and conditions that affect the periodontal supporting tissues.[16] It is recognized that there are rare systemic disorders, such as Papillon Lefèvre Syndrome, that generally result in the early presentation of severe periodontitis. Such conditions are grouped as "Periodontitis as a Manifestation of Systemic Disease", and classification should be based on the primary systemic disease.[16] Other systemic conditions, such as neoplastic diseases, may affect the periodontal apparatus independent of dental plaque biofilm-induced periodontitis,[21] and such clinical findings should also be classified based on the primary systemic disease and be grouped as "Systemic Diseases or Conditions Affecting the Periodontal Supporting Tissues". There are, however, common systemic diseases, such as uncontrolled diabetes mellitus, with variable effects that modify the course of periodontitis. These appear to be part of the multifactorial nature of complex diseases such as periodontitis and are included in the new clinical classification of periodontitis as a descriptor in the staging and grading process.[20] Although common modifiers of periodontitis may substantially alter disease occurrence, severity, and response to treatment, current evidence does not support a unique pathophysiology in patients with diabetes and periodontitis.[22]

CHANGES IN THE CLASSIFICATION OF PERIODONTAL DEVELOPMENTAL AND ACQUIRED DEFORMITIES AND CONDITIONS[21,23–25]

Mucogingival conditions

The new case definitions related to treatment of gingival recession are based on interproximal loss of clinical attachment and also incorporate the assessment of the exposed root and cemento-enamel junction.[23] The consensus report presents a new classification of gingival recession that combines clinical parameters including the *gingival phenotype* as well as characteristics of the exposed root surface.[21] In the consensus report the term *periodontal biotype* was replaced by *periodontal phenotype* (Table 4).[21]

Occlusal trauma and traumatic occlusal forces

Traumatic occlusal force, replacing the term *excessive occlusal force*, is the force that exceeds the adaptive capacity of the periodontium and/or the teeth. Traumatic occlusal forces can result in occlusal trauma (the lesion) and excessive wear or fracture of the teeth.[21] There is lack of evidence from human studies implicating occlusal trauma in the progression of attachment loss in periodontitis (Table 4).[24]

Prosthesis- and tooth-related factors

The section on prostheses-related factors was expanded in the new classification. The term *biologic width* was replaced by *supracrestal attached tissues*.[21] Clinical procedures involved in the fabrication of indirect restorations was added because of new data indicating that these procedures may cause recession and loss of clinical attachment (Table 4).[25]

A NEW CLASSIFICATION FOR PERI-IMPLANT DISEASES AND CONDITIONS[26]

A new classification for peri-implant health,[27] peri-implant mucositis[28] and peri-implantitis[29] was developed by the workshop

TABLE 3

Periodontitis Consensus Report	Staging and Grading of Periodontitis:
Papapanou, Sanz et al. 2018	Framework and Proposal of a New Classification and Case Definition
Active link to consensus report	Tonetti, Greenwell, Kornman 2018
	Active link to case definitions

FORMS OF PERIODONTITIS

1. Necrotizing Periodontal Diseases

Herrera et al. 2018 link

a. Necrotizing Gingivitis
b. Necrotizing Periodontitis
c. Necrotizing Stomatitis

2. Periodontitis as Manifestation of Systemic Diseases

Jepsen, Caton et al. 2018 Consensus Rept link | Albandar et al. 2018 link

Classification of these conditions should be based on the primary systemic disease according to the International Statistical Classification of Diseases and Related Health Problems (ICD) codes

3. Periodontitis

Fine et al. 2018 link | Needleman et al. 2018 link | Billings et al. 2018 link

a. **Stages:** Based on Severity[1] and Complexity of Management[2]
   - Stage I: Initial Periodontitis
   - Stage II: Moderate Periodontitis
   - Stage III: Severe Periodontitis with potential for additional tooth loss
   - Stage IV: Severe Periodontitis with potential for loss of the dentition

b. Extent and distribution[3]: localized; generalized; molar-incisor distribution

c. **Grades:** Evidence or risk of rapid progression[4], anticipated treatment response[5]
   i. Grade A: Slow rate of progression
   ii. Grade B: Moderate rate of progression
   iii. Grade C: Rapid rate of progression

[1] Severity: Interdental clinical attachment level (CAL) at site with greatest loss; Radiographic bone loss & tooth loss
[2] Complexity of management: Probing depths, pattern of bone loss, furcation lesions, number of remaining teeth, tooth mobility, ridge defects masticatory dysfunction
[3] Add to Stage as descriptor: localized <30% teeth, generalized ≥ 30% teeth
[4] Risk of progression: direct evidence by PA radiographs or CAL loss, or indirect (bone loss/age ratio)
[5] Anticipated treatment response: case phenotype, smoking, hyperglycemia

(Table 5). An effort was made to review all aspects of peri-implant health, diseases, and relevant aspects of implant site conditions and deformities to achieve a consensus for this classification that could be accepted worldwide. Case definitions were developed for use by clinicians for individual case management and also for population studies.[26,30]

Peri-implant health

Peri-implant health was defined both clinically and histologically.[27] Clinically, peri-implant health is characterized by an absence of visual signs of inflammation and bleeding on probing. Peri-implant health can exist around implants with normal or reduced bone support. It is not possible to define a range of probing depths compatible with peri-implant health.[26,30]

Peri-implant mucositis

Peri-implant mucositis is characterized by bleeding on probing and visual signs of inflammation.[28] While there is strong evidence that peri-implant mucositis is caused by plaque, there is very limited evidence for non-plaque induced peri-implant mucositis. Peri-implant mucositis can be reversed with measures aimed at eliminating the plaque.

TABLE 4

Periodontal Manifestations of Systemic Diseases and Developmental and Acquired Conditions: Consensus Report
Jepsen, Caton et al. 2018
Active link to consensus report

PERIODONTAL MANIFESTATIONS OF SYSTEMIC DISEASES AND DEVELOPMENTAL AND ACQUIRED CONDITIONS

1. **Systemic diseases or conditions affecting the periodontal supporting tissues**
   Albandar et al. 2018 link
2. **Other Periodontal Conditions**
   Papapanou, Sanz et al. 2018 link
   Herrera et al. 2018 link
   a. Periodontal Abscesses
   b. Endodontic-Periodontal Lesions
3. **Mucogingival deformities and conditions around teeth**
   Cortellini & Bissada 2018 link
   a. Gingival phenotype
   b. Gingival/soft tissue recession
   c. Lack of gingiva
   d. Decreased vestibular depth
   e. Aberrant frenum/muscle position
   f. Gingival excess
   g. Abnormal color
   h. Condition of the exposed root surface
4. **Traumatic occlusal forces**
   Fan & Caton 2018 link
   a. Primary occlusal trauma
   b. Secondary occlusal trauma
   c. Orthodontic forces
5. **Prostheses and tooth-related factors that modify or predispose to plaque-induced gingival diseases/periodontitis**
   Ercoli & Caton 2018 link
   a. Localized tooth-related factors
   b. Localized dental prostheses-related factors

Peri-implantitis

Peri-implantitis was defined as a plaque-associated pathologic condition occurring in the tissue around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone.[29] Peri-implant mucositis is assumed to precede peri-implantitis. Peri-implantitis is associated with poor plaque control and with patients with a history of severe periodontitis. The onset of peri-implantitis may occur early following implant placement as indicated by radiographic data. Peri-implantitis, in the absence of treatment, seems to progress in a non-linear and accelerating pattern.[29]

Hard and soft tissue implant site deficiencies

Normal healing following tooth loss leads to diminished dimensions of the alveolar process/ridge that result in both hard and soft tissue deficiencies. Larger ridge deficiencies can occur at sites associated with severe loss of periodontal support, extraction trauma, endodontic infections, root fractures, thin buccal bone plates, poor tooth position, injury and pneumatization of the maxillary sinuses. Other factors affecting the ridge can be associated with medications and systemic diseases reducing the amount of naturally formed bone, tooth agenesis, and pressure from prostheses.[31]

TABLE 5

Peri-implant Diseases and Conditions Consensus Report
Berglundh, Armitage et al. 2018
Active link to consensus report

PERI-IMPLANT DISEASES AND CONDITIONS

1. **Peri-implant health**
   Araujo & Lindhe 2018 link
2. **Peri-implant mucositis**
   Heitz-Mayfield & Salvi 2018 link
3. **Peri-implantitis**
   Schwarz et al. 2018 link
4. **Peri-implant soft and hard tissue deficiencies**
   Hammerle & Tarnow 2018 link

Renvert et al. 2018 Case Definitions link

CONCLUSIONS

This overview introduces an updated classification of periodontal diseases and conditions and a new classification of peri-implant diseases and conditions. The publication represents the work of the worldwide community of scholars and clinicians in periodontology and implant dentistry. This paper presents an abbreviated overview of the outcome of the consensus workshop, and the reader is encouraged to review the entire publication to receive comprehensive information about the rationale, criteria and implementation of the new classifications.

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The authors filed detailed disclosure of potential conflicts of interest relevant to the workshop topics, and these are kept on file. Additional disclosures can be found in each of the four consensus reports published in these proceedings.

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2017 WORLD WORKSHOP

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Periodontal health

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objectives: To date there is a paucity of documentation regarding definitions of periodontal health. This review considers the histological and clinical determinants of periodontal health for both intact and reduced periodontium and seeks to propose appropriate definitions according to treatment outcomes.

Importance: Defining periodontal health is can serve as a vital common reference point for assessing disease and determining meaningful treatment outcomes.

Findings: The multifactorial nature of periodontitis is accepted, and it is recognized that restoration of periodontal health will be defined by an individual's response to treatment, taking into account allostatic conditions.

Conclusions: It is proposed that there are 4 levels of periodontal health, depending on the state of the periodontium (structurally and clinically sound or reduced) and the relative treatment outcomes: (1) pristine periodontal health, with a structurally sound and uninflamed periodontium; (2) well-maintained clinical periodontal health, with a structurally and clinically sound (intact) periodontium; (3) periodontal disease stability, with a reduced periodontium, and (4) periodontal disease remission/control, with a reduced periodontium.

KEYWORDS

Clinical health, gingiva, periodontal remission, periodontal stability, pristine health

INTRODUCTION

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1] In accordance with this definition by the World Health Organization, periodontal health should be defined as a state free from inflammatory periodontal disease that allows an individual to function normally and not suffer any consequences (mental or physical) as a result of past disease. However, while this definition is holistic and patient-outcome based, it seems an impractical and limiting definition for the purposes of clinical management of periodontal diseases. Therefore, a more practical definition of periodontal health would be a state free from inflammatory periodontal disease. This, in turn, means that absence of inflammation associated with gingivitis or periodontitis, as assessed clinically, is a prerequisite for defining periodontal health.

It is a matter of debate if altered morphological conditions resulting from previous exposure to disease processes (eg, gingival recession, loss of attachment, and bone loss) may be redefined as novel healthy conditions in the absence of clinical signs and symptoms of inflammation.

Interestingly, there are almost no studies or reports attempting to define periodontal health.[2] Defining periodontal health is very important if we are to have a common reference point for assessing periodontal disease and determining meaningful treatment outcomes. Health can be evaluated at both the histological and clinical levels and should be considered in the context of a preventive starting point and a therapeutic end point. Thus, periodontal health can exist before disease commences but, conversely, periodontal health can be restored to an anatomically reduced periodontium. In this review, the clinical criteria for distinguishing pristine health from health on a reduced periodontium are presented and discussed.

HISTOLOGICAL EVIDENCE OF HEALTH

Animal studies – pristine periodontal health and early gingival inflammation

During the 1970 and 1980s, various animal studies assessed the health status of gingival tissues that were exposed to oral biofilms.[3–5] These tissues were usually taken as baseline prior to commencement of plaque accumulation for studies on the development and pathogenesis of gingivitis. Clearly, most of the evidence for such healthy conditions (homeostasis) was defined by a complete absence of inflammatory infiltrate concomitant with gingival and plaque indices, yielding zero values.

Histologically, composition of the gingival biopsies was analyzed using a sampling microscope. It was stated that biopsies at day zero (commencement of plaque accumulation) did not contain any inflammatory cell infiltrates. The original delicate vascular capillary network of uninflamed gingival tissue has been described using vital microscopy, perfusion, and histological techniques in young dogs and cats.[4,5] However, after 4 days of plaque accumulation, a significant number of leukocytes were found in the collagen-poor connective tissue immediately beneath the junctional epithelium. The size of the infiltrated connective tissue (ICT) gradually increased during the experimental period and the volumetric density of collagen in the noninfiltrated connective tissue (NCT) was always much higher than in the ICT. In the ICT, however, collagen density remained constant throughout the study. By days 4 and 7, neutrophilic granulocytes constituted 60% to 70% of the leukocyte population. On day 28, the infiltrate comprised mainly mononuclear leukocytes, especially plasma cells; at that time neutrophils occupied only a small fraction of the infiltrate.[3]

The presence of biofilm and overt inflammation, occurring with eruption of deciduous teeth in dogs and cats, has been related to concomitant changes in gingival vascular morphology. Although localized, acute inflammation accompanies biofilm formation at the time of weaning, it rarely develops into a chronic inflammation. Infiltration of gingival tissue by chronic inflammatory cells occurred in only a few specimens and was associated with increased biofilm and replacement of the gingival vessel network by loop patterns. This, in turn, meant the original delicate vascular network was replaced with loop configurations of capillaries once challenged by biofilm-induced inflammation.[4]

A subsequent study investigated whether the regular vasculature of noninflamed marginal gingiva would become re-established following plaque control, scaling, and gingivectomy in dogs with and without pre-experimental gingivitis at 4, 8, and 12 weeks.[5] Noninflamed gingiva that was previously inflamed was characterized by a series of looped vessels that could be readily distinguished from the regular network of vessels described for the marginal gingiva that had neither been inflamed nor resected previously.[5]

Human histological studies on health and gingivitis

The cellular composition of developing infiltrated connective tissue was analyzed in human volunteers participating in a 21 day experimental gingivitis model in which oral hygiene practices were abolished.[6] As the clinical index (gingival index) for inflammation increased, the volumetric density of infiltrated connective tissue within the noninfiltrated connective tissue in an area subjacent to the junctional epithelium increased significantly and almost linearly.[7] The infiltrated connective tissue demonstrated a significant increase in lymphocytes from health to inflammation (17.0% to 29.9%) concomitant with a decrease in the numerical density of fibroblasts, from 48.1% to 34.9%. Moreover, the numerical density of polymorphonuclear leukocytes was between 20.8% and 22.6% at all stages, from health to gingivitis. These results indicate that an inflammatory infiltrate subjacent to the junctional epithelium is always present in gingival tissues that are clinically healthy.

To study the influence of long-term gingival health, 5 dental hygienists with optimal personal oral hygiene were supervised regarding their oral hygiene performance for 6 months.[8] It was assured that at all observation times (0, 1, 4, and 6 months) clinical indices for plaque and inflammation were close to zero. The volumetric density of infiltrated connective tissue versus noninfiltrated connective tissue decreased significantly from month 1 to month 4. This indicated that a long-standing optimal oral hygiene regime is necessary for any histological improvement of the inflammatory infiltrate. Nevertheless, even after 6 months of supervised oral hygiene practices, the infiltrate was still present.[8]

While the numerical density of lymphocytes within the infiltrate decreased significantly, from 18.4% to 5.6%, after 6 months of meticulous oral hygiene, the numerical density of fibroblasts increased significantly, from 57.7% to 71.0%. This clearly reflected a positive healing outcome. However, it must be recognized that even during this 6 month period of optimal oral hygiene, the numerical density of polymorphonuclear leukocytes remained relatively stable, varying from 20.6% to 17.7%. This, in turn, means that in humans a status of clinically healthy gingiva, even for a prolonged period, is always histologically characterized by a small inflammatory cell infiltrate.[7,8] This indicates polymorphonuclear leukocyte surveillance, which is a very important physiological (not pathological) process. Most recently, in human biopsies from clinically healthy sites, memory B cells were identified within the connective tissue subjacent to the junctional epithelium. This suggests a role for memory B cells in maintaining homeostasis.[9]

Thus, the term *pristine clinical health* represents a rare, but realistic entity, ie, no attachment loss, no bleeding on probing (BoP), no sulcular probing >3 mm and no redness, clinical swelling/edema, or pus. It should be recognized that this condition is associated with physiological immune surveillance rather than pathological inflammation. The term *clinically healthy* should refer to tissue that demonstrates an absence, or very low level, of clinical indicators of inflammation such as BoP and inflammatory markers in gingival crevicular fluid. This review did not consider gingival crevicular fluid biomarker research in periodontal health and disease, as crevicular fluid analysis is not generally practical to implement in clinical practice at this time due to the need for specialized equipment.

DETERMINANTS OF CLINICAL PERIODONTAL HEALTH

No longer can periodontal diseases be considered simple bacterial infections. Rather, they are complex diseases of multifactorial nature involving an intricate interplay between the subgingival microbiota, the host immune and inflammatory responses, and environmental modifying factors.[10] Thus, periodontal health must not be considered solely in the context of plaque/bacteria levels and control but must embrace a holistic consideration and evaluation of all factors responsible for the emergence of disease, as well as the restoration and maintenance of health.[11]

Determinants of periodontal health fall into 3 major categories, namely, microbiological, host, and environment (Table 1). Because many of these factors are addressed in the paper dealing with plaque induced gingival diseases,[12] we will only consider the clinical indicators of clinical periodontal health in this article.

The relevance of recognizing such important determinants of periodontal health and disease as controllable and uncontrollable predisposing and modifying factors cannot be underestimated, and their assessment for each patient is crucial to attaining and maintaining clinical periodontal health. In this context, predisposing factors are defined as any agent or condition that contributes to the accumulation of dental plaque (eg, tooth anatomy, tooth position, restorations). Modifying factors are defined as any agent or condition that alters the way in which an individual responds to subgingival plaque accumulation (eg, smoking, systemic conditions, medications). The threshold(s) to establish when such factors are controlled versus not fully controlled await further elaboration, but it is reasonable to expect that many factors will be determined controllable (eg, removal of overhangs, smoking cessation, good diabetes control) while others will not (eg, genetic predisposition, immune status, use of critical medications).

TABLE 1 Determinants of clinical periodontal health

Microbiological Determinants of Clinical Periodontal Health
Supragingival plaque composition
Subgingival biofilm composition
Host Determinants of Clinical Periodontal Health
1. Local predisposing factors
1.1 Periodontal pockets
1.2 Dental restorations
1.3 Root anatomy
1.4 Tooth position and crowding
2. Systemic modifying factors
2.1 Host immune function
2.2 Systemic health
2.3 Genetics
Environmental Determinants of Clinical Periodontal Health
Smoking
Medications
Stress
Nutrition

PLAQUE AND CLINICAL PERIODONTAL HEALTH

Subgingival biofilm

The bacterial composition of the subgingival biofilm associated with gingivitis and periodontitis results from dynamic interactions with its microenvironment. In general, the microbial composition is a collection of commensal organisms that coexist in relative harmony. However, should the environment change, either as a result of inflammation within the gingival tissues or other, as yet unidentified, processes within the biofilm, a state of dysbiosis may result in the overgrowth of more virulent components of the biofilm, with ensuing exacerbation of periodontal inflammation.[13] Thus, gingivitis can be considered a relatively nonspecific inflammatory response to nonspecific (indigenous) subgingival microbiota. With the resultant inflammation and development of periodontitis, a shift in microbial composition occurs and several putative pathogens emerge, leading to heightened host-driven tissue damage. Thus, for periodontal health to be attained, or maintained, the composition of the subgingival microbiota needs to be redirected toward one compatible with gingival health.[14]

Oral hygiene

Good oral hygiene has always been considered a mainstay of periodontal health.[15] It is usually achieved by a combination of good personal oral hygiene and regular professional care.[16,17] It must be remembered that plaque accounts for only 20% of the direct risk of developing periodontitis, thus it must not be forgotten that the remaining 80% of direct and indirect risk and modifying factors may be responsible for the development of periodontal diseases.[18] While oral hygiene remains the most important factor in obtaining and maintaining periodontal health, it should not be the sole focus of attention. Additional factors must be addressed in the quest for attaining or maintaining periodontal health.

INDICATORS OF CLINICAL PERIODONTAL HEALTH

In its pristine form, periodontal health would be defined as the absence of histological evidence of periodontal inflammation and no evidence of anatomical change to the periodontium. However, it must be recognized that in most (if not all) adults this is unlikely. Therefore, the term *clinically healthy* should be adopted to cover the absence of (or very significant reduction in) clinical periodontal inflammation on either an anatomically intact periodontium or a reduced periodontium. Furthermore, a compromised definition or paradigm for periodontal clinical health needs to be developed for individuals who have experienced periodontal disease (gingivitis or periodontitis), undergone treatment, then returned to a state of clinical health on either a full periodontium (in the case of gingivitis) or a reduced periodontium (in the case of periodontitis).

Bleeding on probing

Monitoring health or inflammation of the gingival tissues is best documented by the parameter of BoP.[19] Bleeding on probing, in the absence of pocketing, should be understood as bleeding provoked in the coronal marginal gingiva following the application of pressure to the lateral wall of a periodontal sulcus or pocket, reflecting microulceration of the sulcus lining. However, BoP is usually measured as bleeding provoked by applying a probe to the bottom of a sulcus/pocket. In most studies on BoP as a clinical parameter, this latter definition is applied. The histological characteristics of the gingival tissues associated with BoP have been evaluated.[20] Sites that bleed following probing with light pressure applied to the tissues (0.25 N) are associated with a significantly increased percentage of cell-rich and collagen-reduced connective tissue but no increase in vascularity or vessel lumen size that would justify the bleeding tendency. Moreover, clinical and histological data suggest that bleeding is an earlier sign of gingivitis than are the visual signs of inflammation (redness and swelling).

Obviously, BoP may be provoked by trauma to the tissues using a periodontal probe. Hence, the probing pressure to be applied to the tissue (bottom of the sulcus/pocket) when evaluating BoP should not be sufficient to create trauma; rather it should only be enough to provoke tissue to bleed if there is increased blood vessel fragility resulting from inflammation. It has been demonstrated that BoP provoked with pressures greater than 0.25 N results in false-positive readings. By incrementally increasing pressure by 0.25 N, an increase of approximately 13% in BoP sites has been noted.[21,22]

An early retrospective study evaluated the prognostic value of BoP compared with repeated visits in identifying sites at risk for periodontal attachment loss during supportive care following periodontal therapy.[23] The results indicated that sites with a probing depth of ≥5 mm had significantly higher incidence of BoP. Sites with an incidence of BoP at 4 of 4 visits had a 30% chance of attachment loss. This decreased to 14% with an incidence of BoP at 3 of 4 visits, to 6% with an incidence of BoP at 2 of 4 visits, to 3% with an incidence of BoP at 1 of 4 visits, and finally, to 1.5% with no BoP at any of 4 visits. Sensitivity and predictability calculations revealed that BoP is a limited but useful prognostic indicator in monitoring periodontal tissue after active therapy.[23]

Subsequent studies investigated the predictive value of absence of BoP as an indicator for periodontal stability.[24,25] While the positive predictive value remained rather low for repeated BoP prevalence (≤30%), the negative predictive value in the same studies was nearly 100%. This demonstrated that absence of BoP at repeated examinations represented periodontal health and was a very reliable indicator for periodontal stability.[24] Hence, from a clinical point of view, absence of BoP would indicate clinically healthy periodontal tissue. These findings were later validated in a prospective follow-up study applying BoP as a clinical indicator for disease progression or periodontal stability.[25]

As the absence of BoP at 0.25 N indicates periodontal health, with a negative predictive value of 98% to 99%, this clinical parameter appears the most reliable for monitoring patients in daily practice over time.[24,25] Nonbleeding sites may be considered as clinically healthy and periodontally stable. It would be logical to assume that the positive outcomes of periodontal treatment, in receptive patients, would reach a status of nonbleeding on gentle probing.

Because various factors, such as probe dimension, angulation of probe, and applied pressure, can affect the assessment of gingival inflammation, it is imperative to standardize BoP as resulting from a defined level of force (pressure to the tissue), preferably not exceeding 0.25 N.[26]

A multilevel analysis of various site-specific and patient-related factors influencing BoP in 601 adult patients demonstrated that BoP may be associated with site-specific factors (periodontal probing depth [PPD], tooth type, and aspects) as well as patient-related factors (eg, sex and smoking status).[27] While the severity and extent of gingival bleeding are often associated with the degree of bacterial plaque accumulation, it is noted that other factors can lead to increased gingival bleeding. For example, vitamin C deficiency or ingestion of aspirin can cause significant gingival bleeding through mechanisms that may not be primarily related to plaque accumulation.[28,29] In a recent retrospective study of 445 patients in periodontal supportive therapy for at least 5 years, increased mean BoP in patients on supportive periodontal therapy was related to disease severity and periodontal instability irrespective of smoking status; smokers demonstrated lower mean BoP concomitant with increased prevalence of residual PPD.[30]

Standardization of periodontal probe design

The characteristics of an ideal periodontal probe will be central to a future determination of periodontal health. There is need to develop an International Organization for Standardization periodontal probe to ensure not only that probe dimension is consistent but that probing force is standardized to 0.25 N, thus removing the confounding issue of BoP induced by too much pressure, as well as unnecessary bleeding resulting from trauma. This critical issue is discussed in more detail by Trombelli and Tatakis (fourth paper for Working Group 1; in this issue).[31]

Periodontal probing depth

While it would seem intuitive that shallow pockets are consistent with health and deep pockets consistent with disease, there is ample evidence to indicate this may not necessarily be true. For example, deep pockets may remain stable and uninflamed, particularly if careful supportive periodontal care is provided, over very long periods of time.[32,33] Thus, deep pockets may exist as so-called healthy pockets.

It is important to recognize that, following successful treatment, recurrent inflammatory periodontitis can recur at individual sites despite most of the dentition remaining well maintained and in a state of relative health.[33] This has been interpreted to indicate that mean values of clinical parameters such as PPD, attachment levels, and bone height are not adequate predictors for sites that may become

reinfected and undergo recurrent disease.[33] Thus, PPD or probing attachment levels alone should not be used as evidence of gingival health or disease. They must be considered in conjunction with other important clinical parameters such as BoP, as well as modifying and predisposing factors. This highlights, as stated above, that the most useful indicator of disease is clinical evidence of inflammation, and that historical evidence of disease (increased PPD, recession and loss of attachment, bone loss) may be of less relevance in the context of periodontal health on a reduced periodontium.[34]

Radiographic features of periodontal health

Radiographic assessment forms a critical component of clinical assessment of the periodontium. Radiographic features of a normal, anatomically intact periodontium would include an intact lamina dura (both laterally and at the alveolar crest), no evidence of bone loss in furcation areas, and a 2 mm distance, on average, from the most coronal portion of the alveolar bone crest (AC) to the cementoenamel junction (CEJ). The distance from the CEJ to AC in healthy individuals can vary between 1.0 and 3.0 mm.[35,36] It is important to note that factors such as patient age, tooth type, angulation of teeth, and severe attrition can all influence the CEJ-AC height, thus caution must be exercised when assessing this parameter as a measure of periodontal health. While periodontal ligament space is also appraised radiographically, it can vary and is not considered a useful indicator of health (see section below on tooth mobility).

Once periodontitis has developed, by definition, alveolar bone loss has occurred because of the inflammatory process. Thus, clinical periodontal health on a reduced periodontium cannot be determined using radiographs alone; they provide information regarding historical destruction and are of value for longitudinal determination of progressive bone loss.

Tooth mobility

Clinicians often assess the status of a tooth by estimating its mobility. Because teeth are not ankylosed, or *osseointegrated*, as are implants, but are suspended in the alveolar bone by a network of collagenous fibers, they exhibit a degree of physiological mobility. This is usually assessed as the amplitude of crown displacement resulting from the application of a defined force.[37] The magnitude of this movement has been used to distinguish between physiological and pathological tooth mobility, with up to 0.2 mm regarded as physiological. In teeth with noninflamed periodontal tissue, 2 fundamental histological factors determine tooth mobility: 1) the height of the periodontal tissue support and 2) the width of the periodontal ligament.

In a clinically healthy situation, increased tooth mobility associated with widening of the periodontal ligament most likely represents a tooth in occlusal trauma. Furthermore, increased tooth mobility cannot be used as a sign of disease for a tooth with a reduced, but healthy, periodontium. Such increased mobility may be permanently increased due to reduced periodontal support, yet the periodontium may be completely healthy. If the height of the periodontal support is reduced but the width of the ligament is unchanged (approximately 250 μm), it should be appreciated that the amplitude of root mobility within the remaining periodontium is the same as for a tooth with normal height of periodontal support. Hence, the so-called hypermobility of a periodontally healthy tooth with reduced support but normal width of periodontal ligament should be considered physiological tooth mobility.

Increased tooth mobility due to a widening in the periodontal ligament is the result of uni- or multidirectional forces to the crown that are sufficiently high and frequent to induce resorption of the alveolar bone walls in pressure zones. In a series of controlled animal experimental studies in periodontally healthy teeth, the alveolar bone resorption resulted in increased tooth mobility but no loss of connective tissue attachment, irrespective of the height of the supportive bone.[38,39] Because alveolar bone loss has been demonstrated to be reversible upon cessation of applied forces, it was concluded that increased tooth mobility as a result of a widened periodontal ligament represents a physiological adaptation to altered function rather than a sign of pathology.[37] Hence, tooth mobility is not recommended to be used as a sign of either health or disease status.

PERIODONTAL HEALTH AND TREATMENT TARGETS FOR A DISEASED OR REDUCED PERIODONTIUM

While maintaining periodontal health over a lifetime with no adverse changes in the periodontium is desirable, it must be recognized this is unlikely for most of the population.

In Table 2, periodontal conditions and their expected outcomes with respect to periodontal health are detailed within the context of an intact and a reduced periodontium. For the treatment of gingivitis, it is not realistic to return to pristine periodontal health; restoration to full clinical health (no BoP, no anatomical loss of periodontal structures) would be expected following removal of biofilm and calculus and ongoing effective oral hygiene and maintenance. In treating periodontitis, which by definition manifests as loss of periodontal support (both attachment and bone), restoration to pre-disease attachment and bone levels is an unlikely event at the majority of sites; therapeutic targets are to control local and modifying factors, minimize inflammation, and stabilize attachment and bone. Therefore, for a large proportion of the population, the issue of periodontal health must be considered in the context of returning to clinical health from disease (either gingivitis or periodontitis) and what this return entails. According to recent epidemiological data, gingivitis affects up to 95% of the population and chronic periodontitis up to 60% to 65% of the North American population 65 years and older.[40,41] While some variance is to be expected across communities, these figures are likely to be relatively accurate for most populations worldwide.

In the context of our current understanding of the multifactorial nature of (plaque-associated) periodontal diseases, reducing

TABLE 2 Outcomes of periodontal health for plaque-associated periodontal diseases

				Periodontitis (reduced periodontium)	
	Pristine periodontal health	**Clinical periodontal health (intact periodontium)**	**Gingivitis**	**Periodontal disease stability**	**Periodontal disease remission/control**
Bleeding on probing	No	No/Minimal	Yes	No/Minimal	Significantly reduced
Normal gingival sulcus depth	Yes	Yes	Yes	No	No
Normal bone heights	Yes	Yes	Yes	No	No
Modifying factors	Controlled	Controlled	May be present	Controlled	Not fully controlled
Predisposing factors	Controlled	Controlled	May be present	Controlled	Not fully controlled

Pristine periodontal health is defined as no bleeding on probing and no anatomical loss of periodontal structures. *Gingivitis* is defined as a nonspecific inflammatory reaction to a nonspecific accumulation of plaque that is confined to the gingival tissue, with no underlying destruction of the attachment apparatus. *Periodontitis* covers the major plaque-associated periodontal diseases, and treatment outcomes are expected to be either *periodontal disease stability* or *periodontal disease remission/control*. *Periodontal disease stability* is defined as a state in which the periodontitis has been successfully treated and clinical signs of the disease do not appear to worsen in extent or severity despite the presence of a reduced periodontium. *Periodontal disease remission/control* is defined as a period in the course of disease when symptoms become less severe but may not be fully resolved.

inflammation and improving clinical health for a reduced periodontium may be achieved at 2 levels, namely stability and remission/control. These are variants of therapeutic outcomes to restore health on a reduced periodontium.

Periodontal disease stability will be defined as a state in which periodontitis has been successfully treated through control of local and systemic factors, resulting in minimal BoP, optimal improvements in PPD and attachment levels, and a lack of progressive destruction. The principal signs of successful periodontal treatment would be as detailed above with regard to BoP, PPD, and clinical attachment levels. In addition, control of modifying factors such as reduction of daily cigarette smoking and good control of diabetes are achieved. In many respects, attainment of periodontal disease stability can be considered a prognostic definition.

Periodontal disease remission/control is defined as a period in the course of disease during which treatment has resulted in reduction (although not total resolution) of inflammation and some improvement in PPD and attachment levels, but not optimal control of local or systemic contributing factors. This may be a reasonable treatment outcome for individuals with uncontrollable modifying factors. Indeed for many chronic inflammatory medical conditions (eg, diabetes, cardiovascular disease, hyperlipidemia, and rheumatoid arthritis), the goal of disease remission is important and is based on the emerging concept of *treat to target*.[42] This is a treatment paradigm that utilizes specific and well-defined treatment outcomes to monitor the control of the clinical signs and symptoms of a disease and is aimed at attaining a state of putative *health*. For patients with longstanding disease and/or uncontrolled contributing factors, for example smoking or diabetes, low disease activity may be an acceptable therapeutic goal. Thus, the definition of disease remission/control is related to the achievement of other (ie, different from those obtained in the disease stability definition) treatment end points that testify to an improvement in periodontal condition (with respect to baseline status) that, if not achieved, may be associated with progression of attachment loss.

If the concept of disease remission/control is embraced as a treatment target for the management of periodontal diseases, periodontal treatment will move from a solely biofilm-based protocol to a more holistic, inflammation-based model. It is important to note that this model does not discount or diminish the importance of the periodontal microbiome, but refocuses attention on controlling the inflammation to control the infection and the ongoing destruction of the periodontium.

This model requires that modifiable indicators of periodontitis such as traditional markers of periodontitis (attachment and bone loss and PPD), modifiable inflammatory markers (periodontal inflammation score, inflammatory mediators in gingival crevicular fluid) and modifiable systemic risk factors (eg, diabetes, smoking) be accounted for when evaluating the outcome of periodontal treatment and whether there has been a positive response to treatment consistent with progression toward periodontal health and stability. Thus, specific measurable biological and clinical outcomes should be determined to form the basis for assessment of periodontal health based largely (but not exclusively) on the inflammatory response.

CONCLUSIONS

It is proposed that there are 4 levels of periodontal health, depending upon whether the periodontium has normal attachment and

bone level or reduced support, as well as the ability to control modifying factors and relative treatment outcomes. These 4 categories include 1) *pristine periodontal health*, defined as a total absence of clinical inflammation and physiological immune surveillance on a periodontium with normal support (no attachment or bone loss). Pristine periodontal health is not likely to be observed clinically; 2) *clinical periodontal health*, characterized by an absence or minimal levels of clinical inflammation in a periodontium with normal support; 3) *periodontal disease stability* in a reduced periodontium; 4) *periodontal disease remission/control* in a reduced periodontium. Periodontal disease stability and periodontal disease remission/control are differentiated based on the ability to control modifying factors and therapeutic response. Stability is characterized by minimal inflammation and optimal therapeutic response, with control of modifiable risk factors; it is a major treatment goal for periodontitis. For patients in whom it is not possible to fully control modifying and predisposing factors, remission/control may be the more realistically achievable therapeutic goal. Remission/control is characterized by a significant decrease in inflammation, some improvement in other clinical parameters, and a stabilization of disease progression. Ideally, restoration to periodontal stability should be a major treatment goal and can be attained by controlling inflammation and infection, reducing predisposing factors, and controlling any modifying factors. While remission/control should be a clear target, based on available evidence, low disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease.

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2017 WORLD WORKSHOP

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Dental plaque–induced gingival conditions

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Abstract

Objective: This review proposes revisions to the current classification system for gingival diseases and provides a rationale for how it differs from the 1999 classification system.

Importance: Gingival inflammation in response to bacterial plaque accumulation (microbial biofilms) is considered the key risk factor for the onset of periodontitis. Thus, control of gingival inflammation is essential for the primary prevention of periodontitis.

Findings: The clinical characteristics common to dental plaque–induced inflammatory gingival conditions include: a) clinical signs and symptoms of inflammation that are confined to the gingiva: b) reversibility of the inflammation by removing or disrupting the biofilm; c) the presence of a high bacterial plaque burden to initiate the inflammation; d) systemic modifying factors (e.g., hormones, systemic disorders, drugs) which can alter the severity of the plaque-induced inflammation and; e) stable (i.e., non-changing) attachment levels on a periodontium which may or may not have experienced a loss of attachment or alveolar bone. The simplified taxonomy of gingival conditions includes: 1) introduction of the term "incipient gingivitis;" 2) a description of the extent and severity of gingival inflammation; 3) a description of the extent and severity of gingival enlargement and; 4) a reduction of categories in the dental plaque–induced gingival disease taxonomy.

Conclusions: Dental plaque–induced gingival inflammation is modified by various systemic and oral factors. The appropriate intervention is crucial for the prevention of periodontitis.

KEYWORDS
diagnosis, evidence-based dentistry, gingivitis

Plaque-induced gingivitis may exhibit various patterns of observable signs and symptoms of inflammation that are localized to the gingiva and initiated by the accumulation of a microbial biofilm on teeth. Even when dental plaque biofilm levels are minimized, an inflammatory infiltrate is present within gingival tissues as part of a physiologic immune surveillance.[1] However, the initiation of gingivitis occurs if dental plaque accumulates over days or weeks without disruption or removal, due to a loss of symbiosis between the biofilm and the host's immune-inflammatory response, and development of an incipient dysbiosis (Figure 1). Various systemic factors, including endocrinopathies, hematologic conditions, diet, and drugs, can modify the immune-inflammatory response.[2,3]

Gingivitis associated with plaque and/or endogenous hormonal fluctuations, drugs, systemic diseases, and malnutrition, exhibit several essential characteristics. The universal features of these gingival conditions include: clinical signs and symptoms of inflammation that are confined to the free and attached gingiva and do not extend beyond the mucogingival junction; reversibility of the inflammation by disrupting/

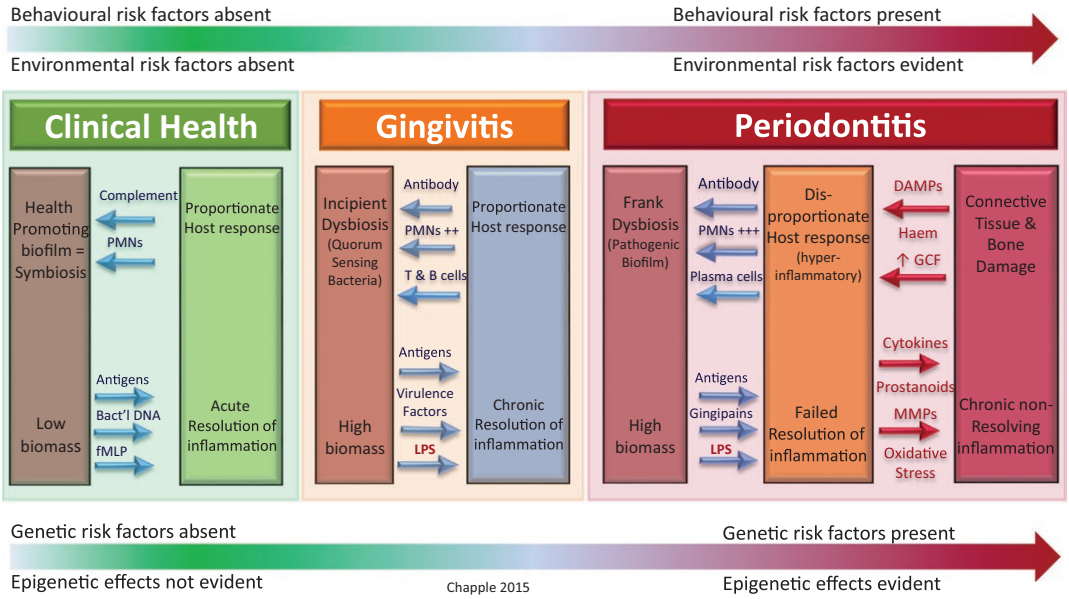

FIGURE 1 Contemporary model of host–microbe interactions in the pathogenesis of periodontitis, in which the host response drives an incipient dysbiosis (gingivitis). If the biofilm is not disrupted/removed, frank dysbiosis results and perpetuates a chronic nonresolving and destructive inflammation. DAMPs, damage-associated molecular patterns; fMLP, N- formylmethionyl- leucyl- phenylalanine; GCF, gingival crevicular fluid; LPS, lipopolysaccharide; MMPs, matrix metalloproteinases; PMNs, polymorphonuclear neutrophils. This figure is referred from ref. 106.

removing the biofilm; the presence of a high bacterial plaque burden to initiate and/or exacerbate the severity of the lesion (although this varies among individuals); and stable (i.e., unchanging) attachment levels on a periodontium, which may or may not have experienced a loss of attachment or alveolar bone. Gingival inflammation is regarded as a necessary prerequisite for the subsequent development of periodontitis and progressive attachment loss around teeth.[4] Management of gingivitis is therefore a key primary preventive strategy for periodontitis and a secondary preventive strategy for recurrence of periodontitis.[5,6]

METHODS

This review updates and revises the previous classification of plaque-induced gingival conditions reported in the 1999 classification system.[5] A literature search was conducted using the PubMed interface with "Gingival diseases" [MeSH] or "Gingivitis" [MeSH] and other related MeSH terms, such as "Microbiota"[MeSH], "Gonadal Steroid Hormones"[MeSH], "Hyperglycemia"[MeSH], "Dental Prosthesis"[MeSH], applied to systematic and narrative reviews as well as original research articles published after 1999. Also utilized were manual search approaches to identify additional primary studies; studies relating to non-plaque-induced gingival lesions were not considered.

Observations and discussion

References employed in the 1999 classification system[5] were reviewed, and the appropriate ones were selected for re-analysis. In addition, papers related to "gingivitis" were retrieved using Medline and were finally selected based on the discussion of the authors and supplemented by suggestions of the co-chairs of the group.

PLAQUE-INDUCED GINGIVITIS

Plaque-induced gingivitis is an inflammatory response of the gingival tissues resulting from bacterial plaque accumulation located at and below the gingival margin.[6] It does not directly cause tooth loss; however, managing gingivitis is a primary preventive strategy for periodontitis.[7] Epidemiologic data have shown plaque-induced gingivitis to be prevalent at all ages in dentate populations,[8–14] and this disease is considered the most common form of periodontal disease[15](Table 1). The initial changes from health to plaque-induced gingivitis may not be detectable clinically,[16] raising important debates concerning clinical thresholds for defining physiologic vs pathologic inflammation. However, as plaque-induced gingivitis progresses to more established forms of this disease, clinical signs and symptoms become obvious. Plaque-induced gingivitis begins at the gingival margin and may spread throughout the remaining gingival unit. Patients may notice symptoms that include bleeding with tooth brushing, blood in saliva, gingival swelling and redness, and halitosis in the case of established forms.[17]

The intensity of the clinical signs and symptoms will vary among individuals[18] as well as among sites within a dentition. The common clinical signs of plaque-induced gingivitis include erythema, edema, bleeding, tenderness, and enlargement.[7,19] The severity

TABLE 1 Summary of epidemiologic studies on gingivitis

Ref.	Author	Year	Population	Age, years	Sample size	Method	Definition	Prevalence
8	U.S. Public Health Service NCHS	1965	Employed adults and seniors in U.S.	18-79	6,672	National survey	PI	85.5% (male) 78.8% (female) including periodontitis
9	U.S. Public Health Service NCHS	1972	Children in U.S.	6-11	7,109	National survey	PI	38.7%
11	U.S. Public Health Service NIDR	1987	Employed adults in U.S.	18-64	15,132	National survey	Bleeding on gentle sweep of the gingival margin	47% (male) 39% (female)
			Retired persons in U.S.	65-80+	5,686			53% (male) 44% (female)
12	Bhat	1991	School children in U.S.	14-17	11,111	National survey	Bleeding on gentle sweep of the gingival margin	58.8%
15	White et al.	2012	Adults in U.K. excluding Scotland	16+	6,469	National survey	BOP, calculus, pocket depth, attachment level	83% including periodontitis

PI, periodontal index; BOP, bleeding on probing

TABLE 2 Classification of plaque-induced gingivitis and modifying factors

A. Associated with bacterial dental biofilm only
B. Potential modifying factors of plaque-induced gingivitis
1. Systemic conditions
a) Sex steroid hormones
1) Puberty
2) Menstrual cycle
3) Pregnancy
4) Oral contraceptives
b) Hyperglycemia
c) Leukemia
d) Smoking
e) Malnutrition
2. Oral factors enhancing plaque accumulation
a) Prominent subgingival restoration margins
b) Hyposalivation
C. Drug-influenced gingival enlargements

of plaque-induced gingivitis can be influenced by tooth and root anatomy, restorative and endodontic considerations, and other tooth-related factors[20] (Table 2). Radiographic analysis and/or probing attachment levels of individuals with plaque-induced gingivitis will generally not indicate loss of supporting structures. Histopathologic changes include the elongation of rete ridges into the gingival connective tissue, vasculitis of blood vessels adjacent to the junctional epithelium, progressive destruction of the collagen fiber network with changes in collagen types, cytopathologic alterations of resident fibroblasts, and a progressive inflammatory/immune cellular infiltrate.[16] Although recent studies suggest that bacterial phylotypes associated with gingivitis are distinct from those associated with health or periodontitis,[21–24] further studies are needed to clearly define the microbial community of gingivitis. In this regard, gingivitis is a non-specific dental plaque–induced inflammatory condition, a concept that remains unchanged from 1999.

The molecular characteristics or the pattern of the gingival transcriptome (i.e., sum total of all mRNA expressed by genes found in the gingiva) during plaque-induced gingival inflammation have been scrutinized since the last classification workshop. Because mRNA transcripts are not always translated into proteins, it is important to understand which transcripts are expressed as proteins[25] and causally related to the onset of gingival inflammation, and which are risk factors or risk predictors of gingival inflammation. Currently, several broad biologic changes in the transcription of genes from non-inflamed to inflamed gingival units have been documented, and ontologic groupings and include: 1) host-bacterial interactions, including but not limited to microbial pattern recognition molecules; 2) host cell chemotaxis; 3) phagocytosis and degranulation; 4) novel cellular/molecular pathway signaling, including but not limited to cytokine signaling and cell adhesion; 6) T lymphocyte response; 7) angiogenesis; and 8) epithelial immune response.[26,27] At this time, the role of the gingival transcriptome is only beginning to be understood in relation to gingival inflammation.

Plaque-induced gingivitis on a reduced periodontium

Following active periodontal treatment and the resolution of inflammation from periodontitis, the periodontal tissue is clinically non-inflamed but with a reduced connective tissue attachment and alveolar bone height. Plaque-induced gingivitis on a reduced periodontium is characterized by the return of bacterially induced inflammation to the gingival margin on a reduced periodontium with no evidence of progressive attachment loss (i.e., no indication of active disease). The common clinical and microbial findings are the same as plaque-induced gingivitis on a full periodontium except for the presence of pre-existing attachment loss and therefore a higher risk of periodontitis, unless professional, tailored supportive care regimens are in place.[28]

MODIFYING FACTORS OF PLAQUE-INDUCED GINGIVITIS

Plaque-induced gingivitis exacerbated by sex steroid hormones

Homeostasis within the periodontium involves complex, multifactorial endocrine relationships.[29,30] Evidence has accrued to show that tissue responses within the periodontium are modulated by androgens, estrogens, and progestins at one time or another in a person's life.[29,30] For endocrinotropic conditions, plaque bacteria in conjunction with elevated steroid hormone levels are necessary to produce a gingival inflammatory response. The composition of the required flora has not been fully elucidated;[31] therefore, bacteriologic analysis of endocrinotropic gingival conditions is not currently useful for diagnosis.[29,30] The following conditions may modify plaque-induced gingivitis but are not considered diagnoses in and of themselves (Table 2).

Puberty

The incidence and severity of gingivitis in adolescents are influenced by a variety of factors, including dental plaque biofilm levels, dental caries, mouth breathing, crowding of the teeth, and tooth eruption.[10] However, the dramatic rise in steroid hormone levels during puberty has a transient effect on the inflammatory status of the gingiva.[29,30] A number of studies have demonstrated an increase in gingival inflammation of circumpubertal age and in both genders, without a concomitant increase in plaque levels.[32–35] Although puberty-associated gingivitis has many of the clinical features of plaque-induced gingivitis, it is the propensity to develop frank signs of gingival inflammation in the presence of relatively small amounts of plaque during the circumpubertal period that are key to distinguishing this condition.

Menstrual cycle

During the menstrual cycle, significant and observable inflammatory changes in the gingiva have been documented in case reports.[36,37] However, most clinical studies have shown there are only modest inflammatory changes that may be observable during ovulation.[33,34,36] More specifically, gingival crevicular fluid flow has been shown to increase by at least 20% during ovulation in over 75% of women tested,[38] and other studies have also shown a modest change in women with pre-existing periodontal inflammation. Although there may be a very small cohort of women who are extremely sensitive to hormonal changes in the gingiva during the menstrual cycle, most women with menstrual cycle–associated gingival inflammation will present with clinically non-detectable signs of the condition[39–41] (Table 3).

Pregnancy

During pregnancy, the prevalence and severity of gingivitis has been reported to be elevated and frequently unrelated to the amount of plaque present.[38,42–45] Both longitudinal and cross-sectional studies have found the prevalence and severity of gingival inflammation significantly higher in the pregnant vs the post-partum patient, even though plaque scores remained the same between the two groups.[38,42] Furthermore, gingival probing depths are deeper,[38,42,44] bleeding on probing or bleeding with toothbrushing is also increased,[42,44] and gingival crevicular fluid flow is elevated[38] in pregnant women. The features of pregnancy-associated gingivitis are similar to plaque-induced gingivitis, except the propensity to develop frank signs of gingival inflammation in the presence of a relatively small amount of plaque during pregnancy.

Pregnancy may also be associated with the formation of pregnancy-associated pyogenic granulomas. This topic is covered by Holmstrup et al. from this workshop.[46]

Oral contraceptives

Oral contraceptive agents were once associated with gingival inflammation and gingival enlargements. In the early studies, the increased gingival inflammation or enlargement was reversed when oral contraceptive use was discontinued or the dosages reduced. The features of gingivitis associated with oral contraceptives in premenopausal women were similar to plaque-induced gingivitis, except the propensity to develop frank signs of gingival inflammation in the presence of relatively small amounts of plaque in women taking these hormones. Current oral contraceptive concentrations are much lower than the original doses that were reported in these early clinical studies, and it is known that current formulations of oral contraceptive do not induce the clinical changes in gingiva that were reported with high-dose contraceptives.[29,30,47]

PLAQUE-INDUCED GINGIVITIS EXACERBATED BY SYSTEMIC CONDITIONS

Hyperglycemia, hematologic malignancies, and nutrient deficiencies are a remarkably diverse collection of systemic states that can

TABLE 3 Summary of studies on menstrual cycle-associated gingival changes

Ref.	Author	Year	Population	Age, years	Sample size	Evaluation	Outcome
39	Baser et al.	2009	Female dental students in Turkey	19-23	27	PI, GI	no change between MD, OD, PgD
						BOP	more in PgD than MD and OD
						GCF amount	more in PgD than OD
						IL-1β, TNF-α in GCF	more IL-1β in PgD than MD and OD
40	Becerik et al.	2010	Premenopausal women in Turkey	21-40	50 (25 gingivitis, 25 healthy subjects)	BOP	more in PM than OV and ME of gingivitis subjects
						PI	more in gingivitis than healthy subjects; same in OV, PM, ME
						GCF amount	more in gingivitis than healthy subjects; same in OV, PM, ME
						IL-6, PGE2, PAI-2, t-PA in GCF	more IL-6 in gingivitis than healthy subjects; same in OV, PM, ME
41	Shourie et al.	2012	Premenopausal women in India	18-40	100 (25 gingivitis, 25 gingivitis treated, 50 no existing gingivitis)	PI	identical in OV, PM, ME
						GI	OV > PM > ME in gingivitis subjects but no difference in treated and no existing gingivitis subjects
						GCF amount	OV > PM > ME in gingivitis subjects but no difference in treated and no existing gingivitis subjects

PI: periodontal index; GCF: gingival crevicular fluid; ME: menstruation; PM: premenstruation; OV: ovulation; MD: the first menstruation day; OD: estimated ovulation day; PgD: estimated progesterone secretion day; IL, interleukin; TNF-α, tumor necrosis factor-alpha; PGE2, prostaglandin E2; PAI-2, plasminogen activator inhibitor-2; t-PA, tissue plasminogen activator.

affect the gingival tissues. For specific systemic conditions, such as hyperglycemia, acute leukemias, and/or vitamin C deficiency, plaque bacteria are necessary to produce a gingival response.

Hyperglycemia

Gingivitis is a consistent feature found in children with poorly controlled type 1 diabetes mellitus, and the level of glycemic control may be more important in determining the severity of gingival inflammation than the quality of plaque control.[48–50] In adults with diabetes mellitus it is much more difficult to detect the effects of this endocrine disease on gingival diseases, and only limited evidence is available[51] since most studies have evaluated gingival inflammation in association with attachment loss.[52]

Leukemia

Oral manifestations have been described primarily in acute leukemia and consist of cervical lymphadenopathy, petechiae, and mucosal ulcers as well as gingival inflammation and enlargement.[53] Signs of inflammation in the gingiva include swollen, glazed, and spongy tissues which are red to deep purple in appearance.[54] Gingival bleeding is a common sign in patients with leukemia and is the initial oral sign and/or symptom in 17.7% and 4.4% of patients with acute and chronic leukemias, respectively.[53] The bleeding is due to thrombocytopenia and clotting factor deficiencies and can present in preleukemic states such as myelodysplasia as an initial sign.[55] Gingival enlargement has also been reported, initially beginning at the interdental papilla followed by the marginal and attached gingiva.[53,54] The enlargement is caused by infiltration of gingivae by leukemic cells.[55] Although local irritants can predispose to exacerbate the gingival response in leukemia, they are not prerequisites for lesions to form in the oral cavity.[54]

Smoking

Epidemiologic studies have revealed that smoking is one of the major lifestyle-related environmental risk factors for periodontal disease.[56] Both the local and systemic effects of cigarette smoke should be intrinsically considered. Inhaled cigarette smoke is absorbed from the capillary vessels via the pulmonary alveolar epithelium and enters the systemic circulation, whereas direct exposure of inhaled cigarette smoke to periodontal tissues causes vasoconstriction of the periodontal microvasculature and gingival fibrosis, which is often observed in smokers.[57] Although plaque accumulation and disease progression are exacerbated in smokers, smokers have fewer clinical signs and symptoms of gingival inflammation, and therefore smoking can mask an underlying gingivitis.[58,59]

Malnutrition

The precise role of nutrition in the initiation or progression of periodontal diseases remains to be elucidated, leading to a paucity of information available regarding the effects of almost all nutritional deficiencies on human periodontal tissues. The one nutritional deficiency that has well-documented effects on the periodontium involves depletion of plasma ascorbic acid (i.e., vitamin C). Even though scurvy is unusual in areas with an adequate food supply, certain populations on restricted diets (e.g., infants from low socioeconomic families, the institutionalized elderly, and alcoholics) are at risk of developing this condition.[60] Although there is no dispute about the necessity of dietary ascorbic acid for periodontal health,[61] in the absence of frank scurvy, the effect of declining ascorbic acid levels on the gingiva can be difficult to detect clinically,[62] and when it is detected, it usually has characteristics that are similar to plaque-induced gingivitis.

PLAQUE-INDUCED GINGIVITIS EXACERBATED BY ORAL FACTORS

The onset and progress of gingival inflammation can be modified/exacerbated by various oral (local) factors as documented below.

Prominent subgingival restoration margins

The subgingival convexity and margin of a restoration is very important in site-specific plaque control and is closely related to gingival health. Although higher level clinical evidence in the field is not available, the concept that restoration margins placed apical to the gingival margin are detrimental to gingival health has been confirmed by a 26-year longitudinal study.[63] Prominent subgingival restoration margins promote gingivitis by increasing the local accumulation of bacterial plaque. Thus, subgingival restoration margins need to be carefully designed in order to minimize plaque retention.

Hyposalivation

Xerostomia is a symptom caused by a perceived lack of saliva in the oral cavity, rather than a diagnosis per se;[64,65] hence, the term "hyposalivation" is employed here as a diagnostic term. It is known that some health conditions/diseases such as Sjögren's syndrome, anxiety, and poorly controlled diabetes may cause xerostomia due to hyposalivation. Importantly, it is frequently observed as a side effect of medications such as antihistamines, decongestants, antidepressants, antihypertensive medications. Hyposalivation may cause progressive dental caries, taste disorders, halitosis, and inflammation of the oral mucosa, tongue, and gingiva.[66,67] Dryness in the mouth may make plaque control difficult, and gingival inflammation may be worsened.

DRUG-INFLUENCED GINGIVAL ENLARGEMENTS

There are an assortment of medications that have been reported to affect the size of the gingival tissues.[68] In the literature, the drugs

primarily associated with gingival tissue enlargement have included the antiepileptic drugs phenytoin and sodium valproate, certain calcium channel–blocking drugs (e.g., nifedipine, verapamil, diltiazem, amlodipine, felodipine), immunoregulating drugs (e.g., ciclosporine), and high-dose oral contraceptives.[69–71] For drug-influenced gingival conditions, plaque bacteria in conjunction with the drug are necessary to produce a gingival response. Nonetheless, not all individuals who take these medications will develop enlargements of the gingival tissues, suggesting a susceptibility requiring specific characteristics.[72] Furthermore, some sites/patients with drug-influenced gingival enlargement present little, if any, clinically evident gingivitis at affected sites.

The common clinical characteristics of drug-influenced gingival enlargements include variations in interpatient or intrapatient patterns of enlargement (i.e., genetic predisposition),[69,70] a tendency to occur more often in the anterior gingiva,[69,70] a higher prevalence in younger age groups,[73–75] onset within 3 months of use[69,74,75] that is usually first observed at the papilla,[69] and, although it can be found in a periodontium with or without bone loss, it is not associated with attachment loss or tooth mortality.[69,70,76] Finally, all of these drugs produce clinical lesions and histologic characteristics that are indistinguishable from one another.[69,70]

REVISIONS TO THE 1999 DENTAL PLAQUE–INDUCED GINGIVAL DISEASES CLASSIFICATION SYSTEM

Plaque-induced gingivitis can arise in any individual due to an increase in biofilm accumulation, and gingivitis may be exacerbated by systemic states. From the previous 1999 taxonomy of plaque-induced gingival conditions, it is believed the classification can be simplified to represent society's current perception of disease and health, which has been influenced by our expanding scientific knowledge base as well as our cultural, social, and individual value judgments.

Similar to the 1999 classification system, plaque-induced gingival inflammatory conditions require the presence of dental plaque coupled with clinical signs and symptoms of gingival inflammation in an otherwise stable periodontium. The revision of the 1999 classification system for dental plaque-induced gingival diseases involved four components: 1) description of the extent and severity of the gingival inflammation, 2) description of the extent and severity of gingival enlargements, 3) a reduction in gingival disease taxonomy, and 4) discussion of whether mild localized gingivitis should be considered a disease or variant of health.

To begin, the extent, or the number of gingival sites exhibiting inflammation, can be described as either localized or generalized. Similar to the manner in which extent is described for chronic periodontitis, a gingival condition would be described as localized when < 30% of the teeth are affected, and generalized would reflect when ≥30% of the teeth are affected by gingival inflammation. In addition, it is proposed to consider introducing the term "incipient gingivitis" where, by definition, only a few sites are affected by mild inflammation, expressed as mild redness and/or a delayed and broken line of bleeding rather than edema or an immediate unbroken line of bleeding on probing. Incipient gingivitis may be regarded as a condition that is part of a spectrum of "clinical health," but may rapidly become localized gingivitis if untreated. The severity, or intensity of inflammation at a site, tooth, or the entire dentition, would be reflected by the gingival index described by Loe (1967).[77] More specifically, mild gingival inflammation would be an area with a minor change in color and little change in the texture of the tissue. Moderate gingival inflammation would be an area with glazing, redness, edema, enlargement, and bleeding upon probing; severe gingival inflammation would be an area of overt redness and edema with a tendency toward bleeding when touched rather than probed.

A system to stage drug-influenced gingival enlargements requires defining the extent and severity of the enlargement. Although there are numerous approaches to evaluate the size of the gingiva,[78–90] selection of a method that is easy to use, non-invasive, and appropriate for chairside clinical assessment was a major consideration. The extent of gingival enlargements were defined as either localized or generalized.[91] Localized gingival enlargement was limited to the gingiva in relation to a single tooth or group of teeth, while generalized enlargement involves the gingiva throughout the mouth. To be considered a gingival enlargement resulting from medications, the size of the gingival unit must be greater than would normally be expected from purely an inflammatory reaction in the gingival tissues. Mild gingival enlargement involves enlargement of the gingival papilla; moderate gingival enlargement involves enlargement of the gingival papilla and marginal gingiva, and severe gingival enlargement involves enlargement of the gingival papilla, gingival margin, and attached gingiva.[90]

The catalog of dental plaque–induced gingival diseases has been condensed to accurately reflect the most common conditions afflicting the gingiva, thereby simplifying the system for clinicians (Table 1). As a result of shifting circumstances represented by the patient, the health care provider, medications, society at large, and the disease itself, the classification of gingival diseases focused on those conditions that were clinically identifiable in the population. Therefore, such terms as "menstrual cycle–associated gingivitis," "oral contraceptive–associated gingivitis," and "ascorbic acid–associated gingivitis" were removed from the classification system. Specifically, menstrual cycle–associated gingivitis was discarded because overt, clinical signs of the disease rarely affect women. Although the clinical signs of gingival inflammation that do occur may be statistically significant, the signs are not clinically significant and therefore not clinically evident to the dentist. In regard to oral contraceptives, as a result of the change to low-dose formulations, the signs and symptoms of gingival inflammation are no longer observable.[47] Finally, when scurvy is considered, the existence of scurvy-influenced gingival conditions is rare and more likely to result in bleeding due to defects in collagen cross-linkage in the gingival tissues. The occurrence of scurvy is unusual but may exist when there is general, severe malnutrition as found in some impoverished, underdeveloped countries.

In industrialized societies, scurvy is not a common nutritional problem. Further, even when considering vitamin C deficiency (i.e., those with reduced but not depleted vitamin C plasma concentrations) in populations, the presentation of gingival inflammation is slight and indistinguishable from a plaque-induced gingivitis.

SIGNIFICANCE OF DENTAL PLAQUE–INDUCED GINGIVAL CONDITIONS

Although different types of inflammation may be features of a specific diagnosis, possibly inflammation per se is not a diagnosis in itself. More specifically, the clinical presence or absence of an inflammatory response should not necessarily be considered a sign of disease or health. In numerous body organs, inflammation is a protective mechanism necessary for survival of the individual. It should be noted that exacerbations of the inflammatory response in the gingiva, either due to pathogenic biofilms or modified by fluctuations in sex steroid hormone secretions, may represent protective responses of an individual to both local and systemic environments by destroying, diluting, and "walling off" the invading organisms.[30] At the other end of the spectrum, the absence of clinical signs of inflammation may not exclude the presence of an ongoing inflammatory process evident at a histologic level. For example, during cigarette smoking, the gingival inflammatory response to plaque accumulation on teeth will be muted, despite distinct gingival host-response patterns.[92,93]

The concept of untreated gingival inflammation progressing to destruction of the periodontium has focused attention on plaque-induced gingivitis and associated gingival conditions being part of the spectrum of periodontal diseases. Although this concept has been propagated by clinical studies showing an association between gingival inflammation and bone loss,[94] longitudinal studies examining the natural history of periodontal disease failed to show complete conversion of long-standing gingival inflammation to periodontitis.[93] Gingival inflammation is associated with progression to periodontitis,[95–100] however, the presence of gingival inflammation does not mean that all affected sites are destined to progress to destructive forms of periodontal disease.[98,99] This information suggests that, consistent with all complex diseases, gingival inflammation may be a sufficient cause for destruction of the periodontium but insufficient on its own to cause the disease in all people.[101] More specifically, how can it be determined which inflamed sites within particular individuals are susceptible to conversion to periodontitis? Presently, no one knows the answer to this question, but there has been an awareness that differences in the inflammatory responsiveness of dental plaque cannot be fully accounted for by the quantity or quality of the biofilm.[59] In other words, the predilection for attachment loss at inflamed gingival sites may be dependent on the susceptibility and responsiveness of the individual to the inflammatory insult.[102–105] Moreover, specific types of inflammatory responses in the gingiva are necessary to initiate destruction of the connective tissue attachment apical to the cemento-enamel junction. The inter-relationships between health and gingivitis and periodontitis are complex and depend upon a symbiotic or a dysbiotic biofilm and the proportionality of the host's immune-inflammatory response and its ability to resolve inflammation.[106]

It is plausible that, since gingival inflammation is a ubiquitous and endemic finding in children and adults worldwide and destruction of the periodontal attachment apparatus is associated with only a select number of inflamed gingival sites and since this is generally not a painful nor functionally destructive state resulting in loss of function, gingival inflammation may not be a disease but a variant of health. Given that inflammation is a natural and important defensive process in the body, the real problem is that when gingival inflammation is discussed, it is not clear what is actually meant. The ability to determine gingival inflammation clinically relies upon crude tools for assessment (visual acuity and a rigid metal probe), whereas a molecular approach, identifying genetic and epigenetic conditions, would clarify what type of inflammatory state is present and identify who is at risk for future destruction of the periodontium. As knowledge of gingival inflammation evolves, the impact of superficial gingival inflammation on the periodontium will become more transparent.

The debate about the fundamental nature of disease continues because of the dynamic and interactive foundation related to social and cultural norms combined with the explosion of new scientific information. As a result of the shifting circumstances represented by the patient, the health care provider, the basic clinical and/or public health scientist, society at large, and the disease itself, it is essential that periodontists continue to refine the classification of periodontal diseases and conditions through evidence from the expanding knowledge base. As a consequence of seeking to enhance periodontal health, dentistry must continually examine the basic nature of periodontal disease by seeking new knowledge; evaluating what we believe is important in our society, in our dental specialty, and in ourselves; acknowledging our limitations; and contemplating the significance of data, definitions, and classifications.

CONCLUSIONS

It is evident that dental plaque (a microbial biofilm) causes gingival inflammation, and the extent and severity of the inflammation are influenced by various systemic conditions and oral factors at this stage. Moreover, plaque accumulates more rapidly at inflamed gingival sites than non-inflamed sites, creating a complex dynamic between the dental plaque biofilm and the host's immune-inflammatory response.[107] On the other hand, it should be noted that not all inflammatory sites are destined to progress to periodontitis. To date, however, no scientific evidence allows us to diagnose which gingivitis sites are susceptible to progression to periodontitis. Thus, to prevent attachment loss and destruction of periodontal tissue, dealing with gingivitis by appropriate local therapeutic intervention is still essential. In the future, gingival conditions may be diagnosed by objective analytic approaches such as transcriptome characterization and/or categorization of epigenetic changes.

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2017 WORLD WORKSHOP

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Non–plaque-induced gingival diseases

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

While plaque-induced gingivitis is one of the most common human inflammatory diseases, several non–plaque-induced gingival diseases are less common but often of major significance for patients. The non–plaque-induced gingival lesions are often manifestations of systemic conditions, but they may also represent pathologic changes limited to gingival tissues. A classification is proposed, based on the etiology of the lesions and includes: Genetic/Developmental disorders; Specific infections; Inflammatory and immune conditions and lesions; Reactive processes; Neoplasms; Endocrine, Nutritional and metabolic diseases; Traumatic lesions; and Gingival pigmentation.

KEYWORDS

classification, diagnosis oral, epulis, gingiva, gingival diseases, immunological, inflammation, mouth mucosa, oral manifestations, oral medicine, periodontal disease, rare diseases

Human gingiva as well as other oral tissues may exhibit several non–plaque-induced pathologic lesions, which may in some instances be manifestations of a systemic condition or a medical disorder. They may also represent pathologic changes limited to gingival tissues. Although these lesions are not directly caused by plaque, their clinical course may be impacted by plaque accumulation and subsequent gingival inflammation. Dentists are the key healthcare providers in establishing diagnoses and formulating treatment plans for patients affected by such lesions. Specialists in periodontology should be familiar with and be able to diagnose, treat, or refer for treatment any such lesion.

A review of non–plaque-induced gingival lesions was presented at the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions,[1] and the present review aims to add available additional literature as well as diseases and conditions which were not included in the former review. Several of the diseases and their treatment have been reviewed recently.[2–4] The purpose of the current review is not to repeat the details of such texts, but to present a contemporary classification of the most relevant non–plaque-induced gingival diseases and conditions (Table 1) and to discuss briefly the more common of these. The major difference between the present classification proposal and that of the 1999 workshop is creation of a more comprehensive nomenclature and inclusion of ICD-10 diagnostic codes. Because some of the conditions seldom manifest in the oral cavity and some even more seldom present gingival manifestations, detailed appraisal is included within Table 2.

DESCRIPTION OF SELECTED DISEASE ENTITIES:

1 | GENETIC/DEVELOPMENTAL ABNORMALITIES

1.1 | Hereditary gingival fibromatosis (HGF)

Clinically, gingival fibromatosis may present gingival overgrowth in various degrees. Compared to drug-related gingival overgrowth, hereditary gingival fibromatosis is a rare disease which may occur as

TABLE 1 Classification table summary: non–plaque-induced gingival diseases and conditions

1 Genetic/developmental disorders
- 1.1 Hereditary gingival fibromatosis (HGF)

2 Specific infections
- 2.1 Bacterial origin
  - Necrotizing periodontal diseases (*Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., *Prevotella intermedia*, and others)
  - *Neisseria gonorrhoeae* (gonorrhea)
  - *Treponema pallidum* (syphilis)
  - *Mycobacterium tuberculosis* (tuberculosis)
  - Streptococcal gingivitis (strains of streptococcus)
- 2.2 Viral origin
  - Coxsackie virus (hand-foot-and-mouth disease)
  - Herpes simplex 1/2 (primary or recurrent)
  - Varicella-zoster virus (chicken pox or shingles affecting V nerve)
  - Molluscum contagiosum virus
  - Human papilloma virus (squamous cell papilloma, condyloma acuminatum, verrucca vulgaris, and focal epithelial hyperplasia)
- 2.3 Fungal
  - Candidosis
  - Other mycoses (e.g., histoplasmosis, aspergillosis)

3 Inflammatory and immune conditions and lesions
- 3.1 Hypersensitivity reactions
  - Contact allergy
  - Plasma cell gingivitis
  - Erythema multiforme
- 3.2 Autoimmune diseases of skin and mucous membranes
  - Pemphigus vulgaris
  - Pemphigoid
  - Lichen planus
  - Lupus erythematosus
- 3.3. Granulomatous inflammatory conditions (orofacial granulomatosis)
  - Crohn's disease
  - Sarcoidosis

4 Reactive processes
- 4.1 Epulides
  - Fibrous epulis
  - Calcifying fibroblastic granuloma
  - Pyogenic granuloma (vascular epulis)
  - Peripheral giant cell granuloma (or central)

5 Neoplasms
- 5.1 Premalignant
  - Leukoplakia
  - Erythroplakia
- 5.2 Malignant
  - Squamous cell carcinoma
  - Leukemia
  - Lymphoma

6 Endocrine, nutritional, and metabolic diseases
- 6.1 Vitamin deficiencies
  - Vitamin C deficiency (scurvy)

7 Traumatic lesions
- 7.1 Physical/mechanical insults
  - Frictional keratosis
  - Toothbrushing-induced gingival ulceration
  - Factitious injury (self-harm)
- 7.2 Chemical (toxic) insults
  - Etching
  - Chlorhexidine
  - Acetylsalicylic acid
  - Cocaine
  - Hydrogen peroxide
  - Dentifrice detergents
  - Paraformaldehyde or calcium hydroxide
- 7.3 Thermal insults
  - Burns of mucosa

8 Gingival pigmentation
- Gingival pigmentation/melanoplakia
- Smoker's melanosis
- Drug-induced pigmentation (antimalarials; minocycline)
- Amalgam tattoo

an isolated disease or as part of a syndrome. It has a genetic basis in mutations of the *Son of Sevenless* gene[5] (see Table 2).

2 | SPECIFIC INFECTIONS

2.1 | Bacterial origin

Necrotizing periodontal disease

Necrotizing gingivitis (NG), necrotizing periodontitis (NP), and necrotizing stomatitis (NS) are severe inflammatory periodontal diseases caused by bacterial infection in patients with specific underlying risk factors (poor oral hygiene, smoking, stress, poor nutrition, compromised immune status [e.g., HIV]).

Although the necrotizing diseases often run an acute, rapidly destructive course, the term acute has not been included in the diagnoses since 1999. Since superficial necrosis always involves an ulcer, it is requested to delete the term "ulcerative." The term "gingivitis" is used for lesions only involving gingival tissue and characterized by no loss of periodontal attachment.[6] Central necrosis of the papillae may result in considerable tissue destruction with formation of a crater. If loss of attachment is established, the diagnosis consequently becomes NP.[7] For lesions with ulceration extending >1.0 cm from the gingival margin, including tissue beyond the mucogingival junction, the term NS has been used.[8] The three necrotizing diseases appear to represent various stages of the same disease process,[9] and a distinction between the different manifestations has not always been made in the literature. As a result, the term "necrotizing periodontal disease" (NPD) is proposed as a common term encompassing NG, NP, and NS. Further details are presented in Table 2. A constant and variable part of the microflora in NPD lesions have been described. The constant flora primarily contains *Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., and *Prevotella intermedia*; the variable flora consists of a heterogeneous array of bacterial types.[10,11]

Other bacterial infections

Non–plaque-associated bacterial infections of the gingiva are uncommon. Gingivitis caused by a specific bacterial infection may, however, arise due to a loss of homeostasis between non–plaque-related pathogens and innate host resistance.[12] Acute streptococcal gingivitis is an example of a rare acute non–plaque-associated gingival inflammation.[13–15] Other examples of specific bacterial infections of the gingiva may also be due to *Neisseria gonorrhoeae*[16,17] and *Treponema pallidum*.[12,16–18] Orofacial tuberculosis is a rare manifestation of extrapulmonary tuberculosis, occurring in approximately 0.1% to 5% of all tuberculosis infections.[19]

2.2 | Viral origin

The most important viruses to cause gingival manifestations are Coxsackie viruses and the herpes viruses including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus.[20]

Although these viruses most often infect individuals in childhood, primary infections may occur in adult life as well. They may give rise to oral mucosal disease followed by periods of latency and sometimes reactivation.

Coxsackie viruses

Coxsackie viruses may cause herpangina and hand-foot-and-mouth disease (synonym: vesicular stomatitis with exanthema). While herpangina does not involve gingiva, hand-foot-and-mouth disease is a common contagious vesicular viral disease affecting skin and oral mucosa including gingiva. The lesions are primarily seen in children and mainly caused by coxsackie viruses A6, A10, and A16 (see Table 2).[21]

HSV-1 and HSV-2

HSV-1 usually causes oral manifestations, in contrast to HSV-2, which is primarily involved in anogenital infections and only occasionally in oral infections.[20]

Herpetic gingivostomatitis

Primary herpetic infection typically occurs in infants and has an incubation period of 1 week. It may run an asymptomatic course in early childhood, but it may also give rise to gingivostomatitis with severe manifestations. A characteristic feature is the formation of few or many vesicles, which rupture, coalesce, and leave fibrin-coated ulcers often of irregular extension (Table 2).[20,22]

Recurrent intraoral herpes simplex lesions typically occur in adults and have a much less dramatic course (Table 2). As a result, they may remain undiagnosed or mistaken for aphthous ulcerations[23,24] despite the fact that aphthous ulcers do not typically affect keratinized mucosa.[23]

Varicella-zoster virus

The primary infection of varicella-zoster virus causes varicella (chicken pox), which occurs mainly in children (Table 2). Later reactivation of the virus in adults causes herpes zoster (shingles) with unilateral lesions following the distribution of an infected nerve. If the second or third branch of the trigeminal nerve is involved, skin lesions may be associated with intraoral lesions, including gingival lesions,[25,26] and intraoral lesions may occur alone.[26] Initial symptoms are pain and paresthesia, which may be present before lesions appear.[27] The initial lesions are vesicles, which soon rupture and leave fibrin-coated small ulcers, often coalescing to irregular forms (Table 2).[28]

Molluscum contagiosum virus

Molluscum contagiosum virus of the poxvirus family causes molluscum contagiosum, which is a contagious disease with infrequent oral manifestations (Table 2).[29,30] It is seen in infants with immature immune systems and manifests as discrete umbilicated papules on the skin. In adults, the disease appears in the genital areas and is often sexually transmitted.

Human papilloma virus (HPV)

More than 100 types of HPV have been identified, and at least the following 25 types have been detected in oral lesions: 1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 31, 32, 33, 35, 40, 45, 52, 55, 57, 58, 59, 69, 72, 73. The benign oral lesions, associated with HPV infection, include squamous cell papilloma, condyloma acuminatum, verruca vulgaris, and focal epithelial hyperplasia, and they appear to be associated with different distinct HPV subtypes. Oral benign HPV lesions are mostly asymptomatic, and may persist or regress spontaneously (Table 2).[31]

2.3 | Fungal origin

A number of fungi may give rise to oral infections, including candidosis, histoplasmosis, aspergillosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, geotricosis, mucormycosis.[32] Several of these are uncommon, and oral manifestations may more likely occur with immune deterioration.[33,34] Oral mycoses can cause acute, chronic, and mucocutaneous lesions.[35] Candidosis is the most common mouth mycosis, while histoplasmosis and aspergillosis are less common (Table 2).

Candidosis

Several candida species may be isolated from the mouth of humans, including *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and *C. guillermondii*. The most common fungal infection of the oral mucosa is candidosis mainly caused by *C. albicans*. *C. albicans* is a normal commensal organism of the oral cavity but also an opportunistic pathogen.[36] While candidal infection can be seen anywhere in the oral mucosa, lesions of the gingiva are seldom seen in otherwise healthy individuals. The most common clinical characteristic of gingival candidal infection is redness of the attached gingiva, often with a granular surface.

Nodular gingival lesions are uncommon and are characterized by slightly elevated nodules of a white or reddish color.[37] Diagnosis of candidal infection can be accomplished on the basis of culture, smear, and biopsy. "Linear gingival erythema" described in the 1999 International Workshop, sometimes associated with HIV infection, is now generally regarded as gingival candidosis and has therefore been removed from this classification.

3 | INFLAMMATORY AND IMMUNE CONDITIONS AND LESIONS

3.1 | Hypersensitivity reactions

Contact allergy

Oral mucosal manifestations of hypersensitivity (allergy) are very uncommon. As mentioned in the 1999 classification review,[1] such

TABLE 2 Features of the more common non–plaque-induced gingival lesions and conditions

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
1. Genetic/developmental disorders					
1.1. Hereditary gingival fibromatosis	K06.1	Generalized fibrous gingival enlargement of tuberosities, anterior free/attached gingiva and retro-molar pads	Mutation localized to 2p21-p22 (HGF1) & 5q13-q22 (HGF2) Mutations of "Son of Sevenless" genes (SOS 1, SOS2)[119]	N/A	Excisional biopsy for histopathology
2. Specific infections					
2.1. Bacterial origin					
Necrotizing periodontal diseases	A69.0	Ulceration with central necrosis of the papillae may result in considerable tissue destruction with formation of a crater[7,8]	*Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., and *Prevotella intermedia* and others[10,11]	Poor oral hygiene, smoking, stress, poor nutrition, immune compromise e.g. HIV	Characteristic clinical features
Gonorrhea	A54.8	Unspecific lesions with ulcers or fiery red mucosa and white pseudomembrane with or without symptoms[120]	*Neisseria gonorrhoeae*	May be associated with painful pharyngitis and lymphadenopathy. Genital infection of sexual partner.	Microbiological identification of pathogen
Syphilis	A51.2	Fiery red, edematous and often painful ulcerations, asymptomatic chancres or mucous patches, or atypical non-ulcerated, inflamed gingivitis	*Treponema pallidum*		Clinical features combined with dark-field examination of smear. Serologic reactions are present after few weeks.
Tuberculosis	A18.8	Nodular or papillary proliferation of inflamed gingival tissues[19]	*Mycobacterium tuberculosis*	Most often combined with pulmonary infection	Biopsy demonstrating granulomas with multinucleated giant cells
Streptococcal gingivitis	K05.01	Acute gingivitis not associated with plaque	Strains of streptococcus	Sometimes preceded by upper respiratory infection	Biopsy combined with microbiologic examination
2.2. Viral origin					
Hand-foot-and-mouth disease		Small vesicles that after rupture leave fibrinous coated ulcers. Usually in children	Coxsackie virus A 6, A 10 and A 16	Similar skin lesions of hands and feet; sometimes fever	Clinical features with lesions of skin and oral mucosa
Primary herpetic gingivostomatitis	B00.2	Gingivostomatitis with severe manifestations including painful gingivitis, ulcerations, edema and stomatitis	Herpes simplex virus types 1 and 2	Lymphadenitis, eventually fever	Few or many vesicles, which rupture, coalesce, and leave fibrin-coated ulcers often of irregular extension
Recurrent intraoral herpes simplex	B00	Cluster of small painful ulcers in attached gingiva and hard palate[23]	Herpes simplex virus types 1 and 2		Characteristic lesions combined with patient history
Chicken pox (varicella)	B01.8	Usually affecting children: small yellowish vesicles which rapidly rupture	Varicella-zoster virus	Fever, malaise, and a skin rash	Clinical features

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Shingles (herpes zoster)	B02	Unilateral painful ulcers preceded by vesicles. Lesions coalesce to form irregular ulcers.[28]	Varicella- zoster virus	Sometimes combined with skin lesions	Affecting second or third branch of trigeminal nerve
Molluscum contagiosum virus	B08.1	Molluscum contagiosum is a skin and mucosal disease of viral origin with infrequent oral mucosal involvement[30]	Molluscum contagiosum virus, which is a virus of the poxvirus family	Discrete umbilicated papules on the skin of face and[29] trunk or in adults, in the genital areas due to sexual transmission	Clinical features
Squamous cell papilloma, condyloma acuminatum, verrucca vulgaris and focal epithelial hyperplasia	B07.8	Asymptomatic exophytic papillomatosis, verrucous or flat lesions[31]	Human papilloma virus (HPV)		Histopathology of removed lesion
2.3. Fungal					
Candidosis	B37	Various types of clinical manifestations including: • pseudomembranous (also known as thrush in neonates) • erythematous • plaque-like • nodular[37]	Various Candida-species, most commonly *Candida albicans*	Sometimes oral involvement is secondary to a more serious systemic infection	Definitive diagnosis is confirmed with histologic review of biopsied tissue as well as pertinent culture results
Histoplasmosis	B39	Nodular, papillary or granulomatous lesions, which develop loss of tissue with ulcerations and pain[32]	*Histoplasma capsulatum*		Clinical features, histopathologic examination and/or culture
Aspergillosis	B44	Early stage characterized by violaceous marginal gingiva. More advanced lesions become necrotic and covered by a pseudomembrane containing fungal hyphae.	*Aspergillus spp.*	Oral involvement is commonly secondary to more serious systemic infection[33]. In the late stage, the lesions may progress and include destruction of the alveolar bone and surrounding facial muscles.	Clinical features, histopathologic examination and/or culture[34]
3. Inflammatory and immune conditions and lesions					
3.1. Hypersensitivity reactions					
Contact allergy	K08.55/ Z91.01/ Z91.04	Redness and sometimes lichenoid lesions	Type IV hypersensitivity to dental restorative materials, dentifrices, mouthwashes and foods		Histopathology shows chronic inflammatory reaction often lichenoid infiltration of primarily lymphocytes

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Plasma cell gingivitis	C90	Erythematous gingiva with a velvety texture usually affecting the anterior maxillary gingiva[39]			Histopathology reveals dense infiltrate of plasma cells in lamina propria.[121] Allergen to be identified by dermatologist.
Erythema multiforme	L51	The manifestations are varied, the most characteristic having a rounded shape with a central red area, a paler pink or edematous zone, and a red periphery. May also present only with erythema, erosions and ulcers.		May be associated with skin lesions usually appearing symmetrically on the distal extremities and progressing proximally	Clinical manifestations combined with patient history and biopsy
3.2. Autoimmune diseases of skin and mucous membranes					
Pemphigus vulgaris	L10	Gingival manifestation is usually described as desquamative gingivitis and/or as vesiculo-bullous lesions of the free and attached gingiva characterized by intraepithelial bullae which, after rupture, leave erosions[42,62]	The intraepithelial bullae in skin and mucous membranes are due to formation of autoantibodies directed against desmosome-associated protein antigens (desmoglein-3) residing in epithelial and epidermal intercellular substance	Bullous lesions of the skin are common	Diagnosis is based on clinical presentation and confirmed by histopathology and the presence of circulating autoantibody titers to desmoglein 1 and 3 which can be detected by enzyme-linked immunosorbent assay
Pemphigoid	L12.1	Desquamative lesions of the gingiva presenting as intensely erythematous areas. Rubbing of gingiva may precipitate bulla formation, which is called a positive Nicholsky sign and is caused by the destroyed adhesion of the epithelium to the connective tissue.	Caused by autoantibodies towards hemidesmosome or lamina lucida components resulting in detachment of the epithelium from the connective tissue in the basement membrane zone	Scarring is a serious concern for ocular lesions	Clinical features and histopathology. Circulating antibodies are not always found by indirect immunofluorescence.
Lichen planus	L43.8	Papular, reticular, plaque type, erythematous (atrophic), ulcerative (erosive) or bullous lesions[55]	Inflammatory reaction towards an unidentified antigen in the basal epithelial layer/basement membrane zone		Presence of papular or reticular lesions are characteristic of lichen planus. Diagnosis based on clinical features and histopathology[49]
Lupus erythematosus (LE)	L93	The typical lesion presents as a central atrophic area with small white dots surrounded by irradiating fine white striae. Ulcerations may be a sign of systemic LE.[57,59]	Deposits of antigen−-antibody complexes appear to play a role in the tissue damage characteristic of the disease[122]	The dark-red "butterfly" skin lesions are photosensitive, scaly, erythematous macules located on the bridge of the nose and the cheeks[60]	Clinical features and histopathological findings
3.3 Granulomatous inflammatory conditions (orofacial granulomatosis)					
Crohn's disease	K50	Cobblestone appearance of the oral mucosa, linear ulceration and gingival overgrowth[60]	Granuloma in the soft tissue of the oral cavity or the intestinal soft tissue	General complications, intestinal pain, anal fissures, diarrhea. Labial enlargement is common.	Clinical and histopathological findings

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Sarcoidosis	D86.8	Gingival swelling, nodules, ulcerations and gingival recession, loosening of teeth and swelling of salivary glands	Granuloma in the soft tissue of the oral cavity or in the intestinal soft tissue		Clinical and histopathological findings
4. Reactive processes					
4.1 Epulides					
Fibrous epulis	K06.8	Exophytic smooth-surfaced pink masses of fibrous consistency attached to the gingiva[65,66]	Presumably the result of continued physical trauma [65,66]		Clinical and histopathologic features
Calcifying fibroblastic granuloma	L92.8	Pedunculated or sessile red to pink mass usually derived from the interdental papilla			Clinical and histopathologic features
Pyogenic granuloma (vascular epulis)	L98	Ulcerated, smooth or lobulated pedunculated or sessile mass, red to pink in color depending on the duration of the lesion			Clinical and histopathologic features
Peripheral giant cell granuloma (or central)	M27.1	Well-defined, sessile or pedunculated soft tumor-like process with a purple, sometimes bluish to brownish color[123,124]			Clinical and histopathologic features
5. Neoplasms					
5.1 Premalignant					
Leukoplakia	K13.21	Not-removable white spot in the oral mucosa with smooth, corrugated or verrucous surface[72,73]	Tobacco and alcohol usage may be involved		Clinical and histopathologic features ruling out other diagnoses
Erythroplakia	K13.29	Red, often sharply demarcated with the surface below the surrounding mucosa	May be associated with oral lichen planus[125]		Clinical and histopathologic features ruling out other diagnoses.
5.2 Malignant					
Squamous cell carcinoma	44.02	Gingival squamous cell carcinoma often presents as painless exophytic masses, red and white speckled patches or non-healing ulcerations involving the keratinized gingiva	Tobacco and alcohol usage may be involved in the pathogenesis		Clinical and histopathologic features
Leukemia	C95	Various changes including pallor of the oral mucosa, pain, petechiae and ecchymosis, gingival bleeding and gingival swelling due to leukemic cell infiltration.[82–84] Deep punched-out ulcerations and necrosis on gingiva and tooth mobility.[126,127]	Immunosuppression due to malignant transformation of leukocyte production in the bone marrow	Dysphagia, facial paralysis, and paresthesia of the face, lips, tongue and chin, and trismus may occur	Differential blood cell analysis of the venous blood, bone marrow biopsy

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Lymphoma	C85.91	Non-specific gingival swelling may be the first manifestation of non-Hodgkin lymphoma, mimicking a periodontal abscess or pyogenic granuloma[128–130]	Hodgkin lymphoma is associated with Epstein-barr virus and an increased incidence is seen in immunocompromised patients[131,132]	Swelling of lymph nodes	Histopathology of biopsy
6. Endocrine, nutritional and metabolic diseases					
6.1. Vitamin deficiencies					
Vitamin C deficiency (Scurvy)	E64.2	Enhanced gingival bleeding, ulceration, swelling	Changes in connective tissue metabolism due to lack of ascorbic acid	Malaise	Reduced plasma ascorbic acid concentration
7. Traumatic lesions					
7.1. Physical/mechanical insults					
Frictional keratosis	K13.29	White lesion sharply demarcated, leukoplakia-like asymptomatic, homogeneous whitish-plaques that are irremovable usually presenting on facial attached gingiva[92]	Limited trauma often due to inappropriate toothbrushing		Clinical and histopathological features
Toothbrushing-induced gingival ulceration	K05.10	Superficial, often horizontal gingival laceration to major loss of tissue often resulting in gingival recession[93,94]	Excessive trauma, due to inappropriate toothbrushing		Clinical findings
Factitious injury (self-harm)	F68.1	Unusual tissue damage with ulceration in areas that can easily be reached by fingers and instruments[91]	Pressure from fingernails, application of pencils, pocket knives or other types of instruments[91]		Clinical findings combined with patient history
7.2. Chemical (toxic) insults					
Etching, chlorhexidine, acetylsalicylic acid, cocaine, hydrogen peroxide, dentifrice detergents, paraformaldehyde or calcium hydroxide	L43.8	Surface slough or ulceration	May be related to patient's use of chlorhexidine,[97,98] acetylsalicylic acid,[99,100] cocaine,[101] hydrogen peroxide,[102,103] dentifrice detergents,[104] paraformaldehyde or calcium hydroxide		Clinical findings combined with patient history
7.3. Thermal insults					
Burns of mucosa	K13.7	Erythematous lesions that may slough a coagulated surface. Vesicles and sometimes ulceration, petecchia or erosion.[108]			Clinical findings combined with patient history

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
8. Gingival pigmentation					
Gingival pigmentation/ melanoplakia	L81.9	Brownish to black diffusely pigmented areas	Most often physiologic pigmentation in persons with a dark skin complexion	Sometimes combined with endocrine disturbances (Addison's disease), syndromes (Albright syndrome, Peutz Jegher syndrome)	Clinical findings eventually combined with laboratory investigation
Smoker's melanosis	K13.24	Brownish areas most often on mandibular facial gingiva[111,112]	Deposits of melanin synthesized due to influence of smoking		Clinical findings in smokers
Drug-induced pigmentation (antimalarials, minocycline)	L83	Bluish grey or brownish to black diffuse pigmentation	Accumulation of melanin, deposits of drug or drug metabolites, or synthesis of pigments under the influence of a drug or deposition of iron following damage to the vessels		Clinical finding combined with patient history
Amalgam tattoo	L81.8	Usually small bluish or grey to black localized pigmentation, which is not elevated	Accumulation of amalgam fragments or small amalgam particles. May be result of fracture of amalgam filling during extraction or due to small particles of amalgam being spilled into wounds during restorative procedures.		Clinical findings eventually combined with radiographs to identify larger fragments. In cases where amalgam tattoo cannot be differentiated from other causes of oral pigmentation, a biopsy may be performed.[118]

reactions may be due to dental restorative materials, dentifrices, mouthwashes, and foods and are most often type IV hypersensitivity reactions (contact allergy).

Plasma cell gingivitis

Plasma cell gingivitis is an uncommon inflammatory condition usually affecting the anterior maxillary gingiva and of uncertain etiology. While some authors have associated plasma cell gingivitis with a hypersensitivity response to antigens in various substances,[38] others have raised doubt whether plasma cell gingivitis is a distinct clinicopathologic entity.[39]

Erythema multiforme (EM)

EM is an uncommon, self-limiting, acute immune-inflammatory disorder of the oral mucosa (Table 2). The etiology of EM is unclear in most patients, but it appears to be an immunologic hypersensitivity reaction mediated by T-lymphocytes. The disorder may present a diagnostic dilemma because infections (particularly, herpes simplex and mycoplasma pneumoniae) and some drugs seem to predispose toward the development of erythema multiforme, in what are believed to be immune complex disorders.[40]

3.2 | Autoimmune diseases of skin and mucous membranes

Pemphigus vulgaris (PV)

PV is an autoimmune vesiculo-bullous disease of skin and mucous membranes. Involvement of the oral mucosa is common, and in about 54% of cases, the oral cavity has been reported to be the primary site of involvement.[41] The disease is characterized by intraepithelial bullae in skin and mucous membranes due to auto-antibodies directed against desmosome-associated protein antigens (desmoglein-3). Oral mucosal lesions, including gingival lesions, may precede skin involvement.[42] In the literature, gingival localization of PV usually manifests as desquamative gingivitis and/or as vesiculo-bullous lesions of the free and attached gingiva; early lesions only rarely appear as extensive erythema and erosions (Table 2).[43]

Pemphigoid

Pemphigoid is a group of mucocutaneous disorders caused by autoantibodies toward antigens of the basement membrane, resulting in detachment of the epithelium from the connective tissue. If only mucous membranes are affected, the term mucous membrane pemphigoid (MMP) is often used.[44] Scarring is an important ocular complication but not for oral mucosal lesions.[43] Any area of the oral mucosa may be involved in MMP, but the main clinical manifestation is desquamative lesions of the gingiva presenting as intensely erythematous areas (Table 2).[45–47] Usually the bullae rupture rapidly, leaving fibrin-coated ulcers. The separation of epithelium from connective tissue at the basement membrane area is the main diagnostic feature of MMP, and circulating serum antibodies are not always revealed by indirect immunofluorescence.[48]

Lichen planus

Lichen planus is a common mucocutaneous disease with frequent manifestation on the gingiva. Oral involvement alone is common, and concomitant skin lesions in patients with oral lesions have been found in 5% to 44% of the cases.[49,50] The major characteristic of this disease is an inflammatory reaction toward an unidentified antigen in the basal epithelial layer/basement membrane zone. The disease may be associated with severe discomfort. Because it has been shown to possess a premalignant potential,[51–53] it is important to diagnose, treat, and follow patients through regular oral examinations.[51,52,54] Six types of clinical manifestation have been described (Table 2).[55] The lesions, usually bilateral, often involve the gingiva and present as desquamative gingivitis causing pain and discomfort during eating and toothbrushing. The clinical diagnosis is based on the presence of papular- or reticular- type lesions, eventually supported by histopathologic findings of hyperkeratosis, degenerative changes of basal cells, and subepithelial inflammation dominated by lymphocytes and macrophages.[49] In a recent randomized controlled trial, a tailored plaque-control regime was shown to be beneficial in reducing symptoms of gingival lichen planus and improving overall quality of life.[56]

Lupus erythematosus (LE)

LE is a group of autoimmune disorders characterized by autoantibodies to various cellular constituents, including extractable nuclear antigens and cytoplasmic membrane components. Two major forms are described: discoid LE (DLE) and systemic LE (SLE), which may involve a range of organ systems. DLE is a mild chronic form, which involves skin and mucous membranes, sometimes including the gingiva as well as other parts of the oral mucosa.[57,58] The typical lesion presents as a central atrophic area with small white dots surrounded by irradiating fine white striae (Table 2). Eight percent of patients with DLE develop SLE, and ulcerations may be a sign of SLE.[57,59] The characteristic dark red “butterfly” skin lesions are photosensitive, scaly, erythematous macules located on the bridge of the nose and the cheeks.[60] The systemic type may also include skin lesions located on the face, but they tend to spread over the entire body.

3.3 | Granulomatous inflammatory conditions (orofacial granulomatosis)

Persistent enlargement of the soft tissues in the oral cavity as well as the facial region can occur concomitant with various systemic conditions like tuberculosis, Crohn's disease (CD),[61] and sarcoidosis. These changes are also seen as a typical symptom of the Melkersson-Rosenthal syndrome (MRS). In 1985, Wiesenfeld introduced the

term orofacial granulomatosis (OFG) to describe granulomas in the absence of any recognized systemic condition (Table 2).[62] The clinical symptoms of OFG are so similar to CD that OFG may be related to or may be CD. There is still no consensus whether OFG is a distinct clinical disorder, or an initial presentation of CD or sarcoidosis, or indeed an allergic reaction.[63]

4 | REACTIVE PROCESSES

4.1 | Epulides

Epulis is a term often applied to exophytic processes originating from the gingiva. The term is non-specific and histopathology is the basis of a more specific diagnosis. Several of these processes are reactive lesions, i.e., non-neoplastic proliferations with very similar clinical appearance to benign neoplastic proliferations.[64] Usually there are no symptoms, although the reactive processes are thought to represent an exaggerated tissue response to limited local irritation or trauma, and they are classified according to their histology. True epulides include:

- Fibrous epulis
- Calcifying fibroblastic granuloma
- Pyogenic granuloma (vascular epulis)
- Peripheral giant cell granuloma (or central)

Among 2,068 cases of reactive lesions of the oral cavity, the attached gingiva with 1,331 (64.36%) cases was the most frequently affected location.[64]

Fibrous epulis

Fibrous epulides (focal fibrous hyperplasia, irritation fibroma) are common exophytic smooth-surfaced pink masses of fibrous consistency attached to the gingiva. The size varies from small to large tumorlike processes with a diameter of several cm (Table 2).[65,66]

Calcifying fibroblastic granuloma

Calcifying fibroblastic granuloma (ossifying fibroid epulis, peripheral ossifying fibroma) occurs exclusively on the gingiva (Table 2). The lesion, although usually smaller than 1.5 cm in diameter, can reach a larger size and rarely cause separation of the adjacent teeth and resorption of the alveolar crest.[67,68]

Pyogenic granuloma

The pyogenic granuloma (telangiectatic granuloma, pregnancy granuloma, pregnancy tumor, vascular epulis) is rather common and shows a striking predilection for the gingiva, which accounts for 75% of all cases (Table 2).[66] When occurring during pregnancy, the influence of female sex hormones may result in a biologic behavior distinct from other pyogenic granulomas.

Peripheral giant cell granuloma (or central)

Peripheral giant cell granuloma (giant cell epulis, peripheral giant cell reparative granuloma) usually develops from the marginal gingiva. Among 2,068 cases of reactive lesions of the oral cavity, peripheral giant cell granuloma was the most prevalent lesion (30.12%).[64] The swelling may be sessile or pedunculated, sometimes ulcerated, and the appearance may resemble pyogenic granulomas (Table 2).[69,70]

5 | NEOPLASMS

5.1 | Premalignant

Leukoplakia

The term "leukoplakia" refers to a white lesion of the oral mucosa that cannot be characterized as any other definable lesion. It is a clinical diagnosis arrived at by exclusion in that all other potential causes of a white lesion have been ruled out or addressed.[71] Lesions are generally asymptomatic and cannot be rubbed off. Approximately 20% of leukoplakic lesions demonstrate some degree of dysplasia or carcinoma upon biopsy and most oral cancers are preceded by a long-standing area of leukoplakia. As a result, leukoplakia can be considered a premalignant condition. The prevalence of malignant transformation in leukoplakia ranges from 0.13% to 34%.[72] Lesions occur most frequently on the buccal mucosa, mandibular gingiva, tongue, and floor of the mouth.

Leukoplakia manifests clinically as homogeneous and non-homogenous subtypes. The size of the lesions and clinical features are determinants of the prognosis.[73] Thus, larger lesions and non-homogenous types of lesions imply a greater risk of malignant transformation than homogenous leukoplakia.[73,74]

Verrucous leukoplakia is characterized by white papillary lesions that are covered with a thick keratinized surface. Lesions exhibiting exophytic growth and invasion of the surrounding tissues are referred to as proliferative verrucous leukoplakia, a high-risk subtype of non-homogenous leukoplakia.[75]

Erythroplakia

Erythroplakia is the red counterpart of leukoplakia in the sense that it is a red lesion, which cannot be diagnosed as any other disease. Erythroplakia usually has a higher premalignant potential.[76] The lesions are uncommon and seldom affect the gingiva (Table 2).[73]

5.2 | Malignant

Squamous cell carcinoma

Squamous cell carcinoma of the gingiva represents about 20%[77,78] of intraoral carcinomas and occurs most frequently in the mandibular premolar and molar regions. Lesions commonly occur in edentulous areas, but they may also occur at sites in which teeth are present. Mobility of

adjacent teeth is common, and invasion of the underlying alveolar bone is apparent in approximately 50% of cases. Gingival squamous cell carcinoma may mimic other oral lesions affecting the periodontium, most of which are reactive or inflammatory in nature.[79–81]

Leukemia

Leukemias can be classified as acute- or chronic-based on their clinical behavior, and lymphocytic/lymphoblastic or myeloid depending on their histogenetic origin. Oral lesions occur in both acute and chronic leukemia but are more common in the acute form. The signs and symptoms are varied (Table 2). Bacterial, viral, and fungal infections including candidosis, and herpes simplex infection may also be present.[82–84]

Lymphoma

Lymphoma is a general term given to tumors of the lymphoid system and represents the most common hematologic malignancy. Lymphoma may originate from B-lymphocyte and T-lymphocyte cell lines. There are two main types of lymphoma: Hodgkin lymphoma and non-Hodgkin lymphoma, the former being one-sixth as common as non-Hodgkin lymphoma. In contrast to non-Hodgkin lymphoma (Table 2), oral manifestations of Hodgkin lymphoma are extremely rare.[85–87]

6 | ENDOCRINE, NUTRITIONAL, AND METABOLIC DISEASES

6.1 | Vitamin deficiencies

Vitamin C deficiency (scurvy)

Ascorbic acid (vitamin C) is necessary for various metabolic processes in the connective tissue as well as in the formation of catecholamines. Clinically, scurvy is characterized by gingival bleeding and soreness (Table 2), as well as by a depressed immune response. In gingival health, the concentration of ascorbic acid in gingival crevicular fluid is higher than in plasma.[88]

7 | TRAUMATIC LESIONS

Traumatic lesions of the gingiva may be due to a wide range of causes.[89] Such lesions may be self-inflicted, iatrogenic, or accidental. Lesions, whether physical, chemical, or thermal in nature, are probably among the most common in the mouth, yet the periodontal literature contains few references on the topic.[89–91]

7.1 | Physical/mechanical insults

Frictional keratosis

Inappropriate toothbrushing can be injurious to the gingival tissues. Some patients believe they should actively brush the gingiva. Limited physical trauma from brushing may result in gingival hyperkeratosis, a white leukoplakia-like lesion referred to as frictional keratosis (Table 2).[92]

Toothbrushing-induced gingival ulceration

In cases of more violent trauma, toothbrushing damage varies from superficial gingival laceration to major loss of tissue resulting in gingival recession (Table 2).[93,94] Characteristic findings in these patients are extremely good oral hygiene, cervical tooth abrasion, and unaffected tips of the interdental papillae in the site of injury. The condition has been termed traumatic ulcerative gingival lesions.[93] Inappropriate dental flossing may also cause gingival ulceration and inflammation primarily affecting the tip of the interdental papillae. The prevalence of such findings is unknown.[95] Diagnosis of the lesion is based on clinical findings, and an important differential diagnosis includes NG.[96]

Factitious injury (self-harm)

Self-inflicted injury to the gingival tissue is usually seen in young patients, and the lesions may present unusual tissue damage in areas that can easily be reached by fingers and instruments (Table 2).[91]

7.2 | Chemical (toxic) insults

Etching

Toxic chemical products may result in mucosal surface erosions, including reactions of the gingiva. Surface sloughing or ulceration may be related to the use of chlorhexidine,[97,98] acetylsalicylic acid,[99,100] cocaine,[101] hydrogen peroxide,[102,103] or to dentifrice detergents.[104] These lesions are reversible and resolve after removing the toxic influence. Injury to the gingival tissue may also be caused by dentists' incorrect use of substances used for endodontic purposes that may be toxic to the gingiva, including paraformaldehyde or calcium hydroxide, which may give rise to inflammation, ulceration, and necrosis of the gingival tissue if the cavity sealing is insufficient.[105,106] In most instances, the diagnosis is obvious from the combination of clinical findings and patient history (Table 2).

7.3 | Thermal insults

Thermal burns of the gingiva may be prevalent due to a hurried lifestyle with intake of microwave-heated foods and drive-through coffee shops.[89] Any part of the oral mucosa can be involved, including the gingiva.[107] The lesion is erythematous with sloughing of a coagulated surface. Vesicles may also occur,[108] and sometimes the lesions present as ulceration, petechia, or erosions, which may be painful. The clinical characteristics and the history are important for the correct diagnosis (Table 2). Gingival injury due to cold has been described but appears to be very uncommon.[109]

8 | GINGIVAL PIGMENTATION

Gingival pigmentation/melanoplakia

Oral pigmentation (Table 2) is associated with a variety of exogenous and endogenous factors including drugs, heavy metals, genetics, endocrine disturbances (Addison's disease), syndromes (Albright syndrome, Peutz-Jegher syndrome), and postinflammatory reactions.[110] Physiologic pigmentation is usually symmetric, occurring on the gingiva, buccal mucosa, hard palate, lips, and tongue.

Smoker's melanosis

A primary etiologic factor in melanocytic pigmentation of the oral mucosa is cigarette smoking. Smoker's melanosis occurs most frequently on the mandibular anterior facial gingiva.[111,112] Melanosis gradually improves or may completely resolve upon cessation of smoking.

Drug-induced pigmentation (DIP)

DIP may be caused by the accumulation of melanin, deposits of drug or drug metabolites, synthesis of pigments under the influence of a drug, or deposition of iron following damage to the vessels.

Quinine derivatives such as quinolone, hydroxyquinolone, and amodiaquine are antimalarial drugs that cause bluish grey or black mucosal pigmentation occurring most frequently on the hard palate including the palatal gingiva.[113,114]

Long-term use of minocycline is associated with pigmentation of the alveolar bone and teeth. When changes in bone are viewed through relatively thin overlying mucosa, the gingiva may appear grey and is seen primarily in the maxillary anterior region. True minocycline-induced soft tissue pigmentation is much less common and occurs primarily on the tongue, lip, buccal mucosa, and gingiva.[115,116]

Amalgam tattoo

Pigmentation of the oral mucosa due to amalgam is frequently seen in the gingiva and alveolar mucosa. The lesion is a well-defined bluish, blackish, or greyish discoloration, which is not elevated (Table 2).[117,118] Radiographic imaging may demonstrate underlying amalgam debris.

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2017 WORLD WORKSHOP

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Plaque-induced gingivitis: Case definition and diagnostic considerations

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Abstract

Objective: Clinical gingival inflammation is a well-defined site-specific condition for which several measurement systems have been proposed and validated, and epidemiological studies consistently indicate its high prevalence globally. However, it is clear that defining and grading a gingival inflammatory condition at a site level (i.e. a "gingivitis site") is completely different from defining and grading a "gingivitis case" (GC) (i.e. a patient affected by gingivitis), and that a "gingivitis site" does not necessarily mean a "GC". The purpose of the present review is to summarize the evidence on clinical, biochemical, microbiologic, genetic markers as well as symptoms associated with plaque-induced gingivitis and to propose a set of criteria to define GC.

Importance: A universally accepted case definition for gingivitis would provide the necessary information to enable oral health professionals to assess the effectiveness of their prevention strategies and treatment regimens; help set priorities for therapeutic actions/programs by health care providers; and undertake surveillance.

Findings: Based on available methods to assess gingival inflammation, GC could be simply, objectively and accurately identified and graded using bleeding on probing score (BOP%)

Conclusions: A patient with intact periodontium would be diagnosed as a GC according to a BOP score ≥ 10%, further classified as localized (BOP score ≥ 10% and ≤30%) or generalized (BOP score > 30%). The proposed classification may also apply to patients with a reduced periodontium, where a GC would characterize a patient with attachment loss and BOP score ≥ 10%, but without BOP in any site probing ≥4 mm in depth.

KEYWORDS

gingival diseases, gingival hemorrhage, gingivitis

INTRODUCTION

In this review, the term "gingivitis" applies to plaque-induced gingivitis alone, rather than non-dental-biofilm induced forms of gingivitis, which carry the relevant prefix, such as "necrotizing", "plasma cell", "viral", "fungal" or "bacterial" gingivitis. These conditions are reviewed by Holmstrup et al.[1]

Gingivitis is generally regarded as a site-specific inflammatory condition initiated by dental biofilm accumulation[2–4] and characterized by gingival redness and edema[5] and the absence of periodontal attachment loss.[6] Gingivitis is commonly painless, rarely leads to spontaneous bleeding, and is often characterized by subtle clinical changes, resulting in most patients being unaware of the disease or unable to recognize it.[7]

When compared to periodontitis, a peculiarity of plaque-induced gingivitis is the complete reversibility of the tissue alterations once the dental biofilm is removed. Notwithstanding the reversibility of the gingivitis-elicited tissue changes, gingivitis holds particular clinical significance because it is considered the precursor of periodontitis, a disease characterized by gingival inflammation combined with connective tissue attachment and bone loss. The evidence supporting the relationship between gingivitis and periodontitis stems from longitudinal studies, where development and progression of attachment loss was associated with greater baseline levels of gingival inflammation.[8–13] In contrast, sites with no or minimal progression of attachment loss over time were characterized by the consistent absence of gingival inflammation over time.[12,14–18] Overall, these observations suggest that effective long-term control of gingivitis could prevent progressive attachment loss.[13]

The established relationship between gingival inflammation and periodontitis calls for the need to establish the clinical criteria that define a gingivitis case (GC).

From gingival inflammation to gingivitis case definition

It is clear that defining and grading a gingival inflammatory condition at the site level (i.e. a "gingivitis site")[6] is completely different from defining and grading a GC (i.e. a patient affected by gingivitis), and that one "gingivitis site" does not necessarily equate to a GC. In fact, when shifting from the description of a "gingivitis site" to the identification of a GC, the classification process is complicated by the absence of clear-cut criteria that allow for discriminating a patient with a certain extent/severity of inflamed gingival sites from a periodontally healthy patient. In this respect, while clinical gingival inflammation is a well-defined site-specific condition for which several measurement systems have been proposed and validated, the concept of a GC is intended as the means to define the disease at a patient-level. Such a definition, i.e., the selection of appropriate, distinct, and valid criteria for a GC, becomes more challenging when applied to a patient who has experienced attachment loss in the past and has been successfully treated.

Although epidemiologic studies indicate consistently that gingival inflammation is a highly prevalent condition, there is heterogeneity in the reported prevalence of gingivitis (Table 1).[19–30] Even though part of this heterogeneity can be interpreted in the light of real, genuine differences in disease occurrence among studied populations, it is evident that differences among cohorts may well be related to variations in the diagnostic criteria used to define a GC. Epidemiological studies have based the GC definition on epidemiological indices (Table 1)[19–30] such as: the Community Periodontal Index of Treatment Need (CPITN/CPI); average severity of gingival inflammation (as assessed using gingival indices or bleeding scores); average extent of gingival inflammation (assessed as the prevalence of sites with a certain gingival index or bleeding score); combinations of severity and extent measures. The majority of epidemiologic studies investigating the prevalence of periodontal diseases, including gingivitis, are based on the use of CPITN.[31,32] However, the CPITN is not a suitable tool for defining GC.[33] It is designed to screen for the presence of periodontitis, and consequently none of the clinical parameters included in the scoring system (i.e., bleeding, supra- or sub-gingival calculus, pockets) are unique to gingivitis. When using more specific indices to assess gingival inflammation, wide variations of gingivitis prevalence are recorded in relation to varying cut-off values. In general, the more extended and severe the manifestations of the disease that are considered, the less prevalent the gingivitis. In children aged 10 to 17 years, gingivitis prevalence was very high (91%) when calculated as the proportion of individuals with GI > 0, while it was very low (0.4%) when including only those with a mean GI > 1.[23] These observations reinforce the need to identify and grade a GC on specific, straightforward, and pragmatic clinical parameters that combine severity and extent thresholds to assess gingival inflammation on a dentition-wide basis.

Purpose of the review

The purpose of the present review is to summarize the evidence on clinical, biochemical, microbiologic, genetic markers as well as symptoms associated with plaque-induced gingivitis and to propose a set of criteria to define a plaque-induced GC. Such a classification should: (1) Include the necessary information on disease severity/extent for oral health professionals to assess the effectiveness of their preventive measures and treatment regimens; (2) Help set priorities for therapeutic actions/programs, with particular emphasis on their prognostic relevance (prevention of periodontitis) and impact on quality of life; and (3) Allow the undertaking of surveillance studies to monitor the prevalence and distribution of gingivitis consistently within a cohort as well as among different populations.[34]

Collectively, the following facts underscore the paramount clinical relevance of the need for GC classification: gingival inflammation is a ubiquitous and endemic finding in children and adults worldwide; destruction of the periodontal attachment apparatus is associated with only a select number of inflamed gingival sites; gingivitis is generally neither painful nor functionally destructive; and gingival inflammation (as opposed to gingivitis) may not be a disease but a variant of health.[6] Moreover, when defining the healthy condition in a periodontium with normal support, a distinction between "pristine periodontal health", defined as a total absence of clinical inflammation, and "clinical periodontal health", characterized by an absence or minimal levels of clinical inflammation, has been suggested. Overall, these considerations seem to imply that a certain amount (extent/severity) of gingival inflammation of the dentition is compatible with a patient defined as periodontally healthy.[35]

MATERIALS AND METHODS

Although specific criteria have been introduced in some epidemiologic surveys to describe gingival inflammation in large cohorts (Table 1), no definition for a GC has been universally accepted.

TABLE 1 Prevalence of gingivitis as derived from national, large-scale epidemiological studies or reviews

Country	Study	Population	Sample size	Clinical indices to assess gingivitis	Criteria used to identify a gingivitis case	Gingivitis prevalence
United States of America	Albandar and Kingman 1999[19]	Individuals aged 30 to 90, representing approximately 105.8 million civilian, non-institutionalized Americans	9,689	BOP	Individuals with 6 or more teeth present were classified according to the following criteria: -Extensive gingivitis: 5 or more teeth (or 50% or more of the teeth examined) with gingival bleeding; -Limited gingivitis: 2 to 4 teeth (or 25% to 50% of the teeth examined) with gingival bleeding. Individuals who did not fulfill these criteria were regarded as not having an appreciable level of gingival inflammation.	32.3% (limited: 21.8%; extensive: 10.5%)
United States of America	Li et al. 2010[20]	Subjects recruited by placing advertisements in local publications	1,000	GI	Mean full-mouth GI	GI < 0.5%: 6.1% of subjects GI > 0.5: 93.9% of subjects GI≥1: 55.7% of subjects
United Kingdom	Murray et al. 2015[21]	5 to 15-year old individuals	69,318	Not reported in the review (reported only in surveys included in the review)	Not reported in the review (reported only in surveys included in the review)	About 50% of subjects had gum inflammation
Greece	Mamai-Homata et al. 2010[22]	35 to 44-year old individuals	1,182	CPI	Highest CPI score = 1 (gingival bleeding)	16.2%
Romania	Funieru et al. 2017[23]	10 to 17-year old individuals	1,595	GI	Prevalence of gingivitis: proportion of any GI mean score > 0 Extent of gingivitis: site prevalence – proportion of gingival surfaces affected by gingivitis Prevalence of gingival bleeding: proportion of any gingival bleeding [score 2 and 3 of the GI] present in at least one gingival surface	Gingivitis prevalence: 91%
Sweden	Norderyd et al. 2015[24]	Randomly selected individuals in each of the age group of 3, 5, 10, 15, 20, 30, 40, 50, 60, 70 and 80 years	1,010	GI	GI = 2 or 3	Mean % of sites with gingivitis ranged between 1.8% to 19.5% depending on age cohort
Hungary	Hermann et al. 2009[25]	Dentate or partially edentulous adults	4,153	CPI	Highest CPI score = 1 (gingival bleeding)	8%
China	Zhang et al. 2010[26]	Adults with ≥ 20 teeth	1,143	GI	Mean GI	GI≥ 1: 82.2%

(*Continues*)

TABLE 1 (Continued)

Country	Study	Population	Sample size	Clinical indices to assess gingivitis	Criteria used to identify a gingivitis case	Gingivitis prevalence
India	Kundu et al. 2011[27]	Individuals aged 15 years or more	22,366	CPI	Highest CPI score = 1 (gingival bleeding)	4.3%
Australia	Australian Research Center for Population Oral Health 2009[28]	Individuals aged 15 years or more	4,967	GI	Mean GI≥ 2	19.7%
Argentina	De Muniz 1985[29]	7-8 and 12–13 year-old individuals	2,279	CPI	CPI = 1	2.7%-27.2% (depending on age cohort)
Algeria, Benin, Burkina Faso, Cap Verde, Djibouti, Egypt, Ethiopia, Ghana, Kenya, Lesotho, Libya, Malawi, Mauritius, Morocco, Namibia, Niger, Nigeria, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Zaire, Zimbabwe	Baelum and Scheutz 2002[30]	15 to 44-year old individuals	Reported in each study included for review	CPI	Highest CPI score = 1 (gingival bleeding)	0 to 52% (depending on the Country/study)

BOP: bleeding on probing; CPI: Community Periodontal Index; GBI: gingival bleeding index; GI: gingival index.

Murakami and Mariotti[6] suggested that the extent, or the number of gingival sites exhibiting inflammation, can be described as either localized (<30% of sites are affected) or generalized (≥30% of sites are affected). They also proposed the term incipient gingivitis where, by definition, only a few sites are affected by mild inflammation, expressed as mild redness rather than edema or bleeding on probing (BOP). However, no clear definition of the most suitable parameter used to characterize the gingival inflammation on a patient-level is provided. To tackle GC identification and grading, the different parameters and methods that are currently available to define or characterize the gingival inflammation have been thoroughly reviewed.

Clinical and biological parameters used to define gingival inflammation

Clinical parameters

Clinical methods to assess the presence and severity of plaque-induced gingival inflammation at the site level are based on the evaluation of crude macroscopic changes occurring in the marginal gingival tissues during the healthy-inflamed transition.[35] The volume of the gingival crevicular fluid (GCF) has been largely adopted in clinical trials to assess the severity of gingival inflammation at site level. However, the most commonly used clinical measures for gingival inflammation mainly consist of qualitative or semi-quantitative indices based on visual assessment of gingival characteristics (edema/swelling, redness, etc.) and/or the evaluation of the tendency of the marginal gingiva to bleed upon mechanical stimulation exerted typically by a periodontal probe. These methods were first described more than 45 years ago and have not changed much since then (Table 2).[4,36–48]

In an attempt to circumvent the subjectivity of examiner scoring, non-invasive methods based on digital technologies were introduced more recently. These methods mainly aim at measuring the volumetric or color changes that occur in the gingival tissues due to plaque-induced inflammation.[49–56] Although their application would be highly desirable in the diagnosis of gingivitis, no histologic validation of these instruments is currently available. Moreover, few studies have evaluated their reliability in subjects with gingivitis.[49,54,56] While some studies reported a positive association between the gingival volume and GI changes (without reporting the statistical strength of the association),[49] other studies failed to find a significant correlation between colorimetric assessments and variations in GI.[56] Moreover, additional aspects, including need for standardized conditions for their use, restriction of colorimetric assessments to the buccal attached gingiva of anterior teeth and need for specific adjustments for colorimetric evaluations of pigmented gingival tissues in specific ethnic groups, limit the potential to apply these technologies reliably or pragmatically to define a GC.

Therefore, for the purpose of this review, the authors limited the analysis of the available clinical parameters as potential candidates to define a GC to GCF volume, gingival index (GI),[37] and gingival bleeding indices.

TABLE 2 Gingival indices. Re-adapted from: *Bessa Rebelo MA, Corrêa de Queiroz A. Gingival Indices: State of Art. In: Gingival Diseases – Their Aetiology, Prevention and Treatment, 2011 pp: 41–54. Edited by Dr. Fotinos Panagakos*

Index name (authors and year)	Instrument	Sites for assessment	Time delay (seconds)	Graded response
PMA Index (Schour and Massler 1947[36])	Visual assessment	Each gingival unit is scored. Only the labial surfaces are examined.	Not stated	P (papillary) 0 = normal; no inflammation; 1 = mild papillary engorgement; slight increase in size; 2 = obvious increase in size of gingival papilla; hemorrhage on pressure; 3 = excessive increase in size with spontaneous hemorrhage; 4 = necrotic papilla; 5 = atrophy and loss of papilla (through inflammation). M (marginal) 0 = normal; no infiammation visible; 1 = engorgement; slight increase in size; no bleeding; 2 = obvious engorgement; bleeding upon pressure; 3 = swollen collar; spontaneous hemorrhage; beginning infiltration into attached gingivae; 4 = necrotic gingivitis; 5 = recession of the free marginal gingiva below the CEJ due to inflammatory changes. A (attached) 0 = normal; pale rose; stippled; 1 = slight engorgement with loss of stippling; change in color may or may not be present.; 2 = obvious engorgement of attached gingivae with marked increase in redness. Pocket formation present; 3 = advanced periodontitis. Deep pockets evident.
Gingival Index (Löe and Silness, 1963[37])	Probe	It scores the marginal and interproximal tissues (four areas for each tooth). The bleeding is assessed by probing gently along the wall of soft tissue of the gingival sulcus.	Not stated	0 = Normal gingiva; 1 = Mild inflammation – slight change in color and slight edema but no bleeding on probing; 2 = Moderate inflammation – redness, edema and glazing, bleeding on probing; 3 = Severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding.
Sulcus Bleeding Index (Mühlemann and Son 1971[38])	Probe	Four gingival units are scored systematically for each tooth: the labial and lingual marginal gingival (M units) and the mesial and distal papillary gingival (P units).	Not stated	Score 0 – health looking papillary and marginal gingiva no bleeding on probing; Score 1 – healthy looking gingiva, bleeding on probing; Score 2 – bleeding on probing, change in color, no edema; Score 3 – bleeding on probing, change in color, slight edema; Score 4 – bleeding on probing, change in color, obvious edema; Score 5 – spontaneous bleeding, change in color, marked edema.

(Continues)

TABLE 2 (Continued)

Index name (authors and year)	Instrument	Sites for assessment	Time delay (seconds)	Graded response
Gingival Bleeding Index (Carter and Barnes 1974[39])	Unwaxed dental floss	The mouth is divided into six segments and flossed in the following order; upper right, upper anterior, upper left, lower left, lower anterior and lower right.	Not stated; 30 s is allowed for reinspection	Bleeding is recorded as present or absent.
Gingival Bleeding Index (Ainamo and Bay 1975[40])	Probe	Gentle probing of the orifice of the gingival crevice.	10	If bleeding occurs within 10 seconds a positive finding is recorded
Papillary Bleeding Index (Mühlemann 1977[41])	Probe	A periodontal probe is inserted into the gingival sulcus at the base of the papilla on the mesial aspect, and then moved coronally to the papilla tip. This is repeated on the distal aspect of the papilla.	Not stated	Score 0 – no bleeding; Score 1 – A single discreet bleeding point; Score 2 – Several isolated bleeding points or a single line of blood appears; Score 3 – The interdental triangle fills with blood shortly after probing; Score 4 – Profuse bleeding occurs after probing; blood flows immediately into the marginal sulcus.
Papillary Bleeding Score (Loesche 1979[42])	Wooden interdental cleaner	This is performed using a Stim-U-Dent®, which is inserted interproximally. The PBS is determined on all papillae anterior to the second molars.	Not stated	0 = healthy gingiva, no bleeding upon insertion of Stim-U-Dent® interproximally; 1 = edematous, reddened gingiva, no bleeding upon insertion of Stim-U-Dent® interproximally; 2 = bleeding, without flow, upon insertion of Stim-U-Dent ® interproximally; 3 = bleeding, with flow, along gingival margin upon insertion of Stim-U-Dent® interproximally; 4 = copious bleeding upon insertion of Stim-U-Dent ® interproximally; 5 = severe inflammation, marked redness and edema, tendency to spontaneous bleeding.
Modified Papillary Bleeding Index (Barnett et al. 1980[43])	Probe	modified the PBI index (Muhlemann, 1977) by stipulating that the periodontal probe should be gently placed in the gingival sulcus at the mesial line angle of the tooth surface to be examined and carefully swept forward into the mesial papilla. The mesial papillae of all teeth present from the second molar to the lateral incisor were assessed.	0-30	0 = no bleeding within 30 s of probing; 1 = bleeding between 3 and 30 s of probing; 2 = bleeding within 2 s of probing; 3 = bleeding immediately upon probe placement.
Bleeding Time Index (Nowicki et al. 1981[44])	Probe	Inserting a Michigan "0" probe in the sulcus until slight resistance was felt and then the gingiva was stroked back and forth once over an area of approximately 2 mm.	0-15	0 = no bleeding within 15 seconds of second probing (i.e. 30 seconds total time); 1 = bleeding within 6 to 15 seconds of second probing; 2 = bleeding within 11 to 15 of seconds of first probing or 5 seconds after second probing; 3 = bleeding within 10 seconds after initial probing 4 = spontaneous bleeding.

(Continues)

TABLE 2 (Continued)

Index name (authors and year)	Instrument	Sites for assessment	Time delay (seconds)	Graded response
Eastman Interdental Bleeding Index (Caton and Polson 1985[45])	Wooden interdental cleaner	A wooden interdental cleaner is inserted between the teeth from the facial aspect, depressing the interdental tissues 1 to 2 mm. This is repeated four times	0-15	Bleeding within 15 s is recorded as present or absent.
Quantitative Gingival Bleeding Index (Garg and Kapoor 1985[46])	Toothbrush	Takes into consideration the magnitude of blood stains covering tooth brush bristles on brushing and squeezing gingival tissue units in a sextant	Not stated	0 – no bleeding on brushing; bristles free from blood stains; 1 – slight bleeding on brushing; bristle tips stained with blood; 2 – moderate bleeding on brushing; about half of bristle length from tip downwards stained with blood; 3 – Severe bleeding on brushing; entire bristle length of all bristles including brush head covered with blood.
Modified Gingival Index (Lobene et al. 1986[47])	No instrument (visual assessment)	Same as Gingival Index	Not applicable	0 = absence of inflammation; 1 = mild inflammation or with slight changes in color and texture but not in all portions of gingival marginal or papillary; 2 = mild inflammation, such as the preceding criteria, in all portions of gingival marginal or papillary; 3 = moderate, bright surface inflammation, erythema, edema and/or hypertrophy of gingival marginal or papillary; 4 = severe inflammation: erythema, edema and/or marginal gingival hypertrophy of the unit or spontaneous bleeding, papillary, congestion or ulceration.
Modified Gingival Index (Trombelli et al. 2004[4])	No instrument (visual assessment)	Same as gingival index, but without the bleeding on probing component.	Not applicable	0 = Normal gingiva; 1 = Mild inflammation – slight change in color and slight edema; 2 = Moderate inflammation – redness, edema and glazing; 3 = Severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding.
Bleeding on Interdental Brushing Index (Hofer et al. 2011[48])	Interdental brush	Inserting a light interdental brush placed buccally, just under the contact point and guided between the teeth with a jiggling motion, without force. Bleeding is scored for each interdental site.	30	Bleeding is scored as either present or absent

Volume of gingival crevicular fluid

Previous studies demonstrated that the quantification of GCF volume is a reliable and accurate indicator of gingival inflammation.[4,57,58] In 60 gingival samples retrieved from buccal sites, GCF volume increased with increasing site-specific GI. The GCF volume reflected GI values, with an evident difference between bleeding sites with moderate inflammation (GI = 2) compared to non-bleeding sites (GI < 2), and paralleled two objective measures of tissue inflammation, i.e., the percentage of inflamed connective tissue area and the inflammatory infiltrate density.[57] Experimental gingivitis studies demonstrated a clear association between GCF volume and other clinical parameters of gingival inflammation,[4] as well as the concentration of pro-inflammatory biomarkers.[58] Overall, these and other studies clearly indicate that GCF volume represents a reliable quantitative method to assess the severity of site-specific, plaque-induced gingival inflammation in the research setting. However, in clinical practice, measurement of GCF has proven to be challenging, costly and time consuming.[59] Consequently, GCF volume seems to

be unsuitable to use for a GC definition that fulfills the aforementioned pragmatic criteria.

Gingival index

The GI[37] is based on the combination of visual assessment and mechanical stimulation of the marginal periodontal tissues by probing gently along the soft tissue wall of the gingival sulcus/pocket. Technically, to stimulate the gingival tissues the probe engages approximately 1 to 2 mm of the gingival margin with the probe at a 45-degree angle with moderate axial pressure. GI scores are assigned on a 4-point ordinal scale: 0 = absence of inflammation; 1 = mild inflammation – slight change in color and little change in texture; 2 = moderate inflammation – moderate glazing, redness, edema and hypertrophy; bleeding on pressure; 3 = severe inflammation – marked redness and hypertrophy, ulceration with tendency to spontaneous bleeding. The validation of the GI comes from histological studies in humans where GI scores were significantly correlated with histological parameters of inflammation during gingivitis development;[60] specifically, the infiltrated connective tissue volume and its ratio with the volume of non-infiltrated connective tissue increased with increasing GI. Also, a higher percentage of lymphocytes and lower percentage of fibroblasts was associated with high GI scores.[60] Since its introduction, the GI has been widely used in clinical periodontal research and, together with its modifications,[4,47] it currently represents the most widely used index of gingival inflammation in clinical trials on preventive/therapeutic strategies.

To evaluate the GI at the patient-level,[37] a GI score has to be assigned to four areas (buccal, lingual, mesial and distal) for each of six index teeth (maxillary right first molar and lateral incisor; maxillary left first premolar; mandibular left first molar and lateral incisor; mandibular right first premolar – the so-called "Ramfjord teeth"), and scores of the areas can be averaged to give the GI for the patient. The routine application of the GI in clinical practice to define a GC, however, presents potential drawbacks: 1)The GI was originally proposed to describe gingivitis in pregnant women rather than the general population, and the GI scale seems to reflect the specific gingival conditions of such individuals. For example, a score of 3 represents a tendency for spontaneous bleeding, which is a rare occurrence in the general gingivitis population in contrast to women with pregnancy gingivitis;[6] 2) Since it is based on both visual inspection and mechanical stimulation of the gingival margin, the assessment of GI will result in a time-consuming procedure when incorporated in a comprehensive, whole-mouth examination (i.e., 4–6 sites per each tooth present) to obtain data representative of the inflammatory burden of the entire dentition; and 3) Intra- and inter-examiner reliability and reproducibility of the GI, particularly the component associated with visual inspection, while reported as very good in some studies,[61] appears problematic even after calibration and training sessions in other reports.[62,63]

Gingival bleeding

Gingival bleeding was first incorporated in a clinical periodontal index in 1958.[64] Much interest was given to this clinical sign in the following years, based on evidence that during the development of gingivitis the appearance of bleeding on probing typically precedes other clinically detectable signs, such as color (redness) or volume changes (edema).[38,65] Indeed, apart from a sparse number of studies that failed to show significant differences at the histological level between bleeding and non-bleeding gingiva,[66,67] the great majority of studies found that gingival bleeding is an early and accurate sign of gingival inflammation; some studies reported that sites with gingival bleeding are histopathologically characterized by a larger and/or denser inflammatory connective tissue infiltrate than non-bleeding sites while others reported a significant reduction in inflamed connective tissue with the suspension of bleeding.[60,66,68–73] Available human histology studies have validated both BOP[40] and the bleeding component of GI (i.e., scores 2 and 3)[37] as measures of gingival inflammation. In these studies, gingival biopsies were obtained at buccal gingival sites with shallow probing depth in subjects undergoing a 21-day experimental gingivitis trial[60] or periodontal surgery for interproximal pocket elimination.[68,74] The results showed an association between BOP and quantitative/qualitative alterations of the inflammatory infiltrate within the connective tissue, with the percentage of inflamed connective tissue being significantly greater at BOP-positive sites compared to BOP-negative sites (28.7% vs. 19.1%, respectively).[68] Similarly, the ratio between the volume densities of infiltrated and non-infiltrated connective tissue was found to be higher at sites bleeding upon probe stimulation (i.e., having a GI = 2) compared to non-bleeding sites (GI = 0 or 1). Also, a significant increase in the percentage of lymphocytes and a significant decrease in the percentage of fibroblasts were found for GI = 2 compared to GI = 0.[60]

Gingival bleeding presents additional characteristics in favor of its application in clinical practice: 1) It is an obvious, objective clinical sign that may be easily assessed and recorded;[39,68,75–79] 2) At a site level, it has been correlated with the severity of the inflammatory condition of the gingival tissues;[60,68] 3) With suitable training, it is possible for general dental practitioners to achieve and maintain high levels of inter-examiner consistency in assessing bleeding;[80] 4) It has prognostic relevance for periodontal deterioration at the site level, when persistently present during multiple observation intervals. In this respect, it has been demonstrated that BOP sites (GI = 2) have higher odds for attachment loss and exhibit greater prevalence of progressive severe attachment loss when compared to non-bleeding sites (GI = 0 or 1);[12] and 5) Patient-level (i.e., representative of the entire dentition) data on gingival bleeding can be easily derived from the site-specific measurements, e.g., frequency or proportion of bleeding sites, thus generating parameters that can be effectively used to inform and motivate the patient[41,70,71,81] as well as monitor the efficacy of preventive and treatment strategies of periodontal diseases.[82–84]

Methods to assess gingival bleeding: gingival stimulation

Varying methods have been proposed to assess gingival bleeding. Among those, the most commonly used are: BOP score,[40] scores of 2 to 3 of the gingival index[37] and the angulated bleeding index (AngBS).[4,85–87] These methods are based on a different diagnostic

maneuver with respect to probing stimulation of the gingival tissues. While the probe is inserted to the bottom of the gingival sulcus/pocket with a standardized force when assessing BOP, it is used to exert a gentle pressure on the gingival margin with a specific angulation when assessing GI or AngBS. Under conditions of naturally occurring gingivitis, a significant intra-subject correlation was observed between BOP and bleeding of the marginal gingiva (i.e., GI 2 and 3).[88,89] Concordance between BOP and GI bleeding was found to be dependent on the probing depth (PD) of examined sites. While 85.4% of agreement was found for the detection of bleeding at sites with PD > 4 mm, 77.7% of agreement was observed between absence of GI bleeding (i.e., GI ≤ 1) and absence of BOP at shallow (≤2 mm) pockets.[88] Despite their correlation, however, GI bleeding and BOP seem not to have the same potential to detect gingival inflammation and, therefore, should not be considered as equivalent parameters. In this respect, some studies reported a tendency towards higher bleeding prevalence for GI assessment compared to BOP,[88] while others reported a consistently higher (about 10%) proportion of bleeding sites when probing at the bottom of the sulcus/pocket.[89] On the basis of the finding that in young systemically healthy dental students the number of GI bleeding sites was similar to the number of BOP+ sites after a period of supervised oral hygiene, while it was double after a 21-day period of experimentally-induced plaque accumulation, it has been suggested that bleeding upon stimulation of the marginal gingiva seems to be a better indicator of early inflammatory changes in the gingival tissues when compared to BOP to the bottom of the pocket.[87] In contrast, a large scale study has confirmed that outcomes of the two stimulation approaches (marginal versus bottom of the pocket) are highly correlated (r = 0.89), with probing the bottom of the pocket resulting in 1.5-fold increase in average prevalence of bleeding-positive sites per patient.[90] Therefore, there is no consensus on the best gingival bleeding measure to incorporate in a GC definition.

Within the context of a GC definition, some practical considerations may point to probing to the bottom of the sulcus/pocket (as performed when assessing BOP) as the preferred method to stimulate and assess gingival bleeding: 1) The detection and recording of bleeding upon stimulation by a probe inserted in the gingival sulcus is a part of the comprehensive periodontal examination as included in periodontology education programs; 2) Probing to the bottom of the sulcus/pocket may diagnose the presence of gingival inflammation while simultaneously assessing other relevant clinical parameters (attachment level, probing depths), which gingival margin bleeding cannot achieve. Since a site (and thus, a patient) with gingivitis should not present with attachment loss, a single probing maneuver allows collection of the information necessary to detect the presence of both gingival inflammation and attachment loss. On the contrary, gingival bleeding assessment using GI does not incorporate the evaluation of the integrity of the periodontal support and, therefore, cannot be considered exhaustive when aiming to definitively establish a GC diagnosis, i.e., when needing to differentiate between gingivitis and periodontitis; 3) Bleeding following probing to the sulcus/pocket base is performed as part of the CPITN/CPI screening system in both clinical and epidemiological practice; and 4) The BOP score is the bleeding index that has most often been correlated with patient-related periodontal prognosis, self-reported symptoms[91] and quality of life.[35,92–94]

Methods to assess gingival bleeding: dichotomic or graded assessment

Given that the clinical assessment of gingival inflammation at a site-specific level is based on BOP, the extent of gingival inflammation in a dentition is related to the proportion of BOP+ sites. However, BOP may also be used to provide the severity of the inflammatory condition of the gingival tissues, as expressed by qualifying the bleeding tendency[42,46,95] or its timing after probe insertion.[41,44] Although useful for research purposes, it appears that the use of quantification indices to routinely qualify BOP at a site level may be time consuming, with variations in the grading scale difficult to detect during a routine comprehensive periodontal examination.[96]

Methods to assess gingival bleeding: probe/probing characteristics

The periodontal clinical signs detected through probing include bleeding tendency, PD, and clinical attachment level (CAL). Early on, it became evident that assessments of PD and CAL are subject to significant variability.[97] In fact, a large body of literature is dedicated to the technical and clinical aspects of periodontal probing as it relates to PD and CAL assessments.[98–104] The development of pressure-sensitive, controlled-force, automated, and computer controlled probes[105–113] was the result of the strong interest in determining the relationship between CAL and histologic attachment level and efforts to minimize the variability associated with probing determinations. Despite providing controlled forces, improved instrument precision, and electronic data capture, electronic probes do not offer a substantially improved measurement error.[100,114] This fact, combined with the increased time and cost associated with the use of electronic probes,[115] makes it easy to understand why manual probes remain the instrument of choice in clinical practice. There is also evidence that this lack of improved reproducibility with certain electronic probes may be related to patient discomfort, with the patient being a significant variable when determining probing reproducibility.[116]

Available data showed that probing force is a significant factor in determining BOP response. Probing force has a direct and linear effect on BOP prevalence, with forces greater than 0.25 N (25 g) increasing the risk of false-positive readings,[117–119] while use of constant force results in greater reproducibility of bleeding scores.[120] The probing force applied by different clinicians varies significantly and often exceeds the 25-g threshold.[105,121,122] From a patient perspective, greater probing forces are likely to exceed the pain threshold in healthy sites[123] and even more likely in inflamed sites.[124]

Another technique-related factor is angulation/placement of the probe, which was reviewed in the previous section.

In terms of instrument characteristics, probes with different tip diameters exhibit varying abilities to penetrate gingival tissues.[125,126]

This is consistent with the observation that thinner probes may elicit more pain during periodontal examination.[127] Although there is no consensus regarding optimal probe tip diameter specifically for BOP determination, limited evidence suggests that a probe tip diameter of 0.6 mm provides the best discrimination between diseased and healthy sites.[126]

Research has been conducted on the effect of probe tine shape (parallel, tapered, tapered ball-tipped) on PD assessment under different probing forces;[128] the results indicate that tine shape also impacts upon PD measurements. However, specific information on the impact of probe tine shape on BOP has not been reported.

In the context of probe characteristics and BOP assessment, it should be noted that commercially available probes have shown significant variation in dimensions (probe tine diameter and calibration of markings) when different samples were examined, even from the same production batch.[129–131] If millimeter markings are not relevant for BOP assessment, the probe diameter is. Although the available literature suggests that probe diameter variability has declined in more recent years, standardization of the manufacturing parameters for periodontal probes would help minimize such variability.

Although, as mentioned above, clinicians often use a probing force > 25 g,[105,121,122] with the average maximum probing force reported to be in the 50- to 70-g range,[122] such differences in force magnitude have been shown to result in consistent but moderate changes in BOP prevalence. For example, the mean BOP response when a 25- and a 50-g probing force were applied varied by 3 to 16 percentage points, depending on patient status (pre- or post-treatment, high or low BOP tendency) and study.[117–119] The lack of information in the literature on the prevalence of patients who fall within a particular mean BOP range given a specific probing force applied, combined with the fact that the aforementioned studies were based on a limited number of participants (10 to 12), makes it difficult to fully ascertain the true impact of the probing force on the categorization of patients based on their BOP response. Nevertheless, further review of the data reported from patients with optimal oral hygiene[118,119] suggests that use of a 25-g force results in a majority (~70%) of these patients having a BOP response of ≤10%.

Methods to assess gingival bleeding: full-mouth vs. partial-mouth assessment

Although a comprehensive periodontal examination is generally based on the examination of all teeth at mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, disto-lingual (MB-B-DB-ML-L-DL) surfaces,[132] a partial mouth examination protocol (based on a minimum number of selected quadrants, teeth and sites representative of the entire dentition) would be highly desirable for both patients and oral health professionals.

At present, however, the everyday clinical application of a partial-mouth examination protocol in defining the extent of gingival inflammation remains limited by the following issues: 1) Available validation data are not sufficient to identify the most accurate partial-mouth examination protocol. Although the level of agreement between partial-mouth and full-mouth examination protocols in the evaluation of the prevalence, severity and extent of gingival inflammation has been evaluated in a few studies,[133–137] there is limited information on which partial mouth protocol shows the best accuracy in representing the severity/extent of gingivitis as assessed by BOP;[137] 2) Clinical assessments to identify and grade a GC are necessarily incorporated in a comprehensive, full-mouth examination, which also aims at detecting and grading attachment loss. Although a recent systematic review has pointed out that some partial-mouth examination protocols well approximated a full-mouth protocol for prevalence, severity, and extent estimates of periodontitis,[138] their performance when applied to the periodontitis case definitions suggested by the CDC/AAP[139] or the European Federation of Periodontology[140] remains unknown. Therefore, as of now, the case definition of periodontitis (and, consequently, of a GC) remains based on the full-mouth examination of 4/6 sites per each tooth present;[141] and 3) Albeit a viable, and oftentimes, desirable approach in the research setting, the option to partially assess the dentition of a patient presenting in one's clinical practice for comprehensive examination is not really an option.

Consequently, on the basis of the available evidence and the considerations reported above, the definition of a GC should be based on the full-mouth evaluation of all sites available for examination.

Biomarkers in oral fluids

With increasing knowledge of gingivitis pathophysiology, specific biomarkers detected in oral fluids have emerged as potential candidates to help characterize and thus define a GC. Among the most promising biomarkers are inflammatory cytokines, indicators of the inflammatory host response, which can be recovered from GCF and saliva.[142,143]

GCF proteomics

Although several studies have investigated GCF proteomics under conditions of gingival inflammation, most of them concentrated on the healthy-inflamed transition at specific sites. Proteomic analyses conducted on GCF obtained from healthy sites (i.e., sites with GI = 0, PD ≤ 3 mm, attachment loss ≤1.5 mm) of periodontally healthy subjects showed that GCF proteomics is rather complex, consisting of approximately 200 distinct proteins, 57% of which were identified also in plasma and 43% were apparently not plasma related.[144] This clearly indicates that even though serum contributes to GCF composition, GCF is an oral fluid with a distinctive proteomic profile. Moreover, this quantitative analysis of GCF showed that the dominant proteins in conditions of periodontal health were intracellular and nucleotide proteins (25%) and hydrolytic enzymes (19%).[144] Under experimental gingivitis conditions, the GCF proteomic profile of inflamed sites showed substantial changes when compared to that observed in periodontal health. In particular, only 28 proteins out of 186 identified at inflamed sites were found to be common with those detected at healthy sites.[145]

More recently, there has been a further attempt to characterize the GCF profile of a patient with gingivitis (i.e., a patient with a given amount of gingival inflammation and no attachment/bone loss)

TABLE 3 Studies comparing GCF biomarker levels in gingivitis and other periodontal conditions (i.e., health and periodontitis)

Authors	Year of publication	Population	Sites for GCF assessment	Periodontal health (H): case definition	Gingivitis (G): case definition	Periodontitis (P): case definition	Main results
Ulker et al.[146]	2008	Recruited at the Faculty of Dentistry, University of Gazi, Turkey (G = 10, H = 25)	In the G group, GCF samples were collected from four maxillary upper incisors that were affected by gingivitis.	Not reported	Not reported	–	No significant differences in the levels of cystatin C, TNF-α, and IL-1b between G and H.
Perozini et al.[147]	2010	Recruited at the University of Taubatè, Brazil (P = 12, G = 12, H = 12)	Two randomly selected teeth in each patient	According to AAP 1999 (systemically healthy with no history of periodontal disease)	According to AAP 1999 (clinical signs of inflammation without attachment loss)	According to AAP 1999 (clinical signs of inflammation with attachment loss)	In G, IL-1b concentration was significantly lower compared to P and similar to H. ALP levels in G were significantly lower than P and higher than H.
Hardan et al.[148]	2011	Recruited at Temple School University, US (P = 23, G = 18, H = 32)	4 sites (1 per quadrant) The sites were the most representative of each condition.	No CAL loss < 5 sites with GI = 2	No CAL loss ≥ 5 sites with GI = 2	≥ 4 teeth (≥ 1 tooth in each quadrant) with ≥ 1 site with CAL≥ 4 mm	GCF levels of hydrophobic aminoacids showed a significant increase from healthy to G condition. No difference in GCF levels of sulfur compounds between H and G.
Becerik et al.[149]	2012	Recruited at the School of Dentistry, Ege University, Izmir, Turkey (Aggressive P = 20, Chronic P = 20, G = 20, H = 20)	Mesio-buccal aspects of two anterior teeth	PD ≤3 mm No gingival recessions attributable to periodontitis CAL≤ 2 mm at ≥90% of sites BOP score < 10% Radiographic distance between the CEJ and bone crest ≤3 mm at > 90% of the proximal tooth sites	Varying degrees of gingival inflammation CAL ≤2 mm at ≥90% of sites Radiographic distance between the CEJ and bone crest ≤3 mm at > 90% of the proximal tooth sites	Aggressive P: CAL ≥5 mm and PD≥ 6 mm on ≥8 teeth, at least 3 of those are other than central incisors or first molars Radiographic bone loss ≥30% of the root length on affected teeth; Chronic P: CAL ≥5 mm and PD ≥6 mm in multiple sites of all four quadrants of the mouth. Moderate-to-severe alveolar bone loss present on radiographs	IL-11 total amount was significantly higher in Chronic P compared to G. No significant differences in total amounts of IL-1b, IL-6, OSM, and LIF between G and either P or H. G had elevated OSM concentration when compared to H, and significantly higher LIF concentration than Aggressive P. No significant differences in concentration of IL-1b, IL-6, and IL-11 between G and either P or H.
Gokul et al.[150]	2012	Recruited at the Department of Periodontics, Priyadarshini Dental College & Hospital, Chennai, India (P = 20, G = 20, H = 20)	Not reported	Clinically healthy periodontium with no evidence of disease (Ramfjord's Periodontal Disease Index = 0)	Clinical signs of inflammation with no evidence of attachment loss and radiographic bone loss (Ramfjord's Periodontal Disease Index = 1–3)	Clinical signs of inflammation with attachment loss and radiographic bone loss (Ramfjord's Periodontal Disease Index = 4–6)	TNF-α levels in G were significantly higher than H, and similar to P.

(Continues)

TABLE 3 (Continued)

Authors	Year of publication	Population	Sites for GCF assessment	Periodontal health (H): case definition	Gingivitis (G): case definition	Periodontitis (P): case definition	Main results
Ertugrul et al.[151]	2013	Recruited at the Faculty of Dentistry, Yuzuncu Yil University, Turkey (Aggressive P = 21, Chronic P = 21, G = 21, H = 21)	4 sites in 4 Ramfjord teeth in H and G subjects 4 BOP+ sites in 4 Ramfjord teeth in G subjects 4 BOP+ sites in 4 teeth showing the deepest pockets in the chronic and aggressive P subjects	No CAL > 2 mm No PD > 3 mm BOP score < 15% Radiographic distance between the CEJ and bone crest < 3 mm at > 95% of the proximal tooth sites	BOoP score > 50% Radiographic distance between the CEJ and bone crest < 3 mm at > 95% of the proximal tooth sites	Aggressive P: 16–30 years of age ≥ 20 natural teeth ≥ 6 incisors and/or first molars with ≥ 1 site with PD and CAL > 5 mm ≥ 6 teeth other than first molars and incisors with ≥ 1 site with PD and CAL > 5 mm Chronic P: Inflammation in the gingiva Vertical and horizontal bone loss on radiographs PD≥ 5 mm in ≥ 6 sites of at ≥ 4 single-rooted teeth with CAL≥ 4 mm	IN G, CCL28, IL-8, IL-1b and TNF-a levels Were significantly higher compared to H and significantly lower compared to Chronic P and Aggressive P.
Kinney et al.[152]	2014	Recruited at the Michigan Center for Oral Health Research clinic, Ann Arbor, Michigan (P = 44, G = 24, H = 15)	Mesiobuccal aspect of 8 sites. Site selection was based on group classification (in patients without periodontitis, sites with PD less than 4 mm and/or CAL less than 3 mm were ranked higher; in patients with gingivitis, sites were ranked even higher if they had BOP).	CAL < 3 mm No PD > 4 mm BOP score ≤ 20% No radiographic alveolar bone loss	CAL < 3 mm No PD > 4 mm BOP score > 20% No radiographic alveolar bone loss	≥ 4 sites with CAL > 3 mm ≥ 4 sites with PD > 4 mm ≥ 4 sites with radiographic bone loss	GCF biomarkers associated with stable and progressing cases were evaluated.
Huynh et al.[153]	2015	Patients attending the Royal Dental Hospital of Melbourne and staff at the Melbourne Dental School, Australia.	The sites chosen were the most representative of each condition.	PD≤ 3 mm BOP score≤ 5% mGI < 1 PI < 20%	BOP score > 5% mGI≥ 1 PI ≥ 20% No radiographic bone loss	≥ 2 sites with PD≥ 5 mm BOP score≥ 5% mGI≥ 1 PI I≥20% radiographic bone loss	Forty-two proteins were considered to have changed in abundance. Of note, cystatin B and cystatin S decreased in abundance from H to G and further in P. Complement proteins demonstrated an increase from H to G followed by a decrease in P.

(Continues)

TABLE 3 (Continued)

Authors	Year of publication	Population	Sites for GCF assessment	Periodontal health (H): case definition	Gingivitis (G): case definition	Periodontitis (P): case definition	Main results
Köseoğlu et al.[154]	2015	Recruited at the Department of Periodontology, Faculty of Dentistry, Izmir Katip Cxelebi University, Izmir, Turkey (P = 20, G = 20, H = 20)	2 sites in 1 single-rooted and 1 multirooted tooth. In H: BOP- sites with GI≤ 1 and PD≤ 3 mm; In G: BOP+ sites with GI≥ 2 and PD≤ 3 mm; In P: BOP+ sites with GI≥ 2 and PD≥ 5 mm	No CAL loss PD≤ 3 mm BOP score < 20%	No CAL loss PD≤ 3 mm BOP score≥ 20%	≥ 4 teeth in each jaw with PD≥ 5 mm, CAL≥ 4 mm ≥ 50% alveolar bone loss in ≥ 2 quadrants BOP score > 50%	IL-35 levels in G were significantly lower than H and similar to P.
Saglam et al.[155]	2015	Recruited at the Faculty of Dentistry, Izmir, Turkey (P = 20, G = 20, H = 20)	2 non-adjacent sites selected according to the baseline clinical measurements	PD < mm BOP score < 20% Radiographic distance between the CEJ and bone crest≤ 2 mm	PD < 4 mm BOP score≥ 20% Radiographic distance between the CEJ and bone crest≤ 2 mm	≥ 4 teeth in each jaw with PD ≥ 5 mm and CAL ≥ 4 mm BOP score > 80% ≥ 50% alveolar bone loss in ≥ 2 quadrants	The IL-37 total amount was similar between G and either H or P. IL-37 concentration was significantly lower in P compared to G and H.

ALP: alkaline phosphatase; BOP: bleeding on probing; CAL: clinical attachment level; CCL28: mucosa-associated epithelial chemokine; CEJ: cementum-enamel junction; mGI: modified gingival index; IL-1ß: interleukin 1ß; IL-6: interleukin 6; IL-8: interleukin 8; IL-11: interleukin 11; IL-35: interleukin 35; IL-37: interleukin 37; LIF: leukemia inhibitory factor; OSM: oncostatin M; PD: probing depth; PI: Plaque Index; TNF-α: tumor necrosis factor α.

(Table 3).[146–155] Overall, these studies indicate that the GCF proteomic profile of gingivitis subjects is qualitatively and quantitatively different from that of periodontal health; more specifically, a greater number of proteins have been found in gingivitis compared to periodontal health.[153] Moreover, the amount of some proteins (e.g., IL-1b, ALP, complement factors, MMP-9, fibronectin, lactotransferrin precursors, alpha-actinin) is higher in gingivitis compared to periodontal health,[147,153] while other proteins (e.g., cystatin-B, cystatin-S) are present in lower amounts in gingivitis.[153]

Despite these reported GCF proteomic differences between periodontal health and gingivitis, the overall paucity of data on the GCF proteomic profile of gingivitis subjects, along with the heterogeneity between studies in terms of GC definition (Table 3), site selection for GCF sampling, and GCF sampling methods, as well as the practical limitations in performing such an assessment chairside in daily practice, currently eliminate the possibility to use the GCF proteomic profile as the basis for GC definition.

Salivary proteomics

Whole mouth saliva (WMS) is not only composed of major and minor salivary gland secretions but also contains mucosal transudates from all surfaces of the mouth, lymphoid tissues, oropharynx, and GCF. Saliva, a hypotonic aqueous solution that contains proteins, peptides, enzymes, hormones, sugars, lipids, growth factors and a variety of other compounds, has a complex composition.[156] Proteomic studies on human saliva revealed > 1,000 proteins and peptides.[143]

Some studies have characterized the salivary proteomic profile of gingivitis (i.e., a patient with a given amount of gingival inflammation and no attachment/bone loss) compared to periodontal health (Table 4).[146,154,155,157–160] The analyses showed that gingivitis was associated with significantly increased amounts of blood proteins (serum albumin and hemoglobin), immunoglobulin peptides and keratins,[158] PGE2 and MIP-1α,[160] and more than double the amounts of MMP-8, MMP-9, and IL-6.[157] In periodontal health, salivary cystatins appeared to be more abundant.[158] Similarly to GCF proteomics, the use of salivary proteomics to identify a patient with gingivitis has substantial limitations, mainly due to the heterogeneity in gingivitis definition among studies (Table 4), as well as the methodology used for proteomic profiling.

Microbiologic markers

From the earliest studies of Löe and coworkers, which established the bacterial etiology of gingivitis in the 1960s,[2,3] to investigations reported in the late 1990s,[161–165] the microbiological assessment of gingivitis (and periodontitis) was based on bacterial culture, and morphological, biochemical and other targeted analyses of collected plaque samples. These studies identified several Gram-positive anaerobes (e.g., *Actinomyces viscosus*, *Parvimonas micra (formerly Micromonas* and *Peptostreptococcus micros)*), Gram-positive facultative species (*Streptococcus* spp), and Gram-negative anaerobes (e.g., *Campylobacter gracilis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Veillonella parvula*) as associated with gingivitis,[166] with

TABLE 4 Studies investigating salivary biomarker levels in gingivitis and other periodontal conditions (i.e., health and periodontitis)

Authors	Year of publication	Population	Periodontal health (H): case definition	Gingivitis (G): case definition	Periodontitis (P): case definition	Main results
Ulker et al.[146]	2008	Recruited at Faculty of Dentistry, University of Gazi, Turkey (G = 10, H = 25)	Not reported	Not reported	–	No significant differences in cystatin C, TNF-α and IL-1ß levels between G and H
Ramseier et al.[157]	2009	Recruited at the Michigan Center for Oral Health Research clinic, Ann Arbor, Michigan, US (P = 49, G = 32, H = 18)	CAL < 3 mm PD > 4 mm BoP score ≤20% No radiographic bone loss	CAL < 3 mm PD > 4 mm BoP score > 20% No radiographic bone loss	≥4 sites with CAL > 3 mm ≥4 sites with PD > 4 mm ≥4 sites with radiographic bone loss	G showed levels of MMP-8 and MMP-9 that were intermediate between H and P
Da R. Goncalves et al.[158]	2011	Recruited at the School of Dentistry, Federal University of Espirito Santo, Brazil (G = 10, C = 10)	BOP score < 10% PD < 3 mm	No CAL loss BOP score > 50% PD > 3 mm in > 50% of sites	–	G was associated with increased amounts of serum albumin and hemoglobin, immunoglobulin peptides and keratins. Cystatins were more abundant in H
Kinney et al.[159]	2011	Recruited at the Michigan Center for Oral Health Research clinic, Ann Arbor, Michigan, US (P = 41, G = 23, H = 15)	CAL < 3 mm No PD > 4 mm No radiographic bone loss BOP score ≤20%	CAL < 3 mm No PD > 4 mm No radiographic bone loss BOP score > 20%	≥4 sites with CAL > 3 mm ≥4 sites with PD > 4 mm ≥4 sites with radiographic bone loss	Same cohort as Ramseier et al. 2009[157]. The paper focuses on the association of salivary biomarkers and periodontal disease progression.
Köseoğlu et al.[154]	2015	Recruited at the Department of Periodontology, Faculty of Dentistry, Izmir Katip Cxelebi University, Izmir, Turkey (P = 20, G = 20, H = 20)	No CAL loss PD ≤3 mm BOP score < 20%	No CAL loss PD ≤3 mm BOP score ≥20%	≥ 4 teeth in each jaw with PD ≥ 5 mm, CAL ≥ 4 mm ≥ 50% alveolar bone loss in ≥ 2 quadrants BOP score > 50%	IL-35 levels in G were significantly lower than H and significantly higher than P
Saglam et al.[155]	2015	Recruited at the Faculty of Dentistry, Izmir, Turkey (G = 20, H = 20)	PD < 4 mm BOP score < 20% Radiographic CEJ-bone crest ≤ 2 mm	PD < 4 mm BOP score≥20% Radiographic CEJ-bone crest ≤2 mm	≥ 4 teeth in each jaw with PD ≥ 5 mm and CAL ≥ 4 mm BOP > 80% ≥ 50% alveolar bone loss in ≥ 2 quadrants	Similar levels of IL-37 between H, G, and P
Syndergaard et al.[160]	2014	Recruited at the University of Kentucky College of Dentistry, Kentucky, US (G = 40, H = 40)	No CAL ≥2 mm PD ≤4 mm BOP score < 20%	No CAL≥ 2 mm PD≤ 4 mm BOP score≥ 20%	–	Concentrations of MIP-1α and PGE_2 were significantly Higher (2.8 times) in G compared to H

BOP: bleeding on probing; CAL: clinical attachment level; CEJ: cementum-enamel junction; IL-1ß: interleukin 1ß; IL-6: IL-35: interleukin 35; IL-37: interleukin 37; MIP-1α: macrophage inflammatory protein 1α; MMP-8: matrix metalloproteinase 8; MMP-9: matrix metalloproteinase 9; PD: probing depth; PGE_2: prostaglandin E_2; TNF-α: tumor necrosis factor α.

the flora becoming more diverse with time and the development and progression of gingivitis.[167] Efforts to identify microbiologic differences among persons with a stronger or weaker gingival inflammatory response to plaque accumulation did not find significant differences.[161] Although quantitative differences were consistently identified for targeted species among sites characterized by gingivitis and periodontitis or health,[162–164] none of the associated bacterial species were unique to gingivitis and, therefore, their presence cannot be considered pathognomonic.

The introduction in the late 90s of open-ended molecular methods and their application to the detection of microbes broadened significantly the spectrum of bacterial species associated with periodontal diseases, with many previously unidentified and/or uncultivated bacteria linked with periodontitis.[168–171] In the last few years, these molecular techniques have been applied, along with novel statistical approaches, to the study of the biofilm associated with gingivitis and compared to health and periodontitis.[172–177] These studies have demonstrated that the transition from health to disease follows the principles of primary ecological succession, with change in abundances of indigenous species, rather than acquisition of newer organisms. Even as these studies identified previously unrecognized species in gingivitis, they confirmed that the biofilms associated with gingivitis and periodontitis share most species (albeit with quantitative differences). Emerging evidence suggests that clusters of bacteria, rather than individual species, might be of use as diagnostic markers for each disease; and that bacterial functions (e.g., proteolysis, flagellar assembly, bacterial motility) may be a more robust discriminant of disease than species. While these early novel findings support a gene-centric[178–182] rather than a species-centric approach to disease causation, further studies are required to better characterize such bacterial clusters and gene functions and to validate their potential use both as a diagnostic tool and as response to treatment monitoring tool.[183]

Systemic inflammation markers (CRP)

As for other chronic inflammatory diseases, the relationship between periodontal diseases (including gingivitis) and systemic levels of inflammatory markers has been evaluated. The biologic mechanisms supporting the plausibility of this association rely on the entry of pathogenic bacteria from the biofilm of periodontally diseased sites into the blood stream and on the entry into the circulation of excess local levels of host-derived inflammatory mediators.

Among the investigated biomarkers, particular attention has been paid to C-reactive protein (CRP), which is produced in response to many forms of trauma or diseases and contributes to host defense as part of the innate immune response. Studies that evaluated the association between gingivitis and serum levels of CRP universally identified gingivitis as a condition characterized by serum CRP levels which are intermediate between those measured in periodontal health and periodontitis, although differences in serum CRP levels observed between gingivitis and the other periodontal conditions did not consistently reach statistical significance in all studies.[184–186] In subjects with gingivitis, the severity and extent of gingival inflammation were evaluated for their relationship with CRP levels in serum. While in some studies CRP levels were found to be significantly positively correlated with papillary bleeding index[186] or GI,[184] other authors failed to find an association between CRP levels and GI,[185] BOP,[185,187] or the number of sextants with at least one BOP+ site.[188] Certain factors may have contributed to the heterogeneity among these findings. First, criteria for GC definition varied greatly among studies. Second, control of potential confounders through adequate statistical analyses (e.g., multivariate models) was applied only in some studies.[187,188] Overall, the above mentioned findings seem to demonstrate that the inflammation of marginal gingival tissues determines an increase in systemic inflammation, assessed in terms of CRP levels. However, other studies have failed to demonstrate potentially relevant systemic effects during gingivitis development.[189] Therefore, the relationship between severity of gingival inflammation and severity of systemic inflammation in patients with gingivitis remains unclear.

Genetic markers

Two specific pieces of information suggest that susceptibility to gingivitis may be genetically controlled.[190,191] The first line of evidence comes from studies of patients with Down syndrome. Despite no differences in plaque accumulation rates, patients with Down syndrome, compared to age- and sex-matched genetically healthy controls, exhibit more extensive gingival inflammation and at much earlier times.[192] The second line of evidence comes from studies on twins. Michalowicz et al.[193] studied monozygous and dizygous adult twin pairs and reported that, based on ratios of within-pair variances or heritability estimates, there was a significant genetic component for gingivitis and other clinical parameters. For gingivitis, in particular, they estimated from reared-apart monozygous twins that 82% of the population variance may be attributed to genetic factors.[193] These findings provide strong support for the role of genetic make-up in gingivitis susceptibility.

Recent evidence is available evaluating whether genetic characteristics, in general, and gene polymorphisms, in particular, may contribute to exacerbated gingival inflammation in response to plaque accumulation. Since the host immune response is a dominant gene expression pathway during the onset and resolution of gingival inflammation, with several genes being significantly up- or downregulated,[194] particular emphasis has been placed upon evaluating the potential association between cytokine gene polymorphisms and gingival inflammation in either observational, cohort studies[195–200] or experimental gingivitis trials.[201–204] Although the available evidence suggests a role for some gene polymorphisms in determining the susceptibility to plaque-induced gingival inflammation, definitive associations between ≥1 genetic indicators and the severity of gingival inflammation are not yet available, in part because of the limited number of gene loci investigated and the small number of subjects included in pertinent studies.[205] To date, a limited number of studies have attempted to investigate the genetic profile of gingivitis and healthy cases (Table 5).[197,200,206–208] However, large-scale

TABLE 5 Case-control studies investigating the association between gene polymorphisms and gingivitis (versus healthy controls)

Authors	Year of publication	Population	Periodontal health (H): case definition	Gingivitis (G): case definition	Investigated gene polymorphisms	Main results
Dashash et al.[206]	2006	248 whites Aged 8 to 12 years (G = 164, H = 84)	Healthy gingiva And no evidence of bleeding on probing or clinical signs of inflammation	Clinical evidence of gingivitis assessed by gingival and bleeding on probing indices	IL-10$_{-1082}$ IL-10$_{-819}$ IL-10$_{-592}$	The GCC/GCC genotype, which has been associated with increased production of IL-10, was significantly more frequent in H than in G.
Dashash et al.[197]	2007	146 whites Aged 8 to 12 years (G = 98, H = 48)	Healthy gingiva and had Neither evidence of bleeding on probing nor clinical signs of inflammation	Presence of Bleeding on probing at any site, as determined by gingival and papillary bleeding on probing indices	IL-1RN	Significant association between IL-1Ra genotype and periodontal status (H vs G). The IL-1RN*2 allele (A2) was significantly more frequent in H, and the carriage of A2 seemed to be protective against gingivitis.
Holla et al.[207]	2008	455 whites Aged 11 to 13 years (G = 272, H = 183)	GI = 0 At all 24 examined sites	Total sum of GI values at 24 examined sites≥ 4	IL-6$_{-174}$ IL-6$_{-572}$ IL-6$_{-597}$	Significant differences in haplotype frequencies between G and H. The CGA haplotype was significantly more frequent in G than in H. The IL-6 – 174C allele was more frequent in G than in H, and allele C remained a risk factor for G regardless of plaque or gender.
Vokurka et al.[200]	2009	298 whites Aged 11 to 13 years (G = 147, H = 151)	GI = 0 At all 24 examined sites	Total sum of GI values at 24 examined sites≥ 4	MMP-9$_{-1562}$ IL-18$_{-607}$	The prevalence of MMP-9$_{-1562}$ alleles was significantly higher in G compared to H. A highly significant association of the composite genotype (formed by the variants of both genes) with G was found.
Garlet et al.[208]	2012	608 whites and Afro-American/ Mulatto subjects (P = 197, G = 193, H = 218)	BOP score < 10% PD > 3 mm CAL > 1 mm	BOP > 70% ≤ 1 tooth per sextant with CAL loss ≤1 mm No history of tooth loss due to periodontitis	IL1B$_{-3954}$ IL6$_{-174}$ TNFA$_{-308}$ IL10$_{-592}$ TLR4$_{-299}$	Positive associations were found for IL6$_{-174}$, IL10$_{-592}$ and TLR4$_{-299}$

[a]BOP: bleeding on probing; CAL: clinical attachment level; gingival index; IL-1: interleukin 1; IL-1RA: interleukin 1 receptor antagonist; IL-6: interleukin 6; IL-10: interleukin 10; MMP-9: matrix metalloproteinase 9; TNF: tumor necrosis factor.

genome-wide association studies hold promise for the identification of genetic variations that are significantly associated with severe gingival inflammation.[209]

Emerging evidence indicates that the inflammatory response may be modulated in a dynamic way by epigenetic processes, which are heritable and reversible. In particular, the modern concepts of epigenetics imply that gene expression may be modified by environmental exposures such as diet, microbial infections, cigarette smoke, and diabetes. This implies that the genetic component of susceptibility to gingival inflammation could vary during post-natal life, without introduction of any mutations to a specific gene's DNA.[210] Diseases such as cancer, initially identified as genetic, are now known to involve both genetic and epigenetic abnormalities.[211] Even though pertinent studies are still limited in number,[212] it is reasonable to hypothesize that epigenetic modulators will be evaluated in the future for their potential impact on gingivitis.

In conclusion, when considering the pandemic distribution of gingivitis and its high prevalence in different populations, it can be hardly expected that a GC definition can be based exclusively on genetic/epigenetic profiling/susceptibility, which currently remains to be determined.

Self-reported diagnosis

Although studies on self-assessment of oral health demonstrated the validity of self-reporting on teeth present, decayed teeth, missing teeth, malocclusion and prosthetic condition, studies on self-assessment of periodontal condition revealed inconsistent results with varying levels of validity.[7] When considering gingivitis, the most investigated self-reported symptom is "bleeding from gums".[91,213–223] Several studies have validated self-reported bleeding perception with BOP scores.[91,217–219,221,222] Overall, findings seem to indicate that self-perceived bleeding (either spontaneous or evoked by different mechanical stimulations) shows high specificity and low sensitivity. In the study by Schwarz,[83] participants were asked "do you have gum problems?". Participants who self-reported "no gum problems" showed a gingival bleeding index (GBI) of 6.1%, those who self-reported "gum problem often" showed a GBI of 24.5%. Baser et al.[91] showed that 19 out of 20 dental students who presented with BOP < 10% reported no bleeding gums whereas about half of the students with gingival bleeding (i.e. BOP > 10%) correctly identified themselves as having gingival disease. In conclusion, the available data suggest that the self-assessment of bleeding does not have sufficient validity for screening individuals affected by gingivitis. Interestingly, a limited number of bleeding sites (i.e. < 10%) appears to be associated with a self-perception of periodontally-healthy conditions.

Oral health-related quality of life (OHRQoL)

Few studies evaluated the impact of gingivitis on OHRQoL.[92,93,224] In a cohort of 1,034 Thai children, Tsakos et al.[224] showed that, while the prevalence of periodontal treatment need (CPI > 0) was 97%, the perception of a condition-specific (CS) impact was limited to 27.1% of subjects. Specificity with respect to individuals with no CS-impact among periodontally healthy subjects was 0.83. Similarly, in a sample of 1,100 12-year old and 871 15-year old Thai children, <30% of subjects had CS-impact on their quality of life related to gingivitis and calculus despite the high prevalence (about 80%) of gingivitis and/or calculus. The impact of gingivitis on children's OHRQoL was mostly at low levels of extent and intensity. However, extensive gingivitis was significantly associated with a moderate/higher level of CS-impacts.[92] In a random sample of 1,134 12-year-old Brazilian schoolchildren, gingivitis extent showed an impact on OHRQoL, with mean quality of life scores being 1.15 higher for children with ≥15% BOP+ sites than for children with < 15% BOP+ sites.[93] Extent of gingival bleeding (≥15% BOP) was significantly associated with emotional well-being, oral symptoms, functional limitations and social well-being domains.[93]

Overall, data from these studies indicate that, although highly prevalent, gingivitis has a limited impact on OHRQoL. However, gingivitis extent, in terms of BOP score, may increase the negative effects on CS and general OHRQoL. Interestingly, an increasing level of agreement between the impact of gingivitis (CPI = 1 vs. CPI = 2) on patient's quality of life and the presence of a normative need for periodontal treatment has been reported.[224]

RESULTS AND DISCUSSION

The use of BOP to define and grade a GC

Based on available methods to assess gingival inflammation, a GC could be simply, objectively and accurately defined and graded using a BOP score (BOP%).[40] A BOP score is assessed as the proportion of bleeding sites (dichotomous yes/no evaluation) when stimulated by a standardized (dimensions and shape) manual probe with a controlled (~25 g) force to the bottom of the sulcus/pocket at six sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) on all present teeth.

BOP may be used for (i) discriminating between a healthy and gingivitis patient,[35] and (ii) classifying a GC (localized, generalized).[6] Use of BOP to identify a GC case would have the following advantages: 1) It is an objective, universally accepted, reliable and accurate clinical sign that may be easily assessed and recorded[39,68,75–79] as part of probing assessments necessary for a comprehensive periodontal examination; 2) Gingival bleeding represents a clinical sign often perceived by the patient, whereas low level of BOP% are consistent with self-reported perception of healthy gingival conditions; 3) BOP recording is user-friendly, economic, and requires minimal/no technology. With suitable training, it is possible for general dental practitioners to achieve and maintain high levels of intra-examiner consistency in assessing bleeding;[80] and 4) Bleeding score can be effectively used to inform and motivate the patient[41,70,71,81] as well as monitor the efficacy of preventive and treatment strategies aimed to control periodontal diseases.[82–84]

The authors are aware that BOP score is merely a measure of the extent of gingival inflammation rather than a method to assess the severity of the inflammatory condition. The limitations arising from the use of semiquantitative indices, such as GI, to diagnose gingivitis patients have been addressed above. Although severity of gingival inflammation may be well defined on a site-specific basis,[35] signs of gingival inflammation, such as gingival volume and color changes (however assessed), can be hardly merged with BOP% at a patient-level, and they would eventually result in a subjective, time consuming and impractical procedure to establish a universally-acceptable GC definition.

Beyond the underlying tissue inflammation, there are patient factors that can affect the gingival response to mechanical stimulation by a probe. Previous studies have clearly shown that the individual tendency to develop gingival bleeding after probe stimulation may be a host-related trait that can depend on several patient-related factors.[6,77,191] Smoking has been consistently shown to suppress the gingival bleeding response during development of gingivitis,[89,225–228] while a limited number of studies have shown that under steady-state conditions smoking increases the likelihood of a gingival bleeding response to probing.[229,230] Patients on anticoagulant medications (e.g., aspirin) exhibit increased bleeding response to probing.[231–234] Among patients with similar ethnic background and plaque levels, differences in genetic background might also account for different BOP responses.[191,198,201] Despite evidence suggesting a greater susceptibility of thin gingival tissues to mechanical trauma,[235,236] the significance of gingival quality/dimensions (i.e., periodontal phenotype) for the BOP response remains unresolved.[230,237] Nevertheless, the presence of patient determinants known to affect the BOP response should be taken in consideration when determining the periodontal inflammatory conditions, in general, and when diagnosing a GC, in particular.

Definition of gingivitis in a patient with an intact periodontium

A patient with an intact periodontium is diagnosed as a GC as follows (Table 6): localized gingivitis, defined as a patient presenting with a BOP score ≥10% and ≤30%, without attachment loss and radiographic bone loss. This case may be associated with patient perception of bleeding gums, and a scarce, if any, impact on quality of life; or generalized gingivitis, defined as a patient presenting with a BOP score > 30%, without attachment loss and radiographic bone loss. This case is often associated with patient perception of bleeding gums, and a modest impact on quality of life.

TABLE 6 Case definition of gingivitis in an intact periodontium

	Localized gingivitis	Generalized gingivitis
Probing attachment loss	No	No
Radiographic bone loss	No	No
BOP score	≥10%, ≤30%	>30%

TABLE 7 Case definition of gingivitis in a reduced periodontium without history of periodontitis

	Localized gingivitis	Generalized gingivitis
Probing attachment loss	Yes	Yes
Radiographic bone loss	Possible	Possible
Probing depth (all sites)	≤3 mm	≤3 mm
BOP score	≥10%, ≤30%	>30%

A patient with a reduced periodontium[238] but without a history of periodontitis (e.g. gingival recession, crown lengthening) and a BOP score ≥10% would be diagnosed as a "GC on a reduced periodontium". A GC can also be graded as localized (BOP ≥10% and ≤30%) or generalized (BOP > 30%) (Table 7).

The same criteria may also be applied to a patient with a reduced periodontium[238] who has been successfully treated for periodontitis (periodontally stable patient), provided that no BOP positive sites show a probing depth ≥4 mm.

Both localized and generalized gingivitis should be managed by patient motivation, oral hygiene instruction, professional mechanical plaque removal, and implementation of self-performed mechanical plaque control, which may be supplemented by adjunctive use of antimicrobial/anti-inflammatory oral care products. Dietary advice and tobacco counseling are recommended when indicated.

The proposed GC diagnostic criteria would be of great value for defining and monitoring the disease in an epidemiological context, because such a GC definition should allow: 1) establishment of a framework that favors consistency of data interpretation across global epidemiological studies; 2) calculation of odds ratios and estimates of relative risk, both of which are sensitive to threshold definition, that are directly comparable between different studies; 3) assessment of the effectiveness of preventive measures and treatment regimens on a specific cohort of patients; 4) establishment of priorities for large-scale therapeutic actions/programs, with particular emphasis on their prognostic relevance (prevention of periodontitis) and impact on quality of life; and 5) undertaking of surveillance studies to monitor the prevalence and distribution of gingivitis consistently within a cohort as well as among different populations.[34]

However, it might be considered that in daily practice a patient with an intact periodontium or a reduced periodontium without history of periodontitis who shows even one site with clinical signs of gingival inflammation is worthy of professional intervention and, therefore, should be considered as a patient with sites of gingivitis.

A direct implication of the proposed GC definition is that a patient presenting with a BOP score < 10% without attachment loss and radiographic bone loss (intact periodontium) is considered clinically periodontally healthy. This definition is corroborated by previous studies where a BOP < 10% was used to define a periodontally-healthy case (Tables 3, 4, and 5).[153,158,208]

Consistently, other reviews[6,35] from the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions reinforce the concept that a minimal level of gingival inflammation dispersed throughout the dentition can be considered as compatible with "clinical periodontal health". Hence, the ensuing issue is to identify which is the "minimal" amount of gingival inflammation within a dentition (i.e., a BOP score threshold) to distinguish a periodontally-healthy patient from a GC.[35] Some considerations support the use of minimal proportion of BOP+ sites as extent threshold in the definition of a GC: 1) the presence of a BOP < 10% is perceived as a clinically healthy condition by the patient;[91] 2) patients with a BOP score ≥15% have poorer quality of life compared to patients with BOP score < 15%;[93] and 3) a minimum extent threshold limits the possibility to categorize as GC those patients who present with a substantial transition of inflamed to healthy sites.[229]

For the patient with a reduced periodontium, without a history of periodontitis, or with successfully treated periodontitis (stable patient), the same criteria may be applied to define periodontal health, provided that no BOP positive sites show a probing depth ≥4 mm.

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2017 WORLD WORKSHOP

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Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions

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Abstract

Periodontal health is defined by absence of clinically detectable inflammation. There is a biological level of immune surveillance that is consistent with clinical gingival health and homeostasis. Clinical gingival health may be found in a periodontium that is intact, i.e. without clinical attachment loss or bone loss, and on a reduced periodontium in either a non-periodontitis patient (e.g. in patients with some form of gingival recession or following crown lengthening surgery) or in a patient with a history of periodontitis who is currently periodontally stable. Clinical gingival health can be restored following treatment of gingivitis and periodontitis. However, the treated and stable periodontitis patient with current gingival health remains at increased risk of recurrent periodontitis, and accordingly, must be closely monitored.

Two broad categories of gingival diseases include non-dental plaque biofilm–induced gingival diseases and dental plaque-induced gingivitis. Non-dental plaque biofilm-induced gingival diseases include a variety of conditions that are not caused by plaque and usually do not resolve following plaque removal. Such lesions may be manifestations of a systemic condition or may be localized to the oral cavity. Dental plaque-induced gingivitis has a variety of clinical signs and symptoms, and both local predisposing factors and systemic modifying factors can affect its extent, severity, and progression. Dental plaque-induced gingivitis may arise on an intact periodontium or on a reduced periodontium in either a non-periodontitis patient or in a currently stable "periodontitis patient" i.e. successfully treated, in whom clinical inflammation has been eliminated (or substantially reduced). A periodontitis patient with gingival inflammation remains a periodontitis patient (Figure 1), and comprehensive risk assessment and management are imperative to ensure early prevention and/or treatment of recurrent/progressive periodontitis.

Precision dental medicine defines a patient-centered approach to care, and therefore, creates differences in the way in which a "case" of gingival health or gingivitis is defined for clinical practice as opposed to epidemiologically in population prevalence surveys. Thus, case definitions of gingival health and gingivitis are presented for both purposes. While gingival health and gingivitis have many clinical features, case definitions are primarily predicated on presence or absence of bleeding on probing. Here we classify gingival health and gingival diseases/conditions, along with a summary table of diagnostic features for defining health and gingivitis in various clinical situations.

KEYWORDS

allergic reaction, amalgam tattoo, aspergillosis, biofilm, blastomycosis, calcifying fibroblastic granuloma, candidosis, chemical trauma, clinical health, coccidioidomycosis, condylomata acuminatum, contact allergy, coxsackie virus, Crohn's disease, dental plaque-induced gingivitis, disease control, disease remission, disease stability, drug-induced gingival enlargement, drug-induced pigmentation, dysbiosis, erythema multiforme, erythroplakia, factitious injury, fibrous epulis, focal epithelial hyperplasia, frictional keratosis, geotricosis, gingival pigmentation, hand foot and mouth, hereditary gingival fibromatosis, herpangina,

herpes simplex, histoplasmosis, Hodgkin lymphoma, hyperglycemia, hyposalivation, intact periodontium, leukemia, leukoplakia, lichen planus, local risk factors, lupus erythematosus, melanoplakia, Melkersson-Rosenthal, menstrual cycle, modifying factors, molluscum contagiosum, mucormycosis, *Mycobacterium tuberculosis*, necrotizing periodontal diseases, *Neisseria gonorrhoeae*, non–dental plaque-induced gingival conditions, non-Hodgkin lymphoma, oral contraceptive, orofacial granulomatosis, paracoccidioidomycosis, pemphigoid, pemphigus vulgaris, periodontal disease, peripheral giant cell granuloma, plasma cell gingivitis, predisposing factors, pregnancy, puberty, pyogenic granuloma, reduced periodontium, resolution of inflammation, restoration margins, sarcoidosis, scurvy, smoker's melanosis, smoking, squamous cell carcinoma, squamous cell papilloma, stable periodontitis, streptoccocal gingivitis, symbiosis, systemic risk factors, thermal trauma, toothbrush trauma, *Treponema pallidum*, varicella zoster, vascular epulis, verruca vulgaris

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[1] Based upon this definition from the World Health Organization (WHO), it follows that periodontal health should be defined as a state free from inflammatory periodontal disease that allows an individual to function normally and avoid consequences (mental or physical) due to current or past disease. Based upon this overall framework of health, periodontal health should be predicated upon the absence of disease, as assessed clinically, associated with gingivitis, periodontitis, or other periodontal conditions, and may include patients who have had a history of successfully treated gingivitis or periodontitis, or other periodontal conditions, who have been and are able to maintain their dentition without signs of clinical gingival inflammation. Additionally, clinical periodontal health embraces physiological immune surveillance involving levels of biological and inflammatory markers compatible with homeostasis.[2] Periodontitis is a chronic inflammatory disease that currently can be successfully controlled, and teeth can be retained for life. Periodontitis can remain stable (in remission) or enter periods of exacerbation. A stable periodontitis patient remains at higher risk for recurrent disease compared to a gingivitis patient or a healthy patient. Therefore, precision dental medicine requires ongoing, individual risk assessment as part of optimal patient management.

A definition of periodontal health and wellness is critical to establish ideal and acceptable therapeutic end points to periodontal therapies, to systematically assess the biological burden of periodontal inflammation, to categorize gingival and periodontal disease prevalence in populations, and to evaluate individualized risk for future disease development. Periodontal health must be assessed and defined at both the patient and site level to achieve these goals. Furthermore, definitions of periodontal health that are used to inform treatment decisions for individual patients may differ from those used in epidemiological studies.

Is there a level of gingival inflammation that is consistent with clinical periodontal health at a site level?

There is a biological level of immune surveillance, manifesting as a predominantly neutrophilic infiltrate that is consistent with clinical gingival health.[2]

What is the spectrum of clinical periodontal health at a site level?

What is the biology of clinical gingival health?

Clinical gingival health is generally associated with an inflammatory infiltrate and a host response consistent with homeostasis.

On a site level, how do we classify clinical gingival health?

- Clinical gingival health on an intact periodontium
- Clinical gingival health on a reduced periodontium
    - Stable periodontitis patient
    - Non-periodontitis patient (e.g. recession, crown lengthening)

What are the clinical features of gingival health on an intact periodontium?

Clinical gingival health on an intact periodontium is characterized by the absence of bleeding on probing, erythema and edema, patient symptoms, and attachment and bone loss. Physiological bone levels range from 1.0 to 3.0 mm apical to the cemento-enamel junction.

What are the clinical features of gingival health on a reduced periodontium?

Clinical gingival health on a reduced periodontium is characterized by an absence of bleeding on probing, erythema, edema and patient symptoms in the presence of reduced clinical attachment and bone levels. However, it should be recognized that successfully treated and stable periodontitis patients remain at increased risk of recurrent progression of periodontitis. In non-periodontitis patients, there is no current evidence for increased risk of periodontitis.

What are the clinical features of gingival health following treatment of gingivitis on an intact periodontium?

Clinical gingival health following treatment of gingivitis on an intact periodontium is characterized by the absence of bleeding on probing, erythema and edema, patient symptoms, and attachment and bone loss.

What are the clinical features of gingival health following successful treatment of periodontitis?

Clinical gingival health following successful treatment of periodontitis is characterized by an absence of bleeding on probing, erythema, edema, and patient symptoms in the presence of reduced clinical attachment and bone levels.

CASE DEFINITIONS FOR PERIODONTAL HEALTH AND GINGIVITIS

Based on available methods to assess gingival inflammation, a gingivitis case can be simply, objectively and accurately defined and graded using a bleeding on probing score (BOP%),[3] assessed as the proportion of bleeding sites (dichotomous yes/no evaluation) when stimulated by a standardized (dimensions and shape) periodontal probe with a controlled (~0.25 N) force to the apical end of the sulcus at six sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) on all teeth present. Limitations of these clinical criteria arise from a lack of standardized periodontal probes (e.g. probe dimensions, taper), examiner variability (probe pressure, angle), patient related factors (biotype, medications, etc.) and smoking.

In all references to an "intact periodontium" within this consensus, an absence of detectable attachment and/or bone loss is implicit.

How do we define a case of gingival health on an intact and a reduced periodontium for epidemiological purposes?

For an intact periodontium and a reduced and stable periodontium, gingival health is defined as < 10% bleeding sites[4,5] with probing depths ≤3 mm.

How do we define a case of gingival health on an intact and a reduced periodontium for clinical practice?

Due to limitations in, and a lack of uptake of, standardized ISO probes and techniques leading to inherent measurement variability in the parameters of gingival health, a patient with periodontal health may exhibit one or two sites with some evidence of clinical gingival inflammation. Moreover, localized mild and delayed bleeding to probe at isolated sites is ubiquitous, but may fall within the spectrum of "clinical health".

In clinical practice, a case of gingival health on an intact periodontium would be a patient with no signs of gingivitis as defined above.

In clinical practice, the goal of periodontal treatment on a reduced periodontium is a patient with no signs of gingivitis as defined above. A case of gingival health on a reduced periodontium in a stable periodontitis patient must be distinguished from a case of periodontal health in a reduced periodontium in a non-periodontitis patient (recession, crown lengthening), because there is a difference in risk for periodontal disease progression.

Following treatment of periodontitis, periodontitis patients may not attain a status of complete gingival health based on the above definition. However, evidence has demonstrated that a patient may achieve periodontal stability. Periodontal stability is characterized by successful treatment through control of local and systemic risk factors, resulting in minimal (< 10% of sites[4]) BOP, no probing depths of 4 mm or greater that bleed on probing, optimal improvement in other clinical parameters and lack of progressive periodontal destruction.[6] The treated and stable periodontitis patient with current gingival health remains at increased risk of recurrent periodontitis and accordingly must be closely monitored. Figure 1 summarizes the various scenarios that may arise following the transition from health, to gingivitis and ultimately periodontitis.

How do we define gingivitis at a site level (biological & clinical)?

Defining inflammation at a site level is quite distinct from defining a case of gingivitis. A universal case definition is essential to facilitate population surveillance, for clinicians setting therapeutic targets, and to enable assessment of the efficacy of prevention and/or treatment regimes.

There are broadly two categories of gingival disease:

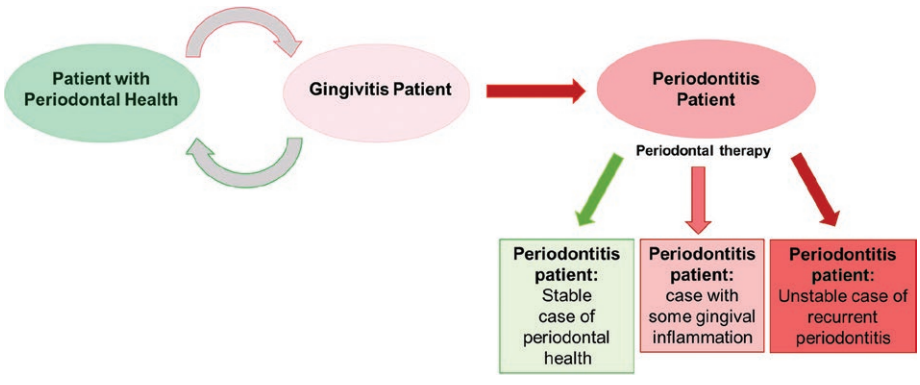

FIGURE 1 The transition from periodontal health to gingivitis is reversible following treatment that resolves gingival inflammation. The transition to periodontitis results in attachment loss which, at the present time is irreversible. More importantly, it signposts patients who are at lifelong high risk of recurrent periodontitis. Optimal periodontal therapy can restore gingival health on a reduced periodontium, or may result in mild marginal gingival inflammation at shallow probing pocket depths (≤ 3 mm). However, a history of periodontitis places patients at high risk of recurrent periodontitis and such patients require careful site-specific monitoring during periodontal maintenance programs

- Dental plaque biofilm-induced gingivitis
- Non–dental plaque-induced gingival diseases

Dental plaque biofilm-induced gingivitis is defined at the site level as "*an inflammatory lesion resulting from interactions between the dental plaque biofilm and the host's immune-inflammatory response, which remains contained within the gingiva and does not extend to the periodontal attachment (cementum, periodontal ligament and alveolar bone). Such inflammation remains confined to the gingiva and does not extend beyond the mucogingival junction and is reversible by reducing levels of dental plaque at and apical to the gingival margin*".

Depending on whether dental plaque biofilm-induced gingival inflammation occurs on an intact or reduced periodontium, or in a patient diagnosed with periodontitis, gingivitis can be further classified as:

- Gingivitis on an intact periodontium
- Gingivitis on a reduced periodontium in a non-periodontitis patient (e.g., recession, crown lengthening)
- Gingival inflammation on a reduced periodontium in a successfully treated periodontitis patient (Note that recurrent periodontitis cannot be ruled out in this case)

Since the 1999 classification, there have been advances in knowledge of the microbiome and the gingival transcriptome. Gingivitis is a non-specific inflammatory condition and is therefore a consequence of sustained plaque biofilm accumulation at and apical to the gingival margin.[7] Longitudinal studies have demonstrated that sites that do not progress to attachment loss are characterized by less gingival inflammation over time, whereas those sites that do progress have persistently greater levels of gingival inflammation.[8–14] Therefore, gingivitis is a major risk factor, and a necessary pre-requisite, for periodontitis. The management of gingivitis is thus a primary prevention strategy for periodontitis.

Periodontitis patients who are currently stable but develop gingival inflammation at specific sites should remain on periodontal maintenance and should be closely monitored during periodontal maintenance for any reactivation of periodontitis. Such patients may not be managed in the same way as non-periodontitis patients with gingivitis.

What are the determinants of the rate of development of gingivitis, its severity and extent?

The threshold of plaque accumulation necessary to induce gingival inflammation and impact upon its rate of progression at specific sites or at a whole mouth level varies between individuals according to both local risk factors, known as predisposing factors, and systemic risk factors, referred to as modifying factors, respectively.

1. *Local risk factors (predisposing factors)*

Local risk factors for gingivitis are those that encourage plaque accumulation at a specific site by either inhibiting its removal during daily oral hygiene practices, and/or creating a biological niche that encourages increased plaque accumulation.[7] These include:

a. Dental plaque biofilm retention factors (including certain tooth anatomical factors) – facilitate plaque accumulation at and apical to the gingival margin, enabling biofilm adherence and maturation and increasing the difficulty of mechanical plaque removal. Several clinical studies providing a moderate level of evidence have demonstrated that subgingival restoration margins may be detrimental to gingival health.[15,16]
b. Oral dryness is a clinical condition often associated with symptoms of xerostomia. Oral dryness manifesting as a lack of salivary flow, availability, or changes in quality of saliva, leading to reduced cleansing of tooth surfaces is associated with reduced dental plaque biofilm removal and enhanced gingival inflammation. Common causes include medications that have anti-parasympathetic action, Sjögrens syndrome when the salivary acini are replaced by fibrosis following autoimmune destruction, and mouth breathing in people who may have enhanced gingival display and/or an incompetent lip seal.[17]

2. *Systemic risk factors (modifying factors)*

Systemic risk or modifying factors are those characteristics present in an individual, which negatively influence the immune-inflammatory response to a given dental plaque biofilm burden, resulting in exaggerated or "hyper" inflammation. Examples include:

a. Smoking – is one of the major lifestyle/behavioral risk factors for periodontitis, but which also has profound effects upon the gingival tissues. Systemic circulatory uptake of components of cigarette smoke as well as local uptake are reported to induce microvascular vasoconstriction and fibrosis. This can mask clinical signs of gingivitis, such as bleeding on probing, despite a significant underlying pathological inflammatory cell infiltrate.[18]
b. Metabolic factors – hyperglycemia in people with or without diabetes. Excess glucose is toxic and directly induces mitochondrial stress and an enhanced respiratory burst in inflammatory cells that may activate various proinflammatory mediator cascades. Formation of advanced glycation end-products (AGEs) may also result in AGE binding to its cell surface receptor (RAGE), which activates proinflammatory signaling cascades and downstream proinflammatory events.[19]
c. Nutritional factors – Severe Vitamin C deficiency, or scurvy, results in compromised antioxidant micronutrient defenses to oxidative stress and also negatively impacts collagen synthesis, resulting in weakened capillary blood vessel walls and a consequent propensity to enhanced gingival bleeding.[20]
d. Pharmacological agents (prescription, non-prescription, and recreational agents) – can act via diverse mechanisms to increase susceptibility to gingivitis. This may include drugs that reduce salivary flow, drugs that impact endocrine function (see below), and drugs that may induce gingival enlargement and pseudo-pocketing.

e. Elevations in sex steroid hormones – at puberty, during pregnancy, or following medication with first generation oral contraceptives may modify the gingival inflammatory response. Complex biological reactions within the gingival tissues result from such elevated sex steroid levels and generate more than expected inflammation, in response to relatively small levels of plaque. However, modern oral contraceptive dosages have been reduced and there is little evidence for exaggerated gingival inflammatory responses to plaque with such drugs.[21]
f. Hematological conditions – particular blood malignancies such as leukemia or pre-malignant conditions such as myelodysplasia are associated with signs of excess gingival inflammation in the absence of excessive plaque biofilm accumulation. Signs include swollen, purple or occasionally pale gingiva due to leukemic cell infiltration, gingival bleeding that is inconsistent with levels of dental plaque biofilm accumulation, due to thrombocytopenia and/or clotting-factor deficiencies.[22]

What are the diagnostic criteria for a gingivitis case?

Given the "spectrum" of presentation of gingival health and gingival inflammation in terms of severity and extent of gingival involvement, it is important to define the features of a universally accepted case of gingivitis.

Current epidemiological data on the prevalence of gingivitis suffer from the lack of a universally adopted case definition and vary as widely as 6% to 94%, due to the use of indices that measure gingival inflammation at individual sites rather than considering the patient's mouth as a whole. Therefore, mild localized clinical inflammation is reported to affect almost 95% of the population, a figure that would incorrectly suggest gingivitis as being a variation of "normality" and thus consistent with the spectrum of "clinical health" rather than being a disease. By contrast, the more extensive the manifestation of disease employed in a case definition, the lower the reported prevalence. A universally agreed case definition should be based upon a pragmatic appraisal of the evidence base derived from longitudinal observation and intervention studies.

Clinical, radiological, and biological signs and symptoms

1. Gingivitis is a clinical diagnosis. While emerging technologies are starting to shed light on the microbiological, molecular, and pathophysiological characteristics of gingivitis, definitive knowledge is not sufficient to supersede current clinical parameters.[7]
2. The clinical signs of inflammation are erythema, edema, pain (soreness), heat, and loss of function.
3. These may manifest clinically in gingivitis as:
   a. Swelling, seen as loss of knife-edged gingival margin and blunting of papillae
   b. Bleeding on gentle probing
   c. Redness
   d. Discomfort on gentle probing
4. The symptoms a patient may report include:
   a. Bleeding gums (metallic/altered taste)
   b. Pain (soreness)
   c. Halitosis
   d. Difficulty eating
   e. Appearance (swollen red gums)
   f. Reduced oral health–related quality of life
5. Radiographs cannot be used to diagnose gingivitis.

Should we classify dental plaque biofilm-induced gingivitis?

There is utility in defining the severity of gingivitis as a patient communication tool, but there are no objective clinical criteria for defining severity. Thus, in this context alone, the extent of gingivitis can be used to communicate "mild, moderate, and severe" gingivitis. Moreover, emerging evidence suggests that the contained gingivitis lesion may have systemic inflammatory consequences.[23,24]

There is no robust evidence to clearly differentiate mild, moderate, and severe gingivitis, and definitions remain a matter of professional opinion. Methods of defining gingivitis may include:

Defining percentages (e.g. mild = < 10%, moderate = 10%-30%, severe = > 30% sites)
Grading (e.g. grade 1 to 5 in 20% quintiles for % sites bleeding on probing).

How do we define a case of dental plaque-induced gingivitis on an intact and a reduced periodontium for epidemiological purposes?

For epidemiological purposes, gingivitis on an intact periodontium and gingivitis on a reduced periodontium in a patient without a history of periodontitis, is defined as ≥10% bleeding sites[4,5] with probing depths ≤3 mm. Localized gingivitis is defined as 10%-30% bleeding sites; generalized gingivitis is defined as > 30% bleeding sites.

For epidemiological purposes alone, a periodontitis case cannot simultaneously be defined as a gingivitis case. Therefore, a patient with a history of periodontitis, with gingival inflammation is still a periodontitis case.

How do we classify a patient with dental plaque-induced gingivitis on an intact and a reduced periodontium for clinical practice?

In clinical practice, a case of gingivitis on an intact periodontium, or a reduced periodontium in a patient without a history of periodontitis, would be a patient with signs of gingival inflammation as defined above (Table 1).

In clinical practice, periodontitis patients, if successfully treated can achieve a reduced and stable periodontium where probing pocket depths are ≤4 mm[27] and there is an absence of clinical inflammation

TABLE 1 Diagnostic look-up table for gingival health or dental plaque-induced gingivitis in clinical practice

Intact periodontium	**Health**	**Gingivitis**
Probing attachment loss	No	No
Probing pocket depths (assuming no pseudo pockets)[a]	≤3 mm	≤3 mm
Bleeding on probing[a]	<10%	Yes (≥ 10%)
Radiological bone loss	No	No
Reduced periodontium Non-periodontitis patient	**Health**	**Gingivitis**
Probing attachment loss	Yes	Yes
Probing pocket depths (all sites & assuming no pseudo pockets)[a]	≤3 mm	≤3 mm
Bleeding on probing[a]	<10%	Yes (≥ 10%)
Radiological bone loss	Possible	Possible
NB: In conditions where there is treatment but not cure, e.g. rheumatoid arthritis, periodontitis, the post-treatment parameters that define stability/health or gingivitis may differ from the parameters for health/gingivitis in a non-periodontitis patient. The threshold for "clinical health" in a treated and stable periodontitis patient is therefore set at ≤ 4 mm.		
Successfully treated stable periodontitis patient	**Health**	**Gingivitis in a patient with a history of periodontitis**
Probing attachment loss	Yes	Yes
Probing pocket depths (all sites & assuming no pseudo pockets)[a]	≤4 mm (no site ≥ 4 mm with BOP)[b]	≤3 mm
Bleeding on probing[a]	<10%	Yes (≥ 10%)
Radiological bone loss	Yes	Yes
NB: A successfully treated periodontitis patient in whom sites of gingival bleeding appear remains at high risk of disease recurrence at those sites and of progressive attachment loss. Therefore, gingivitis is defined as bleeding at a shallow site of ≤ 3 mm rather than ≤ 4 mm, as is the case in gingival heath. Where the probing depth is 4 mm or higher with bleeding, this is no longer a "closed pocket."[21,27]		

[a]**Assumes a light probing pressure of 0.2 to 0.25 N**.

[b]There was a rational minority view expressed that the threshold for defining a clinical case of health in a successfully treated periodontitis patient should be set at ≤ 3 mm with no BOP to acknowledge the elevated risk of recurrent disease. However, the counter and majority view was that the ≤ 3 mm threshold is rarely achieved at 100% of treated sites and could lead to over-treatment, since any non-bleeding site > 3 mm would not be classified as "health" and thus open to further invasive treatment, rather than monitoring and supportive care. The threshold was therefore set at ≤ 4 mm acknowledging that post-treatment clinical phenotypes need to be considered differently to pre-treatment phenotypes.

(bleeding on probing). Gingival inflammation may arise at specific sites, and where probing depths are ≤ 3 mm is termed gingival inflammation in a stable periodontitis patient. However, such patients remain at high risk of recurrent periodontitis and require close monitoring as such sites are at high risk of reverting to periodontitis (Table 1).

How do we classify non–dental plaque-induced gingival conditions?

Although oral health and systemic health are frequently considered as separate entities, both are strongly interrelated. There are numerous examples of how oral diseases may impact systemic health and how the oral cavity may be a window to general health. Consequently, it is crucial for all health-care providers to understand these interrelationships, inform patients of such conditions, and make appropriate referrals.

Non-dental plaque-induced gingival conditions encompass a variety of conditions that are not caused by plaque and usually do not resolve following plaque removal. Such lesions may be manifestations of a systemic condition or may be localized to the oral cavity.[25] Although these lesions are not caused by the dental plaque biofilm, the severity of the clinical manifestations often depends on plaque accumulation and subsequent gingival inflammation.[26]

The proposed classification considers those conditions listed in Table 2.

Which non–dental plaque-induced gingival conditions may have associated systemic involvement and how does that impact upon patient-centered care pathways?

In recent years, the traditional treatment model in which the patient was a passive receiver of care is changing toward patient-centered care in precision dental medicine (PDM). In PDM, an individual's specific health needs and desired health outcomes

TABLE 2 Classification of gingival health and gingival diseases/conditions

1. **Periodontal health**[2]
   - **A.** Clinical health on an intact periodontium
   - **B.** Clinical gingival health on a reduced periodontium
     - (i) Stable periodontitis patient
     - (ii) Non-periodontitis patient
2. **Gingivitis – dental plaque-induced:** ***intact periodontium; reduced periodontium in non-periodontitis patient; reduced periodontium in successfully treated periodontitis patient.***[7]
   - **A.** Associated with biofilm alone
   - **B.** Mediated by systemic or local risk factors
     - **i.** Systemic risk factors (modifying factors)
       - (a) Smoking
       - (b) Hyperglycemia
       - (c) Nutritional factors
       - (d) Pharmacological agents (prescription, non-prescription and recreational)
       - (e) Sex steroid hormones
         Puberty
         Menstrual cycle
         Pregnancy
         Oral contraceptives
       - (f) Hematological conditions
     - **ii.** Local risk factors (predisposing factors)
       - (a) Dental plaque biofilm retention factors (e.g., prominent restoration margins)
       - (b) Oral dryness
   - **C.** Drug-influenced gingival enlargement
3. **Gingival diseases – non–dental plaque-induced**[26]
   - **A.** Genetic/developmental disorders
     - **i.** Hereditary gingival fibromatosis[a]
   - **B.** Specific infections
     - **i.** Bacterial origin
       - (a) *Neisseria gonorrhoeae*[a]
       - (b) *Treponema pallidum*[a]
       - (c) *Mycobacterium tuberculosis*[a]
       - (d) Streptococcal gingivitis
     - **ii.** Viral origin
       - (a) Coxsackie virus (hand-foot-and-mouth disease)[a]
       - (b) Herpes simplex I & II (primary or recurrent)[a]
       - (c) Varicella zoster (chicken pox & shingles – V nerve)[a]
       - (d) Molluscum contagiosum[a]
       - (e) Human papilloma virus (squamous cell papilloma; condyloma acuminatum; verruca vulgaris; focal epithelial hyperplasia)

(*Continues*)

TABLE 2 (Continued)

     - **iii.** Fungal origin
       - (a) Candidosis
       - (b) Other mycoses, e.g., histoplasmosis, aspergillosis
   - **C.** Inflammatory and immune conditions
     - **i.** Hypersensitivity reactions
       - (a) Contact allergy[a]
       - (b) Plasma cell gingivitis[a]
       - (c) Erythema multiforme[a]
     - **ii.** Autoimmune diseases of skin and mucous membranes
       - (a) Pemphigus vulgaris[a]
       - (b) Pemphigoid[a]
       - (c) Lichen planus[a]
       - (d) Lupus erythematosus[a]
         Systemic lupus erythematosis
         Discoid lupus erythematosis
     - **iii.** Granulomatous inflammatory lesions (orofacial granulomatoses)
       - (a) Crohn's disease[a]
       - (b) Sarcoidosis[a]
   - **D.** Reactive processes
     - **i.** Epulides
       - (a) Fibrous epulis
       - (b) Calcifying fibroblastic granuloma
       - (c) Vascular epulis (pyogenic granuloma)
       - (d) Peripheral giant cell granuloma[a]
   - **E.** Neoplasms
     - **i.** Premalignancy
       - (a) Leukoplakia
       - (b) Erythroplakia
     - **ii.** Malignancy
       - (a) Squamous cell carcinoma[a]
       - (b) Leukemic cell infiltration[a]
       - (c) Lymphoma[a]
         Hodgkin
         Non-Hodgkin
   - **F.** Endocrine, nutritional & metabolic diseases
     - **i.** Vitamin deficiencies[a]
       - (a) Vitamin C deficiency (scurvy)
   - **G.** Traumatic lesions
     - **i.** Physical/mechanical trauma
       - (a) Frictional keratosis
       - (b) Mechanically induced gingival ulceration
       - (c) Factitious injury (self-harm)
     - **ii.** Chemical (toxic) burn
     - **iii.** Thermal insults
       - (a) Burns to gingiva

(*Continues*)

TABLE 2 (Continued)

H.	Gingival pigmentation
i.	Melanoplakia[a]
ii.	Smoker's melanosis
iii.	Drug-induced pigmentation (antimalarials, minocycline)
iv.	Amalgam tattoo

[a]Conditions marked with an "a" have associated systemic involvement or are oral manifestations of systemic conditions; therefore, other health-care providers may be involved in diagnosis and treatment.

are the driving force behind all health-care decisions and quality measurements. One of the elements in PDM is that care is collaborative, coordinated, and accessible. The right care is provided at the right time and the right place. Considering that the conditions marked with an "a." (Table 2) have associated systemic involvement or are oral manifestations of systemic conditions, other health-care providers may be involved in diagnosis and treatment.

FUTURE RESEARCH NEEDS

Regarding classification and diagnosis of periodontal health and gingival diseases/conditions, future research is needed on the:

- development and validation of non-invasive diagnostic tools (e.g., saliva-based diagnostics), especially as they relate to detection of gingival inflammation;
- identification of the characteristics (e.g., genetic factors) that distinguish persons who are resistant to the development of dental plaque biofilm-induced or non-dental plaque biofilm–induced gingival diseases from those who are susceptible;
- expansion of our limited knowledge of the determinants that affect the reliability of currently available diagnostic tools (e.g., effects of probe design on bleeding on probing responses);
- characterization of the possible differences (e.g., molecular determinants) between gingivitis on an intact periodontium and other forms of gingival inflammatory disease.

Regarding the current primary periodontal diagnostic tool, the graduated periodontal measuring probe, the following are recommendations for an ISO periodontal probe:

The reliability and reproducibility of any case definition for health, gingival or periodontal conditions relies upon standardization of probing protocols, which is only possible with the implementation of an ISO probe. The current International Organization for Standardization (ISO) for periodontal probes is – ISO 21672, but requires updating in order to define the features of a global standard periodontal probe. These characteristics are:

1. Tip diameter 0.5 mm
2. Cylindrical tine structure
3. Constant force limiter of 0.25 N
4. 15-mm scale with precise individual or banded millimeter markings
5. A taper of 1.75°

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FIGURE 1 Participants of Workgroup 1

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

Acute periodontal lesions (periodontal abscesses and necrotizing periodontal diseases) and endo-periodontal lesions

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*

Abstract

Objective: To critically evaluate the existing literature on acute lesions occurring in the periodontium (periodontal abscesses [PA], necrotizing periodontal diseases [NPD], and endo-periodontal lesions [EPL]) to determine the weight of evidence for the existence of specific clinical conditions that may be grouped together according to common features. The ultimate goal is to support an objective classification system.

Importance: Although PA, NPD, and EPL occur with relatively low frequency, these lesions are of clinical relevance, because they require immediate management and might severely compromise the prognosis of the tooth.

Findings: In general, the evidence available to define these three conditions was considered limited. PA and EPL are normally associated with deep periodontal pockets, bleeding on probing, suppuration, and almost invariably, with pain. EPL are also associated with endodontic pathology. NPDs have three typical features: pain, bleeding, and ulceration of the gingival interdental papilla. The available data suggested that the prognosis of PA and EPL are worse in periodontitis than in nonperiodontitis patients. Lesions associated with root damage, such as fractures and perforations, had the worst prognosis. NPD progression, extent and severity mainly depended on host-related factors predisposing to these diseases.

Conclusions: PA should be classified according to the etiological factors involved, with the most frequent being those occurring in pre-existing periodontal pockets. NPD are clearly associated with the host immune response, which should be considered in the classification system for these lesions. EPLs should be classified according to signs and symptoms that have direct impact on their prognosis and treatment, such as presence or absence of fractures and perforations, and presence or absence of periodontitis.

KEYWORDS

endo-periodontal lesions, necrotizing gingivitis, necrotizing periodontal diseases, necrotizing periodontitis, periodontal abscess

According to the American Academy of Periodontology,[1] acute periodontal diseases are rapid-onset clinical conditions that involve the periodontium or associated structures and may be characterized by pain or discomfort, tissue destruction, and infection. Among these conditions, the following diseases have been listed: gingival abscess, periodontal abscess, necrotizing periodontal diseases, herpetic

gingivostomatitis, pericoronal abscess, or pericoronitis, and combined periodontal-endodontic lesions. Herpetic gingivostomatitis is not included in the present review, whereas the so called gingival and periodontal abscesses were considered within a category named: abscesses in the periodontium (Figure 1).

Acute lesions in the periodontium are among the few clinical situations in periodontics in which patients may seek urgent care, mostly because of the associated pain. In addition, and in contrast to most other periodontal conditions, rapid destruction of periodontal tissues may occur during the course of these lesions, thus emphasizing the importance of prompt diagnosis and treatment. The present review and update focuses on two acute conditions (abscesses in the periodontium and necrotizing periodontal diseases); and on endo-periodontal lesions that can occur in acute or chronic forms.

Periodontal abscesses (PA) are important because they represent common dental emergencies requiring immediate management and can result in rapid destruction of the periodontium with a negative impact on the prognosis of the affected tooth. In certain circumstances, PA may have severe systemic consequences.[2,3] Although the prevalence of **necrotizing periodontal diseases (NPD)** is low, their importance is clear, because they represent the most severe conditions associated with dental biofilm, leading to very rapid tissue destruction.[3] Whereas, **endo-periodontal lesions (EPL),** in spite of being relatively rare in clinical practice, might severely compromise the prognosis of the tooth, and are considered one of the most challenging problem faced by clinicians, because they require multidisciplinary evaluation, diagnosis, and treatment.[4]

The aim of the present review was to critically evaluate the existing literature on acute lesions in the periodontium (PA and NPD) and EPL, with the purpose of determining the weight of evidence of the existence of specific clinical conditions that may be grouped together according to common features. The ultimate goal was to support an objective classification system that may help the clinician to determine the prognosis of the teeth involved, and treatment of these conditions. To achieve this objective, the three conditions were separately assessed.

METHODS

Independent electronic searches were conducted to identify relevant articles dealing with each of the three conditions addressed in this review. In total, 128 studies were included for PA, 138 for NPD and 74 for EPL. Details about the electronic search methods and studies included, flow charts showing the selection of articles for each condition evaluated in this review, and designs of the studies included are described in Appendices 1 and 2, respectively, in the online *Journal of Clinical Periodontology*.

1 | PERIODONTAL ABSCESSES

1.1 | Clinical presentation

Different etiological factors may explain the occurrence of abscesses in the periodontal tissues, such as pulp necrosis (endodontic, periapical or dentoalveolar abscesses), periodontal infections (gingival or periodontal abscess[5]), pericoronitis (pericoronal abscess), trauma, surgery,[6] or foreign body impaction. Together, they are referred to as odontogenic or dental abscesses,[7] and when they are associated with EPL, they could also be considered odontogenic abscesses. PA can specifically be defined as a localized accumulation of pus located within the gingival wall of the periodontal pocket, with an expressed periodontal breakdown occurring during a limited period of time, and with easily detectable clinical symptoms.[2]

Three different reasons could support the importance of PA:

Common dental emergencies, *requiring immediate management* (see Appendix 3, Table A3.1, in online journal)

a. PA represented approximately 7.7–14.0% of all dental emergencies, being ranked the third most prevalent infection demanding emergency treatment, after dentoalveolar abscesses and pericoronitis. In an army dental clinic, 27.5% of periodontitis patients presented with PA, with clear differences between patients undergoing active periodontal treatment (13.5%) and untreated patients (59.7%).[8] Among patients undergoing periodontal maintenance (PeM), PAs were detected in 37% of the patients followed-up for 5–29 years.[9] In the Nebraska prospective longitudinal study, 27 PA were observed during 7 years, and 23 of them occurred in sites that received coronal scaling.[10]
b. *Rapid destruction of periodontal tissues*, *with a negative effect on the prognosis of the affected tooth* (see Appendix 3, Table A3.1, in online journal)

   PAs may lead to tooth loss, especially if they affect teeth with previous moderate to severe attachment loss, as occur during PeM in patients with severe chronic periodontitis. Indeed, they

<table>
<tr><td colspan="10">Acute periodontal conditions</td></tr>
<tr><td rowspan="2">Virus infection</td><td colspan="8">Abscesses in the periodontium</td><td colspan="2">Necrotizing periodontal diseases[1]</td></tr>
<tr><td colspan="2">Other abscesses</td><td colspan="6">Odontogenic or dental abscesses[7]</td><td rowspan="2">Necrotizing gingivitis</td><td rowspan="2">Necrotizing periodontitis</td></tr>
<tr><td>Herpetic gingivostomatitis[6,1]</td><td>Surgery[6]</td><td>Trauma[6]</td><td>Pericoronitis[6,5,1]</td><td>Pulp necrosis</td><td>Endo-perio lesion[6,1]</td><td colspan="2">Periodontal infections[6,5,1]</td></tr>
<tr><td rowspan="2">Out of the scope</td><td rowspan="2">Out of the scope</td><td rowspan="2">Out of the scope</td><td rowspan="2">Out of the scope</td><td>Dentoalveolar abscess</td><td>Endo-perio abscess</td><td>Gingival abscess</td><td>Periodontal abscess</td><td rowspan="2">Part 2.</td><td rowspan="2"></td></tr>
<tr><td>Out of the scope</td><td>Part 3.</td><td colspan="2">Part 1.</td></tr>
</table>

FIGURE 1 List of "acute periodontal conditions," according to different authors, and scope of the present review

have been considered the main cause of tooth extraction during PeM.[9,11–13] Similarly, teeth with repeated abscess formation were considered to have a "hopeless prognosis",[14] and 45% of teeth with a periodontal abscess found during PeM were extracted.[9] The main reason for tooth extraction of teeth with a questionable prognosis, which had been followed-up for 8.8 years, was the presence of periodontal abscess.[11]

c. *Severe systemic consequences*
PA may be associated with systemic dissemination of a localized infection. Numerous case reports and series have described the occurrence of systemic infections resulting from a suspected source in a periodontal abscess, either through dissemination occurring during therapy or related to an untreated abscess (see Appendix 3, Table A3.2, in online journal).

1.2 | Etiology: pathophysiology, microbiology and histological features

1.2.1 | Pathophysiology

The first step in the development of a PA is bacterial invasion of the soft tissues surrounding the periodontal pocket, which will develop into an inflammatory process through the chemotactic factors released by bacteria that attract polymorphonuclear leukocytes (PMN) and other cells. This will trigger intensive release of cytokines; lead to destruction of the connective tissues; encapsulation of the bacterial infection and the production of pus. Once the abscess is formed, the rate of destruction within the abscess will depend on the growth of bacteria inside the foci; their virulence, and the local pH (an acidic environment will favor the activity of lysosomal enzymes).[15]

1.2.2 | Microbiology

In general, microbiological reports on PA have shown a microbial composition similar to that observed in periodontitis (see Appendix 3, Table A3.3, in online journal). The most prevalent bacterial species identified in PA, by means of different techniques (see Appendix 3, Table A3.4, in online journal) were *Porphyromonas gingivalis* (50-100%), *Prevotella intermedia*, *Prevotella melaninogenica*, *Fusobacterium nucleatum*, *Tannerella forsythia*, *Treponema* species, *Campylobacter* species, *Capnocytophaga* species, *Aggregatibacter actinomycetemcomitans* or gram-negative enteric rods (see Appendix 3, Table A3.5, in online journal). Up to now, there has been limited evidence available on the role of viruses, the genetic characteristics of different strains (e.g. *P. gingivalis*), or the antimicrobial susceptibility of strains isolated from these lesions (see Appendix 3, Table A3.6, in online journal).

1.2.3 | Histopathology

The histopathology of periodontal abscess lesions was reported as follows,[15] after observing the lesion from the outside to the inside: a normal oral epithelium and lamina propria; an acute inflammatory infiltrate; intense focus of inflammation, with presence of neutrophils and lymphocytes in an area of destroyed and necrotic connective tissue; and a destroyed and ulcerated pocket epithelium.

1.3 | Etiology: risk factors

PA may develop in a pre-existing periodontal pocket (e.g., in patients with periodontitis) or in the absence of a pre-existing periodontal pocket.

1.3.1 | Periodontal abscess in periodontitis patients

In periodontitis patients, a PA could represent a period of disease exacerbation, favored by the existence of tortuous pockets, presence of furcation involvement[16] or a vertical defect,[16,17] in which the marginal closure of the pocket could lead to an extension of the infection into the surrounding periodontal tissues.[15,18,19] In addition, changes in the composition of the subgingival microbiota, with an increase in bacterial virulence, or a decrease in the host defense, could also result in an inefficient capacity to drain the increased suppuration. Different subgroups could be distinguished (see Appendix 3, Table A3.7, in online journal):

- Acute exacerbation:
  - In untreated periodontitis.[20]
  - In "refractory" periodontitis.[21]
  - In PeM, as previously described.
- After different treatments:
  - Scaling and root planing or professional prophylaxis: dislodged calculus fragments could be pushed into the tissues,[20] or inadequate scaling could allow calculus to remain in deep pocket areas, whereas the coronal part would occlude the normal drainage.[10]
  - Surgical periodontal therapy: associated with the presence of foreign bodies such as membranes for regeneration or sutures.[22]
  - Systemic antimicrobial intake, without subgingival debridement, in patients with severe periodontitis could also cause abscess formation,[23–25] probably related to an overgrowth of opportunistic bacteria.[23]
  - Use of other drugs: e.g., nifedipine.[26]

1.3.2 | Periodontal abscess in non-periodontitis patients

PA can also occur in previously healthy sites, because of (see Appendix 3, Tables A3.8 and A3.9, in on line journal):

- Impaction of foreign bodies: dental floss, orthodontic elastic, toothpick, rubber dam, or popcorn hulls.
- Harmful habits (biting wire, nail biting, clenching) could favor abscess formation because of subgingival impaction of foreign bodies or to coronal closure of the pocket.

- Orthodontic factors, such as inadequate orthodontic forces or a cross-bite, have been reported to favor PA development.
- Gingival enlargement.[27]
- Alterations of the root surface, including:
    - Severe anatomic alterations, such as invaginated tooth, *dens evaginatus* (grooves) or odontodysplasia.
    - Minor anatomic alterations, such as cemental tears, enamel pearls or developmental grooves.
    - Iatrogenic conditions, such as perforations.
    - Severe root damage: vertical root fracture or cracked tooth syndrome extending through the root.
    - External root resorption.

1.4 | Assessment and diagnosis

Data from studies with a relevant number of cases and a comprehensive description were analyzed (Tables 1A and 1B).[13,28–31]

A series of symptoms have been reported by patients suffering from a PA, such as pain, tenderness of the gingiva, swelling, or tooth "elevation." The most prominent sign during the oral examination was the presence of an ovoid elevation in the gingiva along the lateral part of the root. Suppuration on probing or sampling was a common finding (66–93%), whereas a fistula was not. A PA was usually associated with a deep periodontal pocket (7.3–9.3 mm), bleeding on probing (100%), and increased tooth mobility (56.4–100%). Bone loss was normally observed in the radiographic examination. Extraoral findings were uncommon, but could include facial swelling (3.6%), elevated body temperature, malaise, regional lymphadenopathy (7–40%) or increased blood leukocytes (31.6%). Most abscesses affected periodontitis patients (96.3–100%), either untreated (7.14–81.6%), in PeM (11.6–60%) or those undergoing active therapy (6.6–42.9%). Some studies found molars more frequently affected,[13,30] whereas others found equal distribution,[28] or predominance in anterior teeth.[31] One study reported a higher number of abscesses at the interproximal level,[13] whereas others observed more frequent abscess formation at buccal sites.[28,30]

Patient history may also provide relevant information, especially in cases of abscesses associated with previous treatments (scaling and root planing, periodontal surgery, intake of systemic antimicrobials agents, or other drugs [e.g., nifedipine] and endodontic treatment), or in abscesses related to foreign body impaction.

Differential diagnosis (see Appendix 3, Table A3.10, in online journal) is critical, because PA may be like other oral conditions:

- Other odontogenic abscesses (dento-alveolar abscesses, pericoronitis, endo-periodontal abscess), or other acute conditions (lateral periapical cyst and postoperative infection).[32]
- Tumor lesions, including metastatic tumoral lesions, odontogenic myxoma, non-Hodgkin´s lymphoma, squamous cell carcinoma, metastatic carcinoma.
- Other oral lesions: pyogenic granuloma, osteomyelitis, odontogenic keratocyst, eosinophilic granuloma.
- Self-inflicted gingival injuries.
- Sickle cell anemia.
- Abscesses after surgical procedures.

1.5 | Proposed changes to the current 1999 classification

The 1999 classification for abscesses in the periodontium included gingival, periodontal, pericoronal, and periapical abscesses.[5] Relevant problems associated with this classification system included: (1) the differentiation between gingival and PA, which could be confusing, because this differentiation was simultaneously based on location and etiology; (2) considering a PA as chronic or acute may not be adequate, because an abscess, by definition, is an acute lesion; and (3) the inclusion of pericoronitis and periapical abscesses in the classification together with PA might not be appropriate. Pericoronal abscesses were included in the 1999 classification, but no solid scientific basis for this was found in the article associated with the topic.[5] In addition, the terms "pericoronal abscess" or "pericoronitis abscess" were seldom used in the scientific literature; in the present literature search, none of the articles retrieved described a pericoronal abscess as a PA. PAs should be classified based on their etiology (see section 3.3 and Table 2).

2 | NECROTIZING PERIODONTAL DISEASES

2.1 | Clinical presentation

In the 1999 classification, necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP) were included among NDPs.[33] Studies have suggested that they may represent different stages of the same disease, because they have similar etiology, clinical characteristics, and treatment, and may even progress to more severe forms such as necrotizing stomatitis (NS) and noma.[34,35] The terminology "ulcerative" was later eliminated, because ulceration was considered to be secondary to the necrosis.[36]

NPD patients are frequently susceptible to future recurrence of disease[37,38] and NPD could also become a "chronic condition," with a slower rate of destruction.[39] In cases of severe systemic involvement, progression of NPD into other oral lesions could occur.[40,41]

Prevalence/incidence of NG has been reported for the overall population or for specific groups of individuals (for references, see Appendix 4, Tables A4.1a-e, in online journal). In general populations attending dental clinics, the prevalence of NG ranged from 0.51 to 3.3%; in military personnel, the prevalence and incidence reported was higher close to the end of the 2nd World War (3.96–20.6%) than it was in more recent studies (0.19–6.19%). In African populations, highly variable results have been reported. In students, prevalence ranged from 0.9 to 6.7%. And in HIV/AIDS patients data showed wide variations: children (2.2-5.0%), HIV adults (0.0–27.7% for NG and 0.3–9.0% for NP), and HIV/AIDS patients (10.1–11.1% for NG and 0.3–9.0% for NP).

TABLE 1A Diagnosis of periodontal abscesses: studies with series of more than 10 abscesses with comprehensive clinical description

Study			Patient sample			Periodontal status			Abscesses		Etiology				Location	
Reference	Country	Study design	n	Age	% female	MS	Initial	Healthy	n	Name	Untreated	PeM	Perio treatment	Trauma	Teeth affected	Sites affected
Smith	UK	Prospective-3y	55	10-68	50.9%				62	acute lateral PA		60.0%	36.4%		LM (27.6%), UM (25.8%)	interdental (62.9%)
Hafstrom	Sweden	Prospective-6 m	20	24-79	55.0%				20	PA (clear periodontal origin)						
Herrera	Spain	RCT-30d	29	26-65	58.6%	93.1%	6.9%	0.0%	29	PA	62.0%	24.0%	14.0%		69% M (equal U-L)	buccal (48%), interdental (38%), lingual (14%)
Jaramillo	Colombia	Cross-sectional	54	48.3	53.7%	87% ChP, 9.3% AgP		3.7%	60	PA	81.6%	11.6%	6.6%	5.0%	Lant (41.6%), Uant (20%)	
Chan	India	Cross-sectional	14	39.6	50.0%				14	PA	7.1%	50.0%	42.9%		86% U; equal M.PM.ant	buccal (71%), lingual (29%)

RCT, randomized clinical trial; y, year; m, month; d, day; p, patient; MS, moderate-severe
L, lower jaw; U, upper jaw; M, molar; ant, anteriors; PM, premolars; PeM, periodontal maintenance; ChP, chronic periodontitis; AgP, aggressive periodontitis

TABLE 1B Diagnosis of periodontal abscesses: signs and symptoms

	Symptoms			Signs					X-ray	Extraoral		Variety
Reference	Pain	Redness	Swelling	Mean PPD	%PPD > 6 mm	BOP	SUP	Increased mobility	Bone loss	Fever	Lymph-adenophaty	Other findings
Smith	usual		usual		54.8%			56.4% > 0	most, also furcation in most molars	0.0%	40.0%	abscess pointing (69.6%), no fistula, facial swelling (3.6%)
Hafstrom	100%	100%	100%	8.1		100%	68%			none	none	tenderness (100%)
Herrera	62%MS; 10%none	75%MS	93%MS	7.3 (3-13)	62.1%	100%	66%	79%			10.0%	elevated leukocytes (31.6%)
Jaramillo	68.3%	93.3%	95%	9.3±2.5		100%	93.3%	100%	93.3%MS			tooth elevation (23.3%)
Chan				7.4±1.6				71%		36.9±0.5, most afebrile	7.1%	

PPD, probing pocket depth; freq., frequency; BOP; bleeding on probing; SUP, suppuration on probing or sampling; MS, moderate-severe

TABLE 2 Proposal of classification for periodontal abscess, based on the etiological factors involved

Periodontal abscess in periodontitis patients (in a pre-existing periodontal pocket)	Acute exacerbation	Untreated periodontitis	
		Non-responsive to therapy periodontitis	
		Supportive periodontal therapy	
	After treatment	Post-scaling	
		Post-surgery	
		Post-medication	Systemic antimicrobials
			Other drugs: nifedipine
Periodontal abscess in non-periodontitis patients (not mandatory to have a pre-existing periodontal pocket)	Impaction		Dental floss, orthodontic elastic, toothpick, rubber dam, or popcorn hulls
	Harmful habits		Wire or nail biting and clenching
	Orthodontic factors		Orthodontic forces or a cross-bite
	Gingival overgrowth		
	Alteration of root surface	Severe anatomic alterations	Invaginated tooth, dens evaginatus or odontodysplasia
		Minor anatomic alterations	Cemental tears, enamel pearls or developmental grooves
		Iatrogenic conditions	Perforations
		Severe root damage	Fissure or fracture, cracked tooth syndrome
		External root resorption	

2.2 | Etiology and risk factors

NPD are infectious conditions; however, predisposing factors, including a compromised host immune response, are critical in the pathogenesis.

a. *Microbiology* (see Appendix 4, Tables A4.2, in online journal)
The bacterial etiology of NPD, with the presence of spirochetes and fusiform bacteria, was previously demonstrated by Plaut in 1894, and Vincent in 1896 (as reviewed in[35]). Furthermore, clinical improvements observed after mechanical debridement and antimicrobial treatment further supported the bacterial etiology of these conditions.[42] Earlier studies, using electron microscopy, suggested tissue invasion by spirochetes.[43,44] Culture studies identified *P. intermedia*, and *Treponema*, *Selenomonas* and *Fusobacterium* species, which were considered "constant flora" in NPD lesions.[45] The role of spirochetes was confirmed by immuno assays[46,47] and PCR targeting 16s rRNA.[48] Recent studies by phylogenetic analysis also suggested a role of the *P. intermedia* and *Peptostreptococcus* genus in the etiology of NPD.
The microbiota associated with NPD in HIV (see Appendix 4, Tables A4.3, in online journal) was like that of periodontitis in non-HIV patients, with some specific features, such presence and invasion of *Candida albicans*, herpes viruses or superinfecting bacterial species.

b. *Host immune response*
Although the importance of host immune response in the etiopathogenesis of NPD was indisputable, the studies available reported very heterogeneous results, as explained in Appendix 4, Tables A4.4 in online journal.

c. *Predisposing factors*
The most relevant predisposing factors for NPD were shown to be those altering the host immune response and usually more than one factor was necessary to cause onset of the disease.[49]

2.2.1 | Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS)

NPD in HIV patients may be more frequent and show faster progression, with a higher risk of evolving into more severe lesions (NP and NS), and a higher tendency for disease recurrence and poor response to therapy (see Appendix 4, Tables A4.3, in online journal).

2.2.2 | Other systemic conditions

Different reports have found NPD lesions associated with, or because of different systemic conditions (see Appendix 4, Tables A4.5, in online journal), or mimicking NPD, in which the lesions were part of the systemic pathology (see Appendix 4, Table A4.6, in online journal).

2.2.3 | Malnutrition

Malnutrition (see Appendix 4, Tables A4.5, in online journal) could also be an important predisposing factor for NPD,[50] especially in developing countries.[51–53] A marked reduction in key antioxidant

nutrients and an altered acute phase response against infection ("protein energy malnutrition")[54,55] have been reported. Other consequences were an inverse proportion in the ratio of helper and suppressor T-lymphocytes, histaminemia, increased free cortisol in blood and saliva, and defects in mucosal integrity.[54,56]

2.2.4 | Psychological stress and insufficient sleep

Certain situations of acute psychological stress or stressing situations, and some personality traits or the ability to cope with a stressful situation (see Appendix 4, Tables A4.5, in online journal) may predispose individuals to NPD. During stress periods, the immune response is altered and the subject's behavior is changed. The biological plausibility of this assumption is based on the reduction of gingival microcirculation and salivary flow; increase in serum and urine levels of 17-hydroxycorticosteroid (17-OHCS)[57]; change in the function of PMN and lymphocytes, and increase in periodontal pathogen levels (*P. intermedia*).[45]

2.2.5 | Inadequate oral hygiene, pre-existing gingivitis, and previous history of NPD

Plaque accumulation has been considered a predisposing factor for NPD, which may also be aggravated by limited tooth brushing because of pain.[37,58,59] NPD usually occurred secondarily to a previously existing periodontal disease (chronic gingivitis,[39,60] previous NPD[58]) (see Appendix 4, Tables A4.5, in online journal).

2.2.6 | Tobacco and alcohol consumption

Most adult patients with NPD are smokers.[39,61–65] Alcohol consumption has also been associated with the physiological and psychological factors favoring NPD[58,66] (see Appendix 4, Tables A4.5, in online journal).

2.2.7 | Young age and ethnicity

Young people (15-34 years old) in the developed world are at a higher risk of suffering from NPD, frequently in combination with other predisposing factors.[58,64,67,68] Children are at a higher risk in developing countries, and this is normally associated with malnutrition and other infections.[52,53,56,69] Some studies suggested that Caucasians suffered from NPD more frequently[58,64,70] than other ethnic groups, however, this finding needs to be confirmed (see Appendix 4, Tables A4.5, in online journal).

2.2.8 | Seasonal variations

Different studies (see Appendix 4, Table A4.5e in online journal) have evaluated the hypothesis of the effect of seasonal variations on the prevalence of NPD: in central Africa, NPD peaked in the rainy season; less clear patterns were observed in military personnel, students or general populations, although winter months were normally peak periods, except in South Africa.

2.2.9 | Other factors

Local factors (see Appendix 4, Table A4.5d, in online journal), including decorative crowns[71] or orthodontic therapy[72] may favor the onset of NG. Body geometry,[73] thermoregulatory abnormalities,[74] allelic variants for complement factors, and properdin factor B [75] or erythrocyte catalase activity,[76] have also been studied with inconclusive results.

2.3 | Pathophysiology and histological features

NG lesions observed with light microscopy[44] showed the presence of an ulcer within the stratified squamous epithelium and the superficial layer of the gingival connective tissue, surrounded by a nonspecific acute inflammatory reaction. Four regions have been described: the (1) superficial bacterial area; (2) neutrophil-rich zone; (3) necrotic zone; (4) spirochetal infiltration zone. Additional findings included plasma cells in the deeper parts and IgG and C3 between epithelial cells.[77] These observations have been confirmed by electron microscopy, adding areas of transition to a chronic stage of inflammation.[43]

2.4 | Assessment and diagnosis

Diagnosis of NPD should be primarily based on clinical findings.[35,78] Microbiological or biopsy assessment may be recommended in cases of atypical presentations or nonresponding cases.

The most relevant clinical findings in NG (Table 3) reported in relevant studies (with 35 or more patients[58,64,67,70]) were: necrosis and ulcer in the interdental papilla (94–100%), gingival bleeding (95–100%), pain (86–100%), pseudomembrane formation (73–88%), and halitosis (84–97%). Extraoral signs included adenopathy (44–61%) or fever (20-39%). In children,[52] pain and halitosis were less frequent, whereas fever, adenopathy, and sialorrhea were more frequent.

For NP,[79] in addition to the previous signs and symptoms, periodontal attachment and bone destruction were observed, together with more frequent extraoral signs. In severely immune-compromised patients, bone sequestrum could occur.[80] NP could be the result of one or various episodes of NG (less frequent pocket formation), or of NG occurring at a site previously affected by periodontitis (periodontal pocketing would be found).[34,81]

In NS, bone denudation extended through the alveolar mucosa, with larger areas of osteitis and bone sequestrum, in severely compromised systemic patients (HIV/AIDS patients, severe malnutrition). Atypical cases have also been reported, in which NS developed without the appearance of previous NPD lesions.[82–85]

Clinical criteria for identifying NG, NP, NS and Noma, according to the studies included in the present review, are summarized in Appendix 4, Tables A4.7,8,9, in online journal.

2.4.1 | Differential diagnosis

It is mandatory to establish a differential diagnosis with vesicular-bullous diseases, primary or recurrent herpetic gingivostomatitis,[86,87] oral

TABLE 3 Diagnosis of necrotizing periodontal diseases: frequent clinical findings

					Primary symptoms and signs			Other symptoms and signs				
Reference	Country	Study design	Population	Patients, condition	Gingival necrosis	Gingival bleeding	Pain	Pseudo-membranous formation	Halitosis	Adenopathies	Fever	Other features
Barnes	USA	Case-control	Military	218 ANUG	94.0%	95.5%	86.2%	73.4%	84.4%	na	No frequent	Cratering (79.8%); wooden or wedge-like (40.4%); bad taste (39.4%)
Stevens	USA	Epidemiological (1y) and case and control	General population	51 ANUG	100%	100%	100%	na	na	na	20%	na
Falkler	USA	Case and control	Clinic at urban dental school	35 ANUG	100%	100%	100%	85%	97%	61%	39%	na
Horning	USA	5y epidemiological study	Military (10 HIV)	68 NG	100%	100%	100%	88%	87%	44%	24%	Interdental gingival craters (previous NG) (21%)
Jimenez	Colombia	Prospective case series	Children	28 NUG, 9 Noma	100%	96.43%	53.57%	Acute cases	50%	Submaxilar (57.1%), Submaxilar & cervical (21.4%)	67.9%	Tooth mobility (46.43%); sialorrhea (42.86%)
Cobb	USA	Case series	HIV	16 NUP	100%	100%	100%	81.3%	100%	68.8%	43.8%	Advanced generalized alveolar bone loss (100%)

y, years; na, not available; HIV, human immunodeficiency virus; ANUG, acute necrotizing ulcerative gingivitis; NUG, necrotizing ulcerative gingivitis; NG, necrotizing gingivitis; NUP, necrotizing ulcerative periodontitis

TABLE 4 Proposal of classification for necrotizing periodontal diseases (NPD)

Category	Patients	Predisposing conditions	Clinical condition
Necrotizing periodontal diseases in chronically, severely compromised patients	In adults	HIV+/AIDS with CD4 counts < 200 and detectable viral load	NG, NP, NS, Noma. Possible progression
		Other severe systemic conditions (immunosuppression)	
	In children	Severe malnourishments[a]	
		Extreme living conditions[b]	
		Severe (viral) infections[c]	
Necrotizing periodontal diseases in temporarily and/or moderately compromised patients	In gingivitis patients	Uncontrolled factors: stress, nutrition, smoking, habits	Generalized NG. Possible progression to NP
		Previous NPD: residual craters	
		Local factors: root proximity, tooth malposition	Localized NG. Possible progression to NP
		Common predisposing factors for NPD (see paper)	NG. Infrequent progression
	In periodontitis patients		NP. Infrequent progression

NG, necrotizing gingivitis; NP, necrotizing periodontitis; NS, necrotizing stomatitis

[a]Mean plasma and serum concentrations of retinol, total ascorbic acid, zinc, and albumin markedly reduced, or very marked depletion of plasma retinol, zinc, and ascorbate; and saliva levels of albumin and cortisol, as well as plasma cortisol concentrations, significantly increased

[b]Living in substandard accommodations, exposure to debilitating childhood diseases, living near livestock, poor oral hygiene, limited access to potable water and poor sanitary disposal of human and animal fecal waste

[c]Measles, herpes viruses (cytomegalovirus, Epstein-Barr virus-1, herpes simplex virus) chicken pox, malaria, febrile illness

manifestation mimicking NPD lesions (see Appendix 4, Table A4.6, in online journal) and toothbrush abrasion.[88]

2.5 | Proposed changes to the current 1999 classification

In the present 1999 classification, the consensus report established "that necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis should be collectively referred to as Necrotizing Periodontal Diseases." The group agreed that both diseases were associated with a diminished systemic resistance to bacterial infection. This rather simplistic approach did not consider the huge differences in prevalence, risk of progression, and extent and severity of NPD among patients with different predisposing conditions. NPD in HIV/AIDS patients or in malnourished children in developing countries may represent a severe and even life-threating condition (in the latter case). Conversely, NPD in smokers and stress adult patients in developed countries represented a relevant but normally non-threatening condition. Therefore, patients continuously exposed to a severe systemic compromise (see previous examples) have a higher risk of suffering from NPD and of faster and more severe progression (from NG to NP, and even to NS and Noma). Conversely, in patients with a systemic compromise of limited duration (e.g. stressful situation in students or militaries), NG may not progress, although the lesions would be different if they affected a gingivitis or a periodontitis patient. A proposal for a new classification system is presented in Table 4.

3 | ENDO-PERIODONTAL LESIONS

3.1 | Clinical presentation

EPL are clinical conditions involving both the pulp and periodontal tissues and may occur in acute or chronic forms. When they are associated with a recent traumatic or iatrogenic event (e.g. root fracture or perforation), the most common manifestation is an abscess accompanied by pain. However, EPL, in subjects with periodontitis, normally present slow and chronic progression without evident symptoms.

The most common signs and symptoms associated with a tooth affected by an EPL are deep periodontal pockets reaching or close to the apex and negative or altered response to pulp vitality tests. The other signs and symptoms reported, in order of prevalence, are: bone resorption in the apical or furcation region, spontaneous pain or pain on palpation and percussion, purulent exudate, tooth mobility, sinus tract, crown, and gingival color alterations (Table 5).

3.2 | Etiology and risk factors

3.2.1 | Primary etiology

An established EPL is always associated with varying degrees of microbial contamination of the dental pulp and the supporting periodontal tissues. Nonetheless, the primary etiology of these lesions might be associated with (1) endodontic and/or periodontal infections or (2) trauma and/or iatrogenic factors.

TABLE 5 Main characteristic of the studies included in the endo-periodontal lesion review, stratified by the periodontal condition

				Percentage (%) of studies according to each study design								
				Signs						Signs and symptoms		
Periodontal condition	Study design	References	Number of teeth included	Deep periodontal pocket (≥5 mm)	Altered pulp response	Purulent exudate	Apical bone resorption	Sinus tract	Tooth mobility	Gingival color alteration	Crow color alteration	Pain
Periodontitis patients	CR	Aksel; Blanchard	5	100	100	50	100	50	50	0	0	100
	CS	Didilescu; Fatemi; Gomes; Kipioti ; Kobayashi; Rupf; Pereira; Li	190	100	100	0	75	0	12.5	0	0	25
	RCT	Cortellini ; Gupta	62	100	100	0	0	0	0	0	0	0
	TOTAL		**257**	**100**	**100**	**8.3**	**83.3**	**8.3**	**16.6**	**0**	**0**	**33.3**
Nonperiodontitis patients	CR	Asgary; Attam; Ballal; Castelo-Baz; Coraini; Floratos; Fujii; Gandhi; Goyal; Haueisen; Jivoinovici; Kambale; Karabucak; Keceli; Kerezoudis; Kishan; Koyess; Mali; Miao; Nagaveni; Oh; Oh; Pickel; Sharma; Singh; Sooratgar; White	39	100	100	33.3	70.3	33.3	29.6	3.7	7.4	55.5
	CS	Xia	13	100	100	0	100	0	0	0	0	0
	TOTAL		**52**	**100**	**100**	**32.1**	**71.4**	**32.1**	**28.5**	**3.5**	**7.1**	**53.5**
Unclear	CR	Karunakar; Narang; Solomon; Tobón-Arroyave; Tseng; Varughese	8	100	100	83.3	100	33.3	66.6	0	0	50
	CrS	Rhee	168	100	100	0	100	0	0	0	0	0
	CS	Li; Nicopoulou-Karayianni; Pereira	69	100	100	0	100	0	0	0	0	0
	TOTAL		**245**	**100**	**100**	**50**	**100**	**20**	**40**	**0**	**0**	**30**
FINAL TOTAL		**Number of studies: 50**	**554**	**100**	**100**	**30**	**80**	**24**	**28**	**5**	**4**	**44**

CR: Case report; CS: Clinical study; RCT: Randomized clinical trial; CrS: Cross-sectional

Endo-periodontal lesions associated with endodontic and periodontal infections

They might be triggered: (1) by a carious lesion that affects the pulp and, secondarily, affects the periodontium; (2) by periodontal destruction that secondarily affects the root canal; (3) or by both events concomitantly. The latter type occurs less frequently and is usually referred to as a "true-combined" or "combined" lesion.[89,90] These lesions may develop in subjects with periodontal health[91–93] or disease[94,95] (Table 6). The periodontal condition has an important impact in the prognosis of the EPL because of the striking changes in the oral ecology of subjects with periodontal diseases. Converting this ecology back into a healthy state is challenging,[96,97] especially in patients with severe periodontitis and in teeth with deep pockets, as in the case of EPL. Therefore, a detailed periodontal examination is a very important step for the accurate diagnosis and treatment plan of EPL.

Endo-periodontal lesions associated with trauma and iatrogenic factors

These conditions usually have a poor prognosis as they affect the tooth structure. The most common lesions in this category were: (1) root/pulp chamber/furcation perforation (e.g. because of root canal instrumentation or to tooth preparation for post-retained restorations)[98]; (2) root fracture or cracking (e.g., because of trauma or tooth preparation for post-retained restorations)[98]; (iii) external root resorption (e.g., because of trauma)[99]; or (iv) pulp necrosis (e.g., because of trauma) draining through the periodontium[100] (see Appendix 5, Table A5.1, in online journal).

3.2.2 | Microbiology

Only a few studies to date have evaluated the microbiota of EPL using culture,[101–103] "targeted" molecular techniques (polymerase chain reaction [PCR][90,94,103,104] real time PCR[105] and checkerboard DNA-DNA hybridization[90]), or "open-ended" molecular techniques (Next Generation Sequencing [NGS][95] and Denaturing Gradient Gel Electrophoresis [DGGE] or cloning and sequencing[94,104]) (see Appendix 5, Table A5.2, in online journal). Overall, these studies showed a great similarity between the microbiota found in the root canals and periodontal pockets. Most of the bacterial species identified were recognized periodontal pathogens from the so called "red" and "orange" complexes,[106] such as *P. gingivalis*, *T. forsythia*, or *Parvimonas micra*, and species from the genera *Fusobacterium*, *Prevotella* and *Tr eponema*.[90,103,105,107–109] Studies using "open-ended" molecular techniques[94,95,104] observed a higher microbial diversity and identified less common taxa, such as *Filifactor alocis*, *Enterococcus faecalis*, and species from the genera *Desulfobulbus*, *Dialister*, *Fretibacterium*, or *Rothia*. Incidentally, most of these species and genera have recently also been associated with chronic or aggressive periodontitis.[110,111]

Taken together, the above-mentioned data suggest that there are no major differences between the microorganisms found in the endodontic and periodontal lesions, or a specific microbial profile associated with the EPL. This was somehow expected, as both sites of infection (root canal and periodontal pockets) are anaerobic environments exposed to similar nutrients.

3.2.3 | Risk factors

The main risk factors for the occurrence of EPL were advanced periodontitis, trauma, and iatrogenic events. Other reported risk factors were the presence of grooves, furcation involvement, porcelain-fused-to-metal crowns and active carious lesions (see Appendix 5, Table A5.1, in online journal). Furcation involvement, high level of bone destruction around the affected tooth, and anatomic problems (e.g. the presence of grooves), could worsen the prognosis of EPL. Most of the single EPL in non-periodontitis patients reported in the literature were associated with palatal grooves.

3.3 | Pathophysiology and histological features

The dental pulp and the periodontium have different communication pathways, such as the apical radicular foramina, accessory (or lateral) canals, and dentinal tubules.[112] Accessory canals are more prevalent at the apical third of the roots, but they may be found in high numbers in other areas, such as in the furcation regions.[112,113] Pathological communication between these structures, which includes the migration of microorganisms and inflammatory mediators between the root canal and the periodontium, may lead to the EPL.[89,112–116]

3.4 | Assessment and diagnosis

The classification system most commonly used for the diagnosis of EPL was published in 1972 by Simon et al.[89] and included the following categories: (1) primary endodontic lesions; (2) primary endodontic lesions with secondary periodontal involvement; (3) primary periodontal lesions; (4) primary periodontal lesions with secondary endodontic involvement; and (5) "true" combined lesions. The main drawback of this classification and a recent proposed amendment[117] was to base their categories on the primary source of infection (root canal or periodontal pocket). This seemed to be a suitable approach, as lesions of periodontal origin might have a worse prognosis than those of endodontic origin. Nonetheless, using "history of the disease" as the main criteria for diagnosis was not practical, because in the majority of cases the complete history is unavailable to the clinician. In addition, determining the primary source of infection is not relevant for the treatment of EPL, as both the root canal and the periodontal tissues would require treatment.[118,119] Thus, ideally, the diagnosis and classification of EPL should be based on the present disease status and on the prognosis of the tooth involved, which would determine the first step of the treatment planning that would be whether to maintain or extract the tooth.

The three main prognostic groups for a tooth with an EPL are: (1) hopeless, (2) poor, and (3) favorable. The hopeless prognosis is normally associated with EPL caused by trauma or iatrogenic factors, whereas the prognosis of a tooth with an EPL associated with endodontic and periodontal infections may range from favorable to hopeless, depending on the extension of the periodontal destruction around the affected tooth, and the presence and severity of the periodontal disease affecting the patient's oral health.

TABLE 6 Proposal for endo-periodontal lesions classification

Endo-periodontal lesion with root damage	Root fracture or cracking	
	Root canal or pulp chamber perforation	
	External root resorption	
Endo-periodontal lesion without root damage	Endo-periodontal lesion in periodontitis patients	*Grade 1* – narrow deep periodontal pocket in 1 tooth surface
		Grade 2 – wide deep periodontal pocket in 1 tooth surface
		Grade 3 – deep periodontal pockets in more than 1 tooth surface
	Endo-periodontal lesion in non-periodontitis patients	*Grade 1* – narrow deep periodontal pocket in 1 tooth surface
		Grade 2 – wide deep periodontal pocket in 1 tooth surface
		Grade 3 – deep periodontal pockets in more than 1 tooth surface

The first steps in diagnosis should be to assess patient's history and clinical or radiographic examination. Patient history is important for identifying the occurrence of trauma, endodontic instrumentation or post preparation. If one or more of these events are identified, detailed clinical and radiographic examinations should be conducted to seek the presence of perforations, fractures, and cracking or external root resorption. Careful radiographic evaluation and clinical examination of the root anatomy is of great importance at this stage, to assess the integrity of the root and to help with differential diagnosis. A radicular groove, for example, might mimic a vertical root fracture in the radiograph.[120]

If perforations and fractures are not identified, the diagnosis should proceed to a second phase consisting of full-mouth periodontal assessment, including probing depth, attachment level, bleeding on probing, suppuration and mobility, as well as tooth vitality and percussion tests. The presence of a periodontal pocket reaching or close to the apex combined with absence of pulp vitality would indicate the presence of an EPL.

3.5 | Proposed changes to the current 1999 classification

For the first time, the 1999 classification system for Periodontal Diseases and Conditions[118,121] included the EPLs, which were described under Section VII - Periodontitis Associated with Endodontic Lesion, as a single category entitled "Combined Periodontal-Endodontic Lesions." An advantage of this classification over the previous ones[89,117] was that it reflected the current clinical condition of the lesion, thereby overcoming the problem of using "history of the disease" as the main criteria. Nonetheless, the following problems were associated with this classification system: (1) grouping all EPL under a single section entitled "Periodontitis Associated with Endodontic Lesion" was not ideal, as these lesions may occur in subjects with or without periodontitis; (2) the single category presented, "Combined Periodontal-Endodontic Lesions", was too generic and not sufficiently discriminative to help the clinician to determine the most effective treatment for a particular lesion. Finally, EPL should be classified according to signs and symptoms feasible to be assessed at the time that the lesion is detected and that have direct impact on their treatment, such as presence or absence of fractures and perforations, presence or absence of periodontitis, and the extent of the periodontal destruction around the affected teeth (Table 6).

OBSERVATIONS AND DISCUSSION

The present literature review focused on three conditions that have in common a possible acute onset and severe destruction. A comprehensive analysis of the available scientific literature (336 studies were included) allowed for a description of the importance, etiology, pathogenesis and diagnosis, together with the proposal of new classifications.

Quality of the available evidence

In general, the evidence to define the etiology, diagnosis, prognosis and treatment of the teeth affected by the three conditions studied was considered limited. Most of the included studies were case reports with small sample sizes. Very few clinical studies with a reasonable number of cases were found, and no robust epidemiological studies were identified (see Appendix 1 in online journal). To enable solid evidence on these lesions to be made available, additional studies with adequate designs and sample sizes are needed, specifically on the topics with less information available (e.g. PA in non-periodontitis patients, and EPL).

Pending topics for the proposed classification

The topic of whether the lesions associated with root alterations and damage (e.g. fracture, perforation, root resorption), should be classified

in a different category, is debatable. However, because these lesions are EPL in nature (i.e., invariably affect both the periodontium and the pulp-root canal complex, irrespective of being associated with abscess formation, or not), we understand that they should be classified as such. Thus, in the classification system suggested for EPL, these conditions are grouped as "EPL associated with trauma and iatrogenic factors."

Pericoronal abscesses have been excluded from the category of PA.[121] However, pericoronitis may still be considered an acute periodontal condition, but in a separate category.

"Periodontal" abscesses around implant sites have also been described.[122,123] Considering that from a histological point of view the lesions may be similar, it is also debatable whether they should be given a different name should be given to these lesions (e.g. "periimplant" abscesses) and whether they should be classified together with the other abscesses in the periodontium.

In this manuscript, the term "risk factor" was used, however, in some cases, the available literature was insufficient to support the use of this term.

CONCLUSIONS

PAs can present different aetiologies, and they should be classified according to the aetiological factors involved. These lesions are commonly associated with reduced drainage of a deep periodontal pocket. They normally cause rapid tissue destruction, which may compromise the prognosis of teeth, and represent one of the most frequent reasons for tooth extraction during PeM. PAs are also associated with evident systemic risks.

NPD present three typical clinical features: papilla necrosis, bleeding, and pain. They represent the most severe biofilm-related periodontal condition. The onset, severity, extent, and progression of NPD are clearly associated with the host immune response, giving credit to a classification based on this response.

An EPL is a pathological communication between the endodontic and periodontal tissues of a given tooth. It may occur in acute or chronic forms and should be classified according to signs and symptoms that have direct impact on their prognosis and treatment, such as presence or absence of fractures and perforations, presence or absence of periodontitis and the extent of periodontal destruction around the affected teeth.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

Classification and diagnosis of aggressive periodontitis

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objective: Since the initial description of aggressive periodontitis (AgP) in the early 1900s, classification of this disease has been in flux. The goal of this manuscript is to review the existing literature and to revisit definitions and diagnostic criteria for AgP.

Study analysis: An extensive literature search was performed that included databases from PubMed, Medline, Cochrane, Scopus and Web of Science. Of 4930 articles reviewed, 4737 were eliminated. Criteria for elimination included; age > 30 years old, abstracts, review articles, absence of controls, fewer than; a) 200 subjects for genetic studies, and b) 20 subjects for other studies. Studies satisfying the entrance criteria were included in tables developed for AgP (localized and generalized), in areas related to epidemiology, microbial, host and genetic analyses. The highest rank was given to studies that were; a) case controlled or cohort, b) assessed at more than one time-point, c) assessed for more than one factor (microbial or host), and at multiple sites.

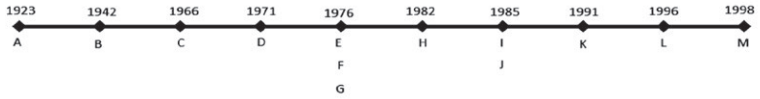
Results: Epidemiologic studies provided insight into ethnic and societal factors affecting AgP. DNA analysis of microbes showed some consistency but significant variability. Host factor analysis was less consistent. Many genetic studies were conducted but few had either sufficient power or looked at multiple genes in AgP.

Conclusions: Conflicting data resulted for several reasons; 1) the classification was too broad, 2) the disease (AgP) was not studied from its inception, at differing time points (temporal), and at different locations (topographic). New technologic advances coupled with a more delimiting definition of disease will allow for genetic, host and microbial factor analyses in an unbiased manner. As such we predict that progress can be made in identifying a robust group of genetic, host, and microbial risk-markers associated with periodontal disease that can improve diagnostic capability in disease associated with juveniles, adolescents, and post-adolescent individuals.

KEYWORDS

aggressive periodontitis, diagnosis, epidemiology, genetics, inflammation and innate immunity, microbiology

This report focuses on aggressive periodontitis (AgP). The most recent effort to classify AgP was presented as a report in 1999 by the American Academy of Periodontology (AAP) committee on the classification of periodontal diseases.[1] This newly proposed terminology was to the greatest extent based on clinical presentation. The committee concluded that all periodontal diseases were infectious in nature but could be categorized as either slowly-progressing (chronic), or, rapidly-progressing (aggressive) diseases.[1,2] The AAP 1999 workshop group concluded that many similarities were seen when chronic periodontitis (CP) and



AgP Timeline Highlights Prior to 1999

A: **1923**: **Gottlieb B.** Z Stomatol 1923;21:195-201.	**[Described AgP as "Diffuse Alveolar Atrophy"]**
B: **1942**: **Orban B, and Weinmann JP.** J Periodontol 1942;13:31-45.	**[Supported Gottlieb's term "Periodontosis" as non-inflammatory form of AgP]**
C: **1966**: American Academy of Periodontology. *World Workshop in Periodontics (Proceedings).* Chicago: American Academy of Periodontology, 1966: 167.	**[Dismissed "Periodontosis as a unique disease entity]**
D: 1971: **Baer PN.** J Periodontol 1971;42(8):516-20.	[**Revived interest in "Periodontosis", promoted term Juvenile Periodontitis]**
E: **1976**: **Newman MG, *et. al.*** J Periodontol 1976;47:373-379	[***Actinobacillus actinomycetemcomitans*** **associated with Juvenile Periodontitis (JP)]**
F: **1976**: **Slots J.** Scand J Dent Res 1976;84:1-10.	[***Actinobacillus actinomycetemcomitans*****(*Aa*) associated with JP]**
G:**1976**: **Listgarten MA.** J Periodontol 1976;47(3):139-47	**[Described thin biofilm on root surfaces of subjects with JP]**
H: **1982: Goodson JM, *et. al.*** J Clin Periodontol 1982;9(6):472-81.	**[Illustrated episodic nature of periodontal diseases]**
I: **1985**: **Moore W, *et. al.*** Infect Immun 1985;48:507-19	[**Challenged microbial disease specificity as related to *Aa* and JP]**
J: **198**5:**Dewhirst FE, *et. al.*** J Immunol 1985;135(4):2562-8.	**[Highlighted the importance of cytokines as related to bone loss]**
K: 1991: **Loe H, and Brown LJ.** J Periodontol 1991;62:608-616	**[Epidemiological analysis of JP or early onset periodontitis]**
L: **1996**: **Brown LJ, *et. al.*** J Periodontol 1996;67(10):968-75	**[Identified the rate of progression in early onset periodontitis or JP]**
M: **1998**: **Socransky SS, *et. al.*** J Clin Periodontol 1998;25(2):134-44.	**[Codified combinations of bacteria related to stages of diseases]**

FIGURE 1 Timeline: research related to aggressive periodontitis prior to 1999. Major events are depicted prior to 1999 (A through M) that influenced our understanding of the disease from its inception in the early 1900s to the most recent 1999 classification system

aggressive periodontitis were compared (Figure 1; highlights of early literature). However, AgP was designated as a separate disease because of its aggressive nature, the location of the lesions, the familial tendencies, and the thinness of its subgingival biofilm.[3] The data suggested that AgP could be provoked by specific bacteria in some well-defined cases. Immune responsiveness was thought to influence disease manifestation and progression. However, age was not considered as part of the distinguishing features of AgP. Both systemic and local factors such as smoking and trauma were proposed as risk modifiers that could complicate diagnostic accuracy.[2]

Overtime this new classification produced an explosion of information. Despite the information generated, roadblocks to a better understanding of "aggressive periodontitis" continue to exist. In many ways the work published since that time has highlighted deficiencies in the definitions proposed in 1999 and has blurred the distinction between the localized (LAgP) and generalized version of disease (GAgP). In this review we focus especially on LAgP and we suggest it needs redefinition; where possible we distinguish this type from GAgP.

Evidence that has undermined defining LAgP as a distinct entity includes challenges to the:

1. Specificity of the microbial infection[4]
2. Immune localization of LAgP[5]
3. Relationship between LAgP and GAgP[6]
4. Unique innate and acquired cellular responses projected for LAgP[7,8]

Evidence that support consideration of LAgP as a distinct entity that remain include:

1. Localization[9,10]
2. Rate of progression[2,10]
3. Age of onset[11]

METHODS FOR LITERATURE SEARCH

After our extensive review of the literature we have come to two conclusions: 1) there is tremendous interest in AgP, which has expanded exponentially probably because of the broader definition provided in 1999, and 2) it is time for a fresh look at the way in which we classify AgP, especially LAgP (see Figure 2).

LITERATURE REVIEW

Epidemiology

Relevant findings

Table 1 provides epidemiologic data that re-enforces differences seen in the prevalence of LAgP in various ethnic and racial populations.[12–22] A higher prevalence of LAgP was seen in individuals of African and Middle Eastern descent and a relatively low prevalence was found in individuals of Caucasian descent.[15,22]

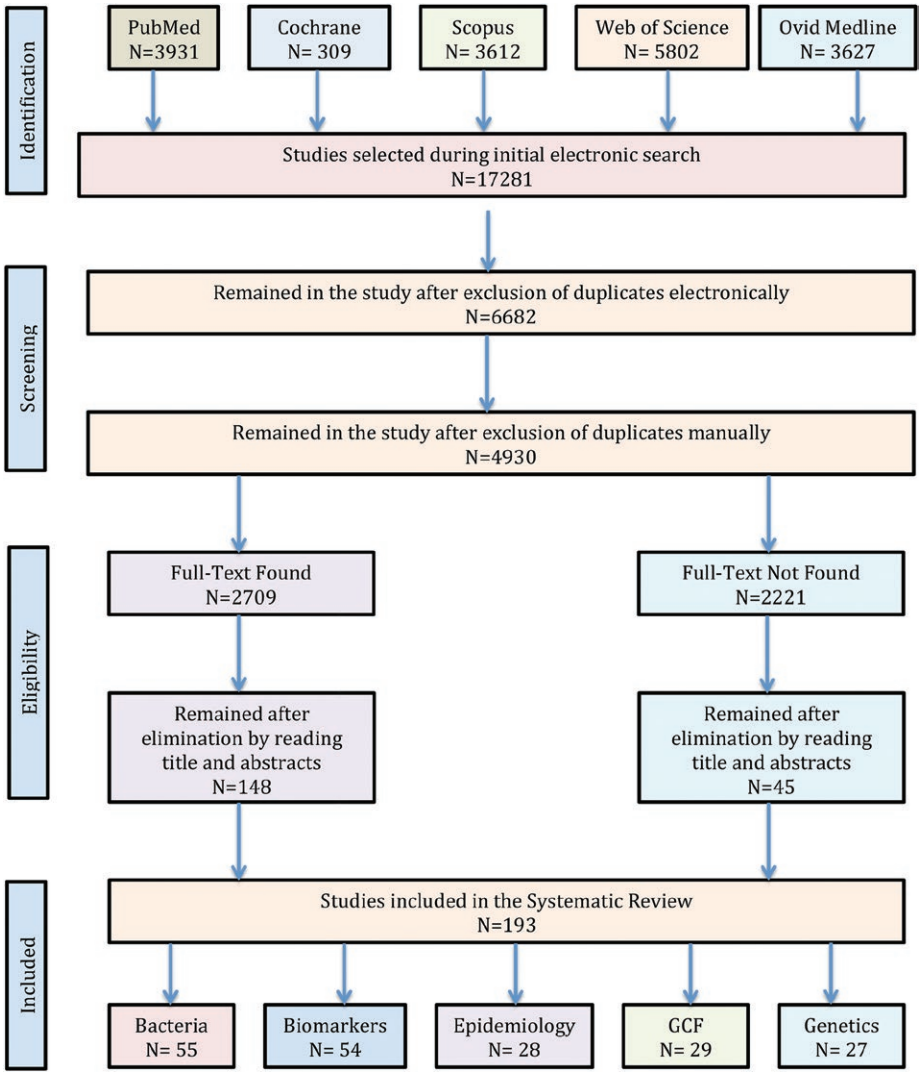


FIGURE 2 Flow-chart depicting the systematic review of the literature. A review of the literature was performed since the last official classification in 1999 was developed using the keywords; "Aggressive Periodontitis," "Severe Periodontitis," "Juvenile Periodontitis," "Localized Juvenile Periodontitis," "Periodontosis," "Early Onset Periodontitis," and "Rapidly Aggressive Periodontitis." Databases in Pub Med, Cochrane, Scopus, Web of Science, Ovid Medline were searched. Duplicates were excluded as were nonEnglish texts and papers without abstracts

Critical evaluation

A variety of methods and endpoints were used for the diagnosis and characterization of disease in these studies (Table 1).[12–22] However, in spite of these differences, the data support the belief that both genetic and perhaps socioeconomic factors are related to disease susceptibility.

Knowledge gaps and suggestions for resolution

Methodologic variations need to be narrowed. New definitions are needed that include; age of onset, lesion location, and rate of progression in the primary case definition. However, key risk modifiers that include familial tendencies, ethnicity, and socio-economic factors need to be considered. Microbiologic and host factors should be included in the assessment if possible to gain a better understanding of etiology and pathogenesis.

Microbiology

Relevant findings

Studies from 1998 forward examined a broad spectrum of bacteria using DNA technologies (Table 2).[23–36] In one-half the studies *Aggregatibacter actinomycetemcomitans* was implicated as a risk marker, and in another half *Porphyromonas gingivalis*,[23,25,27,32–35] *Tannerella forsythia*,[27,29,32,34,35] and *Selenomonads* emerged as markers of risk (Table 2). A recent study[37] showed that in younger individuals *A. actinomycetemcomitans* was associated with disease whereas this was not the case in older subjects.

TABLE 1 Epidemiologic studies of aggressive periodontitis

Author; year	Location	Age in years	Number	Clinical parameters	% aggressive periodontitis	Assessments
Lopez *et. al*,; 2001	Chile	12 – 21	9,203	Full Probing CAL	4.5%	Poor oral hygiene related to disease
Albandar *et. al*,; 2002	Uganda	12 – 25	690	Full Probing CAL	4.2%	High prevalence of LAgP, males higher than females
Collins *et. al*,; 2005	Dominican Republic	12 – 21	1,973	CAL	15% had attachment loss of 2 mm or greater	Attachment loss common in adolescent Dominicans
Levin *et. al*.; 2006	Israel	18 – 30	642	Probing CAL and Radiographs	6.7%	Smoking and ethnicity important
Costa *et. al*.; 2007	Brazil	12- 15 at follow – up	360; 44 with CAL of > 4 mm followed for BL	Probing CAL and Radiographs	BL increased from 2.1 to 7.5% in subjects with disease	Disease progresses rapidly in those with disease; .67 mm rate
Eres *et. al*.; 2009	Turkey	13 – 19	3,056	Probing and Radiographs	0.6%	Female: Male = 1.25: 1.0 Ethnic and social issues related to disease
Lopez *et. al*.; 2009	Chile	16 – 17	160	Probing and Radiographs Progression	Shows elevated extent and severity in cases vs controls	No pattern. Typical plaque and gingivitis levels do not hold. Bleeding related to disease
Elamin *et. al*.; 2010	Sudan	15 – 17	1,200	Probing CAL	African = 6.0% Afro/Arab = 2.3%	Males more at risk; Africans more at risk
Sadeghi; 2010	Iran	15 – 18	5,590	Probing CAL	0.13%	Low prevalence in this population
Susin et. al.; 2011	Brazil	14 -29	612	Probing and Attachment	5.5% AgP twice as frequent in non-whites	Socioeconomic, smoking and calculus significant risk
Kissa *et. al*.; 2016	Morocco	16 – 21	830	Probing CAL	4.9%	High risk population

Inconsistent Study Factors: Age, disease definitions, randomization, enrollment at school or clinic, clinical condition assessed by probing, clinical attachment levels, bone loss, tooth-based or average score? Recession considered or not. Incidence and severity considered or not?

TABLE 2 Studies of multiple bacterial species in localized aggressive periodontitis

Author; year	Country	Number of subjects	Healthy controls yes or no	Multiple bacteria	Culture/DNA/other	Pooled/1 or multiple times	Assessments
Takeuchi *et. al*.; 2003	Japan	50 AgP, 10 LAgP	Yes	7 bacterial species	Culture/DNA	Sites/1 Time	*T. forsythensis*, *C. rectus*, *P. gingivalis*, *T. denticola*, *Aa* there but lower
Cortelli *et. al*.; 2005	Brazil	178 CP, 25 AgP	No	5 bacterial species	DNA	Pooled/1 Time	Aa leukotoxic strain higher
Gajardo *et. al*.; 2005	Chile	LAgP 30, 6 GAgP, 17 CAP	No	8 bacterial species	Culture	Pooled/1 Time	*C. rectus*, *P. gingivalis*, *E. corrodens P. micros Capnos* high
Aberg *et. al*.; 2009	Sweden	13 AgP	No	6 bacterial species	Culture and DNA	Not Pooled/1 Time	*Aa* not necessarily connected with CAL
Faveri *et. al*.; 2009	Brazil	15 LAgP, 25 GAgP, 30 CAP, 50 C	Yes	40 species	DNA/DNA	Not pooled/1 Time	*Aa* associated with onset. *P.gingivalis*, *T. forsythia*, *E. nodatum*, *P. intermdedia*, *T. denticola* associated with progression
Lopez *et. al*.; 2011	Chile	87 AgP, 73 C	Yes	40 species	DNA/DNA	Not Pooled/1 Time	Cluster of bacteria as in above seen in disease
*Shaddox *et. al*.; 2012	USA	31 LAgP, 20 C	Yes	422 species	HOMIM	Not Pooled/1 Time	*Aa*, *Tannerella sp*, *Solobacterium*, *P. micra* and Capnos associated with disease
* Fine *et. al*.; 2013	USA	16 LAgP, 16 C	Yes	422 species	HOMIM	Not Pooled/Several Times	Consortium of *Aa*, *F. alocis* and *S. parasanguinis* associated with disease
Oettinger-Barak *et. al*.; 2014	Israel	21 LAgP, 12 CAP	No	13 species	Culture and PCR	Unknown/1 Time	*Aa*, *P. micra*, *F. nucleatum*, *T. forsythia* associated with disease
Feng *et. al*.; 2014	China	25 LAgP, 56 GAgP, 34 C	Yes	8 species	PCR	Pooled/1 Time	*P. gingivalis*, *T. forsythia*, *C. rectus*, *P. intermedia*, *F. nucleatum* associated
Dahlen *et. al*.; 2014	Ghana	98 AgP	Site Control	9 species	Culture/PCR	Pooled/1 Time	*P. intermedia*, *P. gingivalis* associated with disease
Chahboun *et. al*.; 2015	Morocco	13 LAgP, 37 GAgP, 20 CAP	No	11 species	Culture	Pooled/1 Time	*Aa*, *P. gingivalis*, *T. forsythia*, *P. intermedia*, *F. nucleatum* associated with disease
Li et. al.; 2015	China	10 AgP, 10 C	Yes	> 400	HOMIM	Pooled/1 Time	*P. gingivalis*, *T. denticola*, *T. forsythia* associated with disease
Minguez et. al.; 2016	Morocco	32 AgP, 27 CAP	No	9 species	Culture	Pooled/1 Time	*Aa* found frequently in diseased subjects

Inconsistent Study Factors: Age, disease definitions, randomization, enrollment at school or clinic? Disease assessed by probing, clinical attachment levels, bone loss? Sampling by curette or paper point? Pre-selection of microbes? Identification of microbial species by DNA or culture? Cracking buffer method to isolate and purify microbial DNA?

Abbreviations: *Aa = Aggregatibacter actinomycetemcomitans*; *C. rectus = Campylobacter rectus*; *T. denticola = Treponema denticola*; *P. gingivalis = Porphyromonas gingivalis*; *P. micros = Peptostreptococcus micros*; *Capnos = Capnocytophaga sp.*; *T. forsythia = Tannerella forsythia or forsythensis*; *E. corrodens = Eikenella corrodens*; *E. nodatum = Eubacterium nodatum*; *F. alocis = Fusobacterium alocis*; *S. parasanguinis = Streptococcus parasanguinis*; *P. intermdia = Prevetolla intermedia*; CAL = Clinical Attachment Level; AgP = Aggressive Periodontitis; LAgP = Localized Aggressive Periodontitis; GAgP = Generalized Aggressive Periodontitis; CP = Chronic Periodontitis; CAP = Chronic Adult Periodontitis; C = controls; HOMIM = Human Oral Microbe Identification MicroArray.

Notably, three longitudinal cohort studies assessed disease progression.[29,30,38] All studies were performed in ethnically distinct and socio-economically disadvantaged populations. Two of these examined a broad spectrum of bacteria at specific sites.[29,30] Both examined temporal (time-related) and topographic (site specific) levels of microbial deposits as they related to disease. Both studies indicated that *A. actinomycetemcomitans* was associated with a consortium of other microbes but was; 1) present in low abundance prior to any periodontal destruction, or 2) present in healthy as well as diseased sites in vulnerable individuals and thus not necessarily predictive of future disease, 3) decreased to very low if not undetectable levels after disease occurred. Further, the 3rd cohort study[38] indicated that high leukotoxin producing and "more" virulent strains of *A. actinomycetemcomitans* might act as exogenous agents.

Critical evaluation

In most studies, aside from the cohort studies, the older age of the subjects and the lack of microbial analysis prior to disease weakened conclusions regarding the relationship of microbial factors to disease initiation. Moreover, the lack of standardization in sample collection (point versus scaler) and sample processing (DNA extraction by different methods), made it unlikely that data would lead to identification of unique microbiologic risk-markers. Undoubtedly these methodologic differences could have had a profound influence on outcome measures.

Although it appears as if *A. actinomycetemcomitans* is important in some cases, different combinations of bacteria that occur in different ethnic populations may show similar clinical patterns of destruction.[4] Thus, although the make-up of a microbial consortium may vary from case to case and from population to population, metabolic end-products that can challenge the host, may be similar.[39]

Data suggest that in a subset of African and Middle Eastern subjects *A. actinomycetemcomitans* may occur in the early stages of disease. It appears as if specific *A. actinomycetemcomitans* virulence factors can suppress the host response, which will allow for the overgrowth of a "toxic" combination of "other" bacteria in the local environment. This hypothesis implicates toxic LPS, leukotoxin, and cytolethal distending toxin in disease activity.

Knowledge gaps and suggestions for resolution

Design and methodologic differences confound interpretation. Resolution of these controversies will emerge only after we; 1) better define disease, 2) perform longitudinal studies documenting the early stages of disease, 3) examine suspected microbes in the context of the total flora relative to disease development, and 4) use standardized methods for plaque collection, DNA extraction, microbiologic identification, and statistical interpretation of data in an unbiased manner. Metabolomics may help to sort out these variables in the future.[6] However, this trajectory will only succeed if our definitions of disease and methodologies become more consistent so that they can be reproduced.

Host response elements

Relevant findings

The infectious disease model proposed in 1999 encouraged researchers to examine host/pathogen interactions by comparing antibody responsiveness to *A. actinomycetemcomitans*, *P. gingivalis*, and other putative pathogens.[40] It was proposed that the aggressive form of disease went from the localized to the generalized form if serum IgG or IgA levels to *A. actinomycetemcomitans* or other pathogens were ineffective over time thus allowing other suspected pathogens to overgrow in an unrestrained manner.[40] The International Workshop for the Classification of Periodontal Diseases highlighted the importance of the host antibody response to infectious agents concluding that patients with a robust antibody response would not progress from LAgP to GAgP.

Twelve current studies related to local host responses in AgP were examined (Table 3).[30,41–51] Of these, 9 studies[41,42,44–46,49–52] looked at multiple crevice sites within a patient population. Of these, 5 manuscripts[46,48–50,52] reported multiple mediators at the local site. Two of these[46,52] were cohort in nature and these found macrophage inflammatory proteins (MIP)1a, interleukin (IL)-1b, and tumor necrosis factor (TNF)a, to be elevated prior to disease. These cytokines could act as potential risk markers at the site level. Undoubtedly these cytokines could drive immune responsiveness at that site. Other more restrictive studies[44,45,51] examined individual pre-selected factors, i.e., lactic acid dehydrogenase and matrixmetalloproteinases (MMPs), and thus had a built-in bias (Table 3).

A number of carefully performed studies failed to support the relationship between serum antibody titers to purported pathogens and disease progression.[5] A study of note by Ebersole *et al*. showed that local gingival crevicular antibody responses to *A. actinomycetemcomitans* antigens were elevated at the local site indicating a local antibody response.[42] It is clear that polymorphonuclear leukocytes (PMNs) and macrophages respond to cytokines in the initial stages of infection. Cytokines and chemokines are key elements of the cellular response to inflammatory instigators. Granulocyte colony stimulating factors (GCSFs), (IL)-17/23, TNFa, MIP1a have all shown modest support as biomarkers of disease, but results need further confirmation.[46] More recently MIP1a, IL-6, and IL-1b have been suggested as potential biomarkers and have been promoted as potentially useful biomarkers singly or in concert.[46,52] The relevance of these cytokines to clinical classification and disease initiation and progression is still to be determined.

Knowledge gaps and suggestions for resolution

Cytokine networks are known to act as signaling molecules for cells to perform their host protective functions in both distant (i.e., homing of lymphocytes at the regional lymph nodes) and local sites (repopulation of sensitized lymphocytes to the local tissue). Over the years the importance of systemic as well as local expression of cytokines indicates that cytokines form an overall network that has

TABLE 3 Studies assessing biomarkers associated with localized aggressive periodontitis

Author; year	Country	Number of subjects	GCF-host marker	1 or multiple sites	1 or multiple times	Control yes/no	Conclusions
Kuru *et. al.*; 1999	Turkey	LAgP 15	AST *Aa*, *Pg* and *PI*	4 Sites	1 Time	No	AST elevated as inflammation increases. *Aa*, *Pg* up and *Pi* down
Ebersole *et. al.*; 2000	USA	LAgP 12	Antibody to Aa in serum and GCF	28 Sites	Multiple Times	No	Elevated Ab to *Aa* lower *Aa* at site; GCF parallels serum; specificity changes overtime
Kurtis *et. al.*; 2005	Turkey	LAgP 20	MCP-1 and TNFa	1 Site	1 Time	Yes	Levels higher in LAgP but concentrations not higher
Alfant *et. al.*; 2008	USA	LAgP 23	MMP's	3 Sites	1 Time	Yes	MMPs 1–3, 8,9,12,13 all higher in LAgP deep sites vs. control sites
Castro *et. al.*; 2011	Argentina	LAgP 36	LDH, AST, NE and AP	6-8 Sites Pooled	1 Time	Yes	Only LDH showed best connection to LAgP
Shaddox *et. al.*; 2011	USA	LAgP 34	9 Mediators	2 Sites	1 Time	Yes	TNFa, INFg, IL-1b, IL-2, IL-10, IL-12, GM-CSF, MIP1a all higher in diseased sites vs. normal sites and vs. controls; MCP1 and LL 4 decreased
Khongkhunthian *et. al.*; 2013	Thailand	LAgP 15	ADAM8	1 Site	1 Time	Yes	ADAM8 elevated in all disease categories vs. healthy controls
*Fine *et. al.*; 2013	USA	LAgP 15	7 Mediators	Multiple Sites	Several Times	Yes	MIP1a &b, IL-1 and IL-8 elevated in saliva of LAgP prior to BL, MIP 1a elevated in site prior to BL in LAgP subjects
Goncalves *et. al.*; 2013	USA	LAgP 30	8 Mediators	1 Site	1 Time	No	IL-8 lower in non-*Aa* sites
Zhang *et. al.*; 2016	China	LAgP 15	5 Mediators	4 Sites	1 Time	Yes	AP, TNFa, CRP elevated in diseased groups; IL-6 and IL-10 decreased
Shaddox *et. al.*; 2016	USA	LAgP 13	14 Stimulated Mediators	2 Sites	1 Time	Yes	10 cytokines elevated by stimulation in LAgP blood; IL-6 in control
Gunpinar *et. al.*; 2017	Turkey	AgP 80	MCP-1	4 Sites Pooled	1 Time	Yes	MCP-1 elevated in AgP vs. controls

Inconsistent Study Factors: Age, disease definitions, randomization, enrollment at school or clinic, clinical condition assessed by probing, clinical attachment levels, bone loss? Sampling by pooling? Pre-selection of marker? Identification by split samples or by multiplex system?

Abbreviations: AST = Aspartate aminotransferase; MCP1 = Monocyte chemoattractant protein 1; TNFa = Tumor necrosis factor alpha; INFs = Interferon gamma; ILs = Interleukins; GM-CSF = Granulocyte-Macrophage Colony Stimulatig Factor; MMP = Matrixmettaloproteinases; MIP1a = Macrophage Inflammatory Protein 1 alpha; LDH = Lactic acid dehydrogenase; CRP = C reactive protein; NE = norepinephrine; AP = alkaline phosphatase; ADAMS = A disintegrin and metalloproteinase; *Aa = Aggregatibacter actinomycetemcomitans*; *Pg = Porphyromonas gingivalis*; *Pi = Prevetolla intermedia*; AgP = Aggressive Periodontitis; LAgP = Localized Aggressive Periodontitis.

relevance to the balance between host protection and destruction. Once again because the host response is time-related, these important interactions will not be resolved until time-to-infection-and-disease is considered. Similar principals of standardization described for microbiology need to be applied here.

Genetic factors

Relevant findings

Table 4 summarizes the results derived from 22 studies. In total, 30 loci and genes were identified in which one or several genetic variants were associated with AgP (Table 4).[53–74] Studies were based either on candidate-gene approach (CGA) or genome-wide association studies (GWAS) (Table 4).

In the last 10 years, it has become clear that many chronic diseases (i.e., AgP, chronic periodontitis) as well as LAgP and GAgP, are polygenic. Thus, a single genetic defect of major effect will not be responsible for the development of these forms of periodontitis. Many single nucleotide polymorphisms (SNPs) (perhaps some in linkage disequilibrium) together with environmental and lifestyle factors may be deterministic in phenotypic expression of disease.[39,73] In this respect, the study by Scapoli *et al*., who studied gene-gene interactions, is noteworthy.[62] The strong familial tendency of LAgP and GAgP may be because of the fact that polygenicity is perhaps in the order of 20–50 risk alleles, rather than > 100 risk alleles such as have been found in, for instance, adult rheumatoid arthritis and Crohn's disease.

The most studied genes appeared to be *CDKN2B-AS1* (*ANRIL*), *IL6*, and *GLT6D1*. For *CDKN2B-AS1* (*ANRIL*), where there were three papers reviewed. For *IL6* and *GLT6D1* there were two independent studies reporting an association with AgP. The remaining loci and genes (*n* = 27) proposed to be associated with AgP, were found in just one study each. Three studies out of the total of 22, specifically mentioned genes associated with either LAgP or GAgP.[55,57,58] Thus, *CDKN2B-AS1* (*ANRIL*) appears to be associated with LAgP, whereas the IL6 relationship is unclear because the number of study participants specifically having LAgP was low (n = 24). One study,[62] identified ten gene-gene interactions associated with AgP (Table 4).

Overall, several genetic polymorphisms associated with AgP were located on chromosome 1, in 6 out of 22 studies. This chromosome may contain "hot spots" related to AgP.

Critical evaluation

Over the years, several candidate loci and genes have been proposed for AgP, but because of the absence of; 1) sufficient power, and 2) correction for multiple testing, false positive and negative results (type I and II errors) cannot be excluded.[63,73] Thus, because of underpowering, findings of nonsignificant associations for one selected SNP cannot rule out a potential disease association of the gene in question.[63,73]

The loci and genes *CDKN2B-AS1* (*ANRIL*), *IL6*, and *GLT6D1*, seem sufficiently validated. However, we argue that individuals with the diagnosis AgP may form a heterogeneous group. Thus, there are not yet loci and genes validated sufficiently and specifically for LAgP or GAgP.

Knowledge gaps and suggestions for resolution

Gaps will continue to exist in this area because of the limited number of individuals diagnosed with the AgP, especially LAgP. Genetic analysis requires large and well-defined populations using unbiased methods (thus GWAS is preferable to selection of pre-determined markers). A more restrictive definition of disease will be useful here.

Generalized aggressive periodontitis

Eighteen papers were reviewed. Case definitions and methodologic approaches differed substantially.[27,75–91] Of note, Teles *et. al*.[82] examined IL-10/IL-1b ratios and a broad spectrum of bacteria [more information is provided in; a) Table 5, b) the supplementary table in the online *Journal of Clinical Periodontology*, and c) appendices, also in the online journal].

DISCUSSION

Three focused questions that follow were designed to define the uniqueness of LAgP in support of a new case definition:

1) What are the unique features of LAgP?
2) Is LAgP a distinct entity that differs from Chronic Periodontitis?
3) What are the roadblocks that exist?

Features unique to LAgP

Aside from the age on onset, the location of the lesions, and the rapidity of the breakdown, there are several added features that appear to be unique to LAgP. For example it has been reported that; 1) PMNs and macrophages show a level of hyperactivity,[7] 2) antibody responsiveness can be elevated either at a peripheral or local level,[42] 3) specific subpopulations of bacteria are prevalent in specific populations[23,35] and 4) a particularly thin biofilm composed of Gram negative bacteria have been reported on root surfaces of LAgP subjects.[3,92]

Is LAgP a distinct entity?

Our current literature review suggests that there are phenotypic differences between CP and LAgP that include; age of onset, location of initial lesions, and rate of progression (based on limited exposure because of age). There are several hints as described above that suggest microbiologic, pathophysiologic and genetic differences between CP and LAgP. However, it is premature to point to

TABLE 4 The various genes or loci harboring minor allele frequencies (polymorphisms) significantly associated with aggressive periodontitis

Reference	Ethnicity	Gene (alias)*	Encoded protein or proposed function	Chromosome	GWAS or CGA	Significant rs number(s)
Suzuki *et. al.*[53]; 2004	Japanese	*COL1A1*	Collagen Type I Alpha 1 Chain	17	CGA	48615234[e]
Suzuki *et. al.*[53]; 2004	Japanese	*COL4A1*	Collagen Type IV Alpha 1 Chain	13	CGA	109661461[e]
Suzuki *et. al.*[53]; 2004	Japanese	*IL6ST*	Interleukin-6 Signal Transducer	5	CGA	55215302[e]
Nibali *et. al.*[54]; 2006	British	*CYBA* (*NADPH oxidase*)	NADPH Oxidase 4	11	CGA	rs4673
Nibali *et. al.*[55]; 2009	Caucasian	*IL6*	Interleukin-6	7	CGA	rs2069825[c] rs4719714[c]
Gürkan *et. al.*[56]; 2009	Turkish	*AGT*	Angiotensinogen	1	CGA	rs699
Schaefer *et. al.*[57]; 2009	German	*CDKN2B-AS1 (ANRIL)*	Antisense noncoding RNA in the INK4 locus (the regulatory region influences the activity of CAMTA1)	9	CGA	rs1333048 rs1333042 rs2891168
Ernst *et al.*[58]; 2010	German and Northern Irish	*CDKN2B-AS1 (ANRIL)*	Antisense noncoding RNA in the INK4 locus (the regulatory region influences the activity of CAMTA1)	9	CGA	rs1333048 rs496892 rs2891168
Schaefer *et. al.*[59]; 2010	German and Dutch	*PTGS2* (*COX2*)	Prostaglandin-Endoperoxide Synthase 2 (Cyclooxygenase-2)	1	CGA	rs6681231[h]
Schaefer *et. al.*[60]; 2010	German and Dutch	*DEFB1*	Beta-Defensin-1	8	CGA	rs1047031
Schaefer *et. al.*[61]; 2010	German and Dutch	*GLT6D1*	Glycosyltransferase-6 domain 1	9	GWAS	rs1537415 rs11103111 rs1333239 rs7466817 (rs1537415, rs11103111, rs1333239, rs7466817) (rs11103111, rs1333239, rs7466817, rs1537415)
Scapoli *et. al.*[62]; 2011	Italian	*FCGR2A*	Fc gamma Receptor IIa	1	CGA	rs1801274
Scapoli *et. al.*[62]; 2011	Italian	*IL6*	Interleukin-6	7	CGA	rs4719714
Scapoli *et. al.*[62]; 2011	Italian	*SEPSECS* (*SEPS*)	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase	15	CGA	rs11327127
Scapoli *et. al.*[62]; 2011	Italian	*TNFRSF1B* * *IL2*[f]	TNF Receptor Superfamily Member 1B * Interleukin-2	1 * 4	CGA	rs1061622 * rs2069762
Scapoli *et. al.*[62]; 2011	Italian	*TNFRSF1B* * *IL6*[f]	TNF Receptor Superfamily Member 1B * Interleukin-6	1 * 7	CGA	rs1061622 * rs2069825

(Continues)

TABLE 4 (Continued)

Reference	Ethnicity	Gene (alias)*	Encoded protein or proposed function	Chromosome	GWAS or CGA	Significant rs number(s)
Scapoli *et. al.*[62]; 2011	Italian	*SEPSECS* (*SEPS*) * *IL2*[f]	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase * Interleukin-2	15 * 4	CGA	rs11327127 * rs2069762
Scapoli *et. al.*[62]; 2011	Italian	*IL-6* * *IL18*[f]	Interleukin-6 * Interleukin-18	7 * 11	CGA	rs2069825 * rs1946518
Scapoli *et. al.*[62]; 2011	Italian	*IL-6* * *IL1*[f]	Interleukin-6 * Interleukin-18	7 * 11	CGA	rs4719714 * rs1946518
Scapoli *et. al.*[62]; 2011	Italian	*TNFRSF1B* * *TNF* (*TNF-Alpha*)[f]	TNF Receptor Superfamily Member 1B * Tumor necrosis factor-Alpha	1 * 6	CGA	rs1061622 * rs1799964
Scapoli *et. al.*[62]; 2011	Italian	*IL-6* * *IL-4* (*IL-4STR*) [f]	Interleukin-6 * Short tandem repeat polymorphism within interleukin-4	7 * 5	CGA	rs2069825 * rs8179190
Scapoli *et. al.*[62]; 2011	Italian	*FCGR2A*, *IL6*, *IL-4* (*IL-4STR*)[f]	Fc gamma Receptor IIa, Interleukin-6, Short tandem repeat (STR) polymorphism within Interleukin-4	1, 7, 5	CGA	rs1801274 rs36215817 rs8179190
Scapoli *et. al.*[62]; 2011	Italian	*SEPS*, *IL2*, *IL6*, *IL-4* (*IL-4STR*)[f]	Sep (O-Phosphoserine) TRNA:Sec (Selenocysteine) TRNA Synthase, Interleukin-2, Interleukin-6, Short tandem repeat (STR) polymorphism within Interleukin-4	15, 4, 7, 5	CGA	rs11327127 rs2069762 rs36215817 rs8179190
Scapoli *et. al.*[62]; 2011	Italian	*IL2*, *IL6*, *IL-4* (*IL-4STR*), *FCGR2A*[g]	Interleukin-2, Interleukin-4, Interleukin-6, Short tandem repeat (STR) polymorphism within Interleukin-4, Fc gamma Receptor IIa	4, 7, 5, 1	CGA	rs2069762 rs36215817 rs8179190 rs1801274
Schaefer *et. al.*[63]; 2011	German, Dutch	*CDKN2B-AS1* (*ANRIL*)	Antisense noncoding RNA in the *INK4* locus (the regulatory region influences the activity of *CAMTA1)*	9	CGA	rs3217992 rs518394 rs1360590 rs11790231[d]
Martelli *et. al.*[64]; 2012	Italian	*IL18*	Interleukin-18	11	CGA	(-137)[e] (-607)[e]
Bochenek *et. al.*[65]; 2013	German, Austrian and Dutch	*CAMTA1*	Calmodulin Binding Transcription Activator 1	1	CGA	rs17030881 rs10864294
e Silva *et. al.*[66]; 2013	Brazilian	*CTLA-4*	Cytotoxic T-lymphocyte Associated Protein 4	2	CGA	rs231775
e Silva *et. al.*[66]; 2013	Brazilian	*CD28*	CD28 Molecule	2		rs3116496
Schaefer *et. al.*[67]; 2013	Dutch, German-Austrian	*IL10*	Interleukin-10	1	CGA	rs61815643[d] rs6667202

(Continues)

TABLE 4 (Continued)

Reference	Ethnicity	Gene (alias)*	Encoded protein or proposed function	Chromosome	GWAS or CGA	Significant rs number(s)
Yang *et. al.*[68]; 2013	Chinese	*TNF* (*TNF-Alpha*)	Tumor Necrosis Factor-Alpha	6	CGA	rs1800629
De Jong *et. al.*[69]; 2014	German	*SLC23A1*	Solute Carrier Family 23 Member 1 (Vitamin C transporter)	5	CGA	rs6596473
Schaefer *et. al.*[70]; 2014	German	*IL2RA*	Interleukin-2 Receptor Subunit Alpha	10	CGA	rs4625363
Schaefer *et. al.*[70]; 2014	German, Dutch	*PRDM1*	PR Domain 1	6	CGA	rs6923419 rs6924535[h]
Schaefer *et. al.*[70]; 2014	Dutch	*IRF5*	Interferon Regulatory Factor 1	5	CGA	rs56303857 imm_7_128356335[e]
Gao *et. al.*[71]; 2015	Chinese	*APOE*	Apolipoprotein E	19	CGA	rs429358
Gao *et. al.*[71]; 2015	Chinese	*LRP5*	Low Density Lipoprotein Receptor-Related Protein 5	11	CGA	rs312016 rs682429
Hashim *et. al.*[72]; 2015	Sudanese	*GLT6D1*	Glycosyltransferase-6 domain 1	9	CGA	rs1537415
Schaefer *et. al.*[73]; 2015	German, Dutch and Irish	*TGFBRAP1*	Transforming Growth Factor Beta Receptor Associated Protein 1	2	CGA	rs2679895
Schaefer *et. al.*[73]; 2015	German and Dutch	*PLG* (*PLASMINOGEN*)	Plasminogen	6	CGA	rs4252120
Song *et. al.*[74]; 2016	Chinese	*DBP*	Vitamin D-binding protein	19	CGA	rs17467825, rs17467825 + rs4588[i]

Abbreviations: GWAS = Genome wide association study; CGA = Candidate gene approach

* Current gene names (previous nomenclature, i.e., alias) based on GeneCards® www.genecards.org

[a]Significantly in both LAgP (n = 146) and GAgP cohort (n = 159)

[b]Significantly in a subgroup of GAgP (n = 130) vs. controls (n = 339)

[c]Only significantly in a subgroup of LAgP (n = 24 patients) vs. controls (n = 144)

[d]Significantly associated SNP only in the Dutch cohort

[e]rs number not identified. Therefore chromosome position, imm_number or polymorphism is given

[f]The combination of minor alleles for both genes also appears to be associated with AgP

[g]The nonparametric approach pointed to five markers; the potential role of *IL-4-STR*, *IL-2*, *SEPS* already highlighted by logistic regression, is confirmed by Multifactor Dimensionality Reduction algorithm analysis. Furthermore, a significant involvement of *FCGR2A* and *IL-6* variants was also identified

[h]Haplotype tagging SNP for rs20417

[i]Significantly associated haplotype

TABLE 5 Bacteriology and biomarkers in generalized aggressive periodontitis subjects

Author; year	Country	Number of subjects	Marker	Method of assessment	Multiple sites	Multiple times	Control yes/no	Assessments
Miura *et. al.*; 2005	Japan	GAgP 18	Bacteria	Multiple	Multiple	-	Yes	*Aa* and *Tannerella* co-exist with *Pg*
Emingil *et. al.*; 2005	Turkey	GAgP 26	EMAP and MIP-1	GCF	1 Site	1 Time	Yes	EMAP-II higher volume
Ximenez *et. al.*; 2006	Mexico	GAgP 19	Bacteria	DNA/DNA; Multiple	Multiple	1 Time	Yes	*Pg*, *Tannerella* and *P. nigrecens*
Gurkan *et. al.*; 2006	Turkey	GAgP 30	TGF b	GCF	1 Site	1 Time	Yes	TGF b level higher in GAgP and CP
Bostanci *et. al.*; 2007	Turkey	GAgP 26	RANKL and OPG	GCF	1 Site	1 Time	Yes	Ratio higher in GAgP and CP
Faveri *et. al.*; 2009	Brazil	GAgP 10	Bacteria	16S rRNA/Multiple	3 Sites	-	No	*Selenomonas sp.*
Turkoglu *et. al.*; 2010	Turkey	GAgP 18	Adrenomedullin (ADM) & HNP 1–3	GCF	1 Site	1 Time	Yes	ADM elevated in GAgP and CP
Casarin *et. al.*; 2010	Brazil	GAgP 40	IL-1b, INF g, IL-10 and PGE 2; *Aa* and *Pg*	GCF	2 Sites	1 Time	No	*Aa* and *Pg* higher in GAgP and IgG to *Aa* and *Pg* lower in GCF
Teles *et. al.*; 2010	Brazil	GAgP 31	Eight cytokines; DNA/DNA	GCF and bacteria	14 Sites	1 Time	Yes	IL-1b to IL-10 ratio higher in GAgP subjects and also > in *Aa* and *Capno*
Goncalves *et. al.*; 2012	Brazil	GAgP 15	Bacteria	HOMIM	Multiple	I Time	Yes	*Aa*, *C. hominis*, *Peptostrepto*, *P. alactolyticus*
Shaker and Ghallab.; 2012	Egypt	GAgP 25	IL-17 and IL-11: Red complex by PCR	GCF and Bacteria	4 Sites	1 Time	Yes	IL-17 increased and IL-11 decreased; *Aa* elevated in GAgP
Heller *et. al.*; 2012	Brazil	GAgP 75	Bacteria	DNA/DNA/Multiple	Multiple	1 Time	No	*Eubacterium nodatum*
Ertugrul *et. al.*; 2013	Turkey	GAgP 20	B2microglobula A2 macroglob	GCF	4 Sites	1 Time	Yes	Both higher in GAgP
Lourenco *et. al.*; 2014	Brazil	GAgP 24	Bacteria	HOMIM	Multiple	1 Time	Yes	*Aa*, *C. hominis*, *Peptostrepto*, *P. Alactolyticus*
Baltacioglu *et. al.*; 2014	Turkey	GAgP 30	TOS, RANKL/OPG	GCF	10 Sites	1 Time	Yes	RANKL/OPG ratio higher in GAgP
Sánchez *et. al.*; 2015	Argentina	GAgP 30	Bacteria	PCR	*Aa* and *Pg*	1 Time	Yes	*Aa* associated with GAgP
Elabdeen *et. al.*; 2015	Sudan	GAgP 19	Bacteria	DNA/DNA	Multiple	1 Time	Yes	*Eubacterium yurii* and *E. nodatum*
Toyman *et. al.*; 2015	Turkey	LAgP 23	IL-1b, MMP-3, t-PA, PAI 2	GCF	6 Sites	1 Time	Yes	All higher in CP and GAgP

Inconsistent Study Factors: Age, disease definition, randomization, enrollment at school or clinic? Site of collection? Single sites and single collections vs multiple sites and multiple collections? Method of collection? Method of identification and analysis?

Abbreviations: GCF = Gingival crevicular fluid; GAgP = Generalized aggressive periodontitis; CP = Chronic periodontitis; EMAP = Endothelial-monocyte-activating-protein; MIP-1 = macrophage inflammatory protein 1; TGF b = Transforming growth factor beta; RANKL = Receptor activator of nuclear factor kappa-B ligand; OPG = Osteoprotegerin; ADM = Adrenomedullin; HNP 1–3 = Human neutrophil peptide; IL-1b = Interleukin 1 beta; INF g = Interferon gamma; PGE 2 (Prostaglandin E 2); MMP-3 = Matrixmetalloproteinase-3; t-PA = Tissue plasminogen activator; PAI 2 = plasminogen activator inhibitor 2; B2 microglob = Beta 2 microglobulin; A2 macroglob = A2 macroglobulin; TOS = Total oxygen status; *Aa* = *Aggregatibacter actinomycetemcomitans*; *Pg* = *Porphyromonas gingivalis*; *Pi* = *Prevetolla intermedia*; LAgP = Localized aggressive periodontitis

pathophysiologic differences between these two entities until these data are ascertained in larger, more diverse, better-defined and controlled populations. This can only be resolved if better definitions of disease are provided.

Overall, periodontitis is defined as an inflammatory disease of the supporting tissues around teeth, which can cause irreversible loss of periodontal ligament, alveolar bone, tooth mobility and ultimately, if left untreated, tooth exfoliation. The disease is caused by an aberrant immune response (immunologic intolerance) to resident microbial communities on the teeth, which extend into the submarginal region. Normally, and for most people, the host lives in symbiosis with this biofilm. Often a nonprogressive gingivitis develops (perhaps needed to train the immune system to induce tolerance). However, an individual may convert from a symbiotic microbial and immune state to an aberrant and dysbiotic microbiome and host response. These exaggerated dysbiotic host inflammatory reactions are destined to result in the destruction of the periodontal tissues and can be episodic in nature and nonlinear and disproportionate to an assorted collection of risk factors.[93]

From a pathophysiologic point of view both LAgP and CP have a common end result, the loss of bone and disorientation of the attachment apparatus results from disruption in homeostatic balance between deposition and resorption of bone.[94] Initially identified as a noninflammatory condition (termed periodontosis) it is now clear that both LAgP and CP are entities resulting from inflammatory responses to a biofilm starting point, which results in bone loss. However, overall it is clear that LAgP demonstrates a unique phenotype but a more in depth understanding of the differences among events leading up to bone loss in LAgP as compared to CP need to wait for a more exacting definition of early events.

Roadblocks toward a better understanding

A major roadblock in the current LAgP definition is its failure to identify the early time-dependent issues related to disease. Because a gold standard case definition is still lacking it behooves us to develop the optimal way of describing the disease in each of its stages.

Classifications are used to assess clinical conditions in an individual and in groups of individuals. Diagnosis is used to guide treatment on an individual level. Case definitions are used to differentiate groups of individuals who share similar features with regard to causes, prognosis, and response to treatment.[95] Classification is difficult if a gold standard is lacking as in the case of LAgP.

Every disease has time dependent events that help define disease initiation and progression. A classification scheme that can effectively incorporate early events in disease progression can provide information that could reveal important pathophysiologic events. Early detection typically results in discovery of causal factors and cost effective preventive interventions. Use of a time dependent approach could unravel the initiating microbial causes and host response elements related to LAgP.

Several epidemiologists have focused their attention on the multifactorial approach to disease that specifies that; 1) a single component is rarely a sufficient cause of disease, 2) host susceptibility may play a vital role in disease initiation and development, and 3) a harmless agent could produce disease in an immune-compromised individual.[96] In this approach three overlapping issues are of paramount importance in disease development that include; time, place, and person.

"Time" relates to the extent of exposure to an agent. In the case of LAgP, the more disease seen in younger individuals indicates that either the initiating component or the host response to that component permits disease to occur at a more rapid rate. With respect to bacteria, time relates to the incubation period, or, the time required for the biofilm to reach a critical mass that challenges the host (this can include a broad spectrum of species and bacterial products, e.g., LPS, leukotoxin, other toxins, antigenic proteins). With respect to the host response, time relates to fluctuation in host resistance or susceptibility often determined by genetic and epigenetic risk factors as well as life style and life events that modulate both innate and acquired immunologic responses, effectively determining the immune fitness.[97]

"Place" typically relates to an area of increased risk. In our case, place relates to geographic location (Africa, Middle East, North America, etc.) as well as topographic location (i.e., tooth surface). Geography translates into areas with lower socio-economic status (diet or living conditions, greater exposure to toxins because of crowding), and homogeneity with respect to genetic status (i.e., immune resistance or susceptibility because of lack of population diversity). Although we do have some evidence that the JP2 strain of *A. actinomycetemcomitans* evolved as an exogenous agent from North Africa most of the infections we see are related to members of the indigenous flora.[98] Also, relevant in our case, place refers to the distribution of the disease in the oral cavity, specifically on the interproximal surface of molars and incisors.

"Person" typically relates to the individual who possesses either inherited or acquired risk factors (i.e., lifestyle risk factors related to ethnic and socioeconomic factors) that make him or her more vulnerable to disease. Age, gender, and race are all considered. Of the components described, typically age has the highest significant person feature, but gender and race also apply. Age relates to the opportunity for exposure, latency of incubation period and physiologic responsiveness or lack thereof. This translates into individual susceptibility. Gender could be especially meaningful in pubescent periods when different hormonal products could influence immune responsiveness or the lack thereof. Race could imply genetic susceptibility.

CONSIDERATIONS WHEN REDEFINING AGGRESSIVE PERIODONTITIS

Any new definition should be based on the; a) age of the subject, b) location of lesions, c) extent of disease (stages). The first diagnosis could be in; 1) childhood (prepubertal), 2) adolescence (puberty), and 3) early adulthood (postadolescence).

The definition of disease in addition to age could include; a) the location of the lesion and the stage or extent of disease (one, two or three or more teeth). This staged approach would signify the severity of disease (i.e., one tooth is less severe than two teeth, etc.). This staged approach would also enable the practitioner and researcher to identify the "burned out" or contained disease (i.e., a disease confined to one tooth or two teeth etc.). In its simplest form the staged definition could be categorized as Stage 1, a disease limited to one tooth, Stage 2 limited to two teeth, Stage 3 limited to three teeth (molars and incisors), and Stage 4 the classic Löe and Brown definition of disease.[99]

To prevent confusion with trauma or other noninfectious disease initiators, a diseased tooth would be defined as having proximal attachment loss but would not be based on buccal or lingual recession.

This staged definition would be helpful to examine microbial initiators, host-response elements, and pathophysiologic changes. It would also be helpful in genetic distinctions between the classic Löe and Brown disease and early stage disease that is contained. It should be especially helpful in establishing the multi-causal nature of this localized form of periodontal disease in young individuals.

CONCLUSIONS AND FUTURE DIRECTIONS

In the past, characterizations of the aggressive forms of periodontitis have been limited by; 1) the low number of individuals who have this form of disease, coupled with 2) inconsistency resulting from the broad definitions proposed in the past. Choosing a new definition should not only be based on clinical observations, like the usual medical and dental history, clinical charting, and radiographic examinations, but also it should focus on obvious phenotypic indictors such as age of onset, location of lesions in defined populations.

A new definition of aggressive periodontitis has been suggested; 1) to break the cycle of inertia that has occurred in the last 17 years, 2) to catch the disease in its earliest stages, and 3) to place a greater emphasis on the multi-causal model of disease. Factors such as host response elements, consortia of microorganisms, and many other confounding factors could be assessed for their role in the earliest stages of disease within a new definition. Using these parameters the multiplicity of inherited genes of minor effect can be related to the early stages of disease. To illustrate this point, inheritance of genes that lead to a hyper-inflammatory response may have a greater impact on the disease as it becomes the more generalized Löe and Brown form of disease. Moreover, a new definition could provide a better understanding of the genes involved in containing or limiting the extent of disease to its earliest stages (i.e., burned out form). However, substantiating this hypothesis and the pathophysiologic conditions that follow these parameters, will require populations that contain larger sample sizes using, as we suggest, a more restrictive definition.

The facts that (1) the phenotypic characteristics of what we have called LAgP, show very often alveolar bone loss at first molars as the initial site of destruction; and that (2) this disease occurs typically in an adolescent descending from Africa or the Middle East with strong hints that *A. actinomycetemcomitans* is part of the microbiome, suggests that longitudinal assessments are potentially possible. The fact that the disease we are attempting to define could be considered as an orphan disease (a disease affecting fewer than 200,000 individuals in the United States), that is also silent (presenting symptoms that are not noticed by the individual) makes it even more imperative that we make a vigorous attempt to create a restrictive definition so that we can catch it in its earliest stages.

In conclusion, the emergence of highly sophisticated and reproducible technologies has allowed us to use minimal amounts of plaque, saliva, and serum or crevice fluid to survey many microbiologic, host, and genetic factors simultaneously. In this manner disease related comparisons can be made in a relatively unbiased fashion. A new case definition helps to identify the earliest stages of disease. This should enable significant progress in diagnosis, prevention, and treatment of this aggressive form of periodontal disease.

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TO CLINICIANS

We hope this new definition will permit a more constrained definition that will lead to earlier and more rapid diagnosis that will provide more consistent and better treatment results.

TO RESEARCHERS

We hope this new definition will push the boundaries towards longitudinal cohort studies enrolling subjects in the earliest stages of disease that use the burgeoning research technology available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

Mean annual attachment, bone level, and tooth loss: A systematic review

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Background: Rate of progression of periodontitis has been used to inform the design of classifications of periodontal diseases. However, the evidence underpinning this topic is unclear and no systematic review has yet been conducted.

Objectives: The focused question for this systematic review was: in adults, what is the progression of periodontitis in terms of clinical attachment loss, radiographic bone loss, and tooth loss?

Data sources: Highly sensitive electronic search was conducted for published data in MEDLINE, EMBASE, LILACS, and unpublished grey literature in OpenGrey up to February 2016. Reference lists of retrieved studies for full-text screening and reviews were hand-searched for potentially eligible studies.

Study eligibility criteria and participants: Prospective, longitudinal observational studies with follow-up of at least 12 months and presenting data on the primary outcome, change in clinical attachment level, in adults (age ≥18 years). Secondary outcomes, tooth loss and bone level change, were only assessed in studies reporting the primary outcome. Studies investigating specific disease populations or only on treated periodontitis patients were excluded.

Study appraisal and synthesis methods: Risk of bias and methodology were assessed using the Newcastle-Ottawa Scale with two additional questions on security of outcome assessment. Studies were pooled by abstracting or estimating mean annual attachment or bone level change and annual tooth loss. Random effects meta-analysis was conducted with investigation of effect of potential modifiers where possible.

Results: A total 11,482 records were screened for eligibility; 33 publications of 16 original studies reporting on more than 8,600 participants were finally included as eligible for the review. The studies represented populations from both developing and developed economies. Mean annual attachment loss was 0.1 mm per year (95% CI 0.068, 0.132; I^2 = 99%) and mean annual tooth loss was 0.2 teeth per year (95% CI 0.10, 0.33; I^2 = 94%). Observational analysis of highest and lowest mean attachment change quintiles suggested substantial differences between groups with minimal annual change in the lowest quintile and an average deterioration of 0.45 mm mean

attachment loss per year in the highest group. This value increased to 0.6 mm per year with periodontitis alone. There was surprisingly little effect of age or gender on attachment level change. Geographic location, however, was associated with more than three times higher mean annual attachment loss in Sri Lanka and China (0.20 mm, 95% CI 0.15, 0.27; I^2 = 83%) vs North America and Europe (0.056 mm, 95% CI 0.025, 0.087; I^2 = 99%) P < 0.001.

Limitations: There were a limited number of studies (N = 16), high variability of design in key study components (sampling frames, included ages, data analyses), and high statistical heterogeneity that could not be explained.

Conclusions: Within the limitations of the research, the data show that mean annual attachment level change varies considerably both within and between populations. Overall, the evidence does not support or refute the differentiation between forms of periodontal diseases based upon progression of attachment level change.

KEYWORDS

chronic periodontitis, disease progression, epidemiology, periodontal attachment loss, periodontal diseases, systematic review

Periodontitis is characterized by non-reversible tissue destruction resulting in progressive attachment loss, eventually leading to tooth loss.[1] Severe periodontitis is the sixth most prevalent disease of mankind[2] and is a public health problem since it is so widely prevalent and causes disability, impaired quality of life, and social inequality.[3,4] The prevalence of periodontitis remains high globally, although periodontal health has shown signs of improvement in representative national and regional epidemiologic surveys in recent decades in countries with high incomes.[5,6] However, the most severe forms of periodontitis have remained constantly high, affecting approximately 10% of surveyed populations.[6–8]

Understanding the nature of the disease is crucial to research and development of more effective health promotion, disease prevention, and treatment. For instance, if there are different forms of periodontitis, should management strategies be tailored to the variants? It is unclear whether periodontitis comprises a group of distinct diseases (chronic periodontitis, aggressive periodontitis)[9,10] or a syndrome with a range of presentations.[11,12] In attempting to address these issues, the two most common criteria used to evaluate similarities and differences during the last half century or more of periodontal disease classification have included age of onset of disease and rate of progression. The word "rate" is used here, not in the usual epidemiologic sense of proportion of people affected by a condition, but instead in the sense of how quickly the disease deteriorates. Age of onset is not the topic of this review and will not be addressed further, although is investigated by another review.[13]

Rate of progression could be important as a distinguishing criterion of forms of periodontitis, and there is general consensus in most disease definitions that the primary measure of the condition is attachment level change.[14] Rapid disease progression was a criterion for periodontosis nearly half a century ago.[15] Rate of progression became embedded in the identity of certain classifications with labels such as rapidly progressive periodontitis and aggressive periodontitis.[9] However, even with promotion of this criterion to a defining characteristic, there was widespread unease about whether it was truly distinctive.[9,10,12,16,17]

Clearly, much uncertainty remains about the progression of attachment loss. Systematic reviews are designed to assemble, appraise, and make sense of the totality of the evidence[18] as far as possible. No previous systematic review has investigated rate of progression of attachment loss; therefore, the aim of this study was to critically and comprehensively evaluate the evidence for progression of periodontitis and associated determinants of progression.

METHODS

Focused question

In adults, what is the progression of periodontitis in terms of clinical attachment loss, radiographic bone loss, and tooth loss? The reason for limiting the investigation to adults, i.e., persons aged ≥18 years was a request to constrain the investigation in this manner to avoid overlap with a separate investigation into periodontal diseases in younger individuals for the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.[13]

Objectives:

- To investigate the evidence for progression of periodontitis, defined as change in attachment level during a period of 12 months or more – What is the evidence for different mean values of progression?

- Which risk factors are associated with different mean values of progression of periodontitis?
- Which etiologic factors are associated with different mean values of progression of periodontitis?

The protocol was registered prior to commencing the study on the PROSPERO database: CRD42016035581 (www.crd.york.ac.uk/PROSPERO). The manuscript has been prepared following the PRISMA statement for reporting of systematic reviews.[19]

Population

Included were studies on periodontally untreated adults aged ≥18 years. Studies including both adults and younger individuals without distinction were eligible, and it was planned to stratify for this criterion. The plan was to stratify data into studies based on baseline status of periodontitis populations, non-periodontitis populations, and mixed/unclear populations if available. Studies with participants in continuous periodontal maintenance after periodontal therapy were excluded.

Exposure

The primary outcome measure was clinical attachment level (CAL) change (or variants including relative attachment level change). All probing methods (manual, controlled force, etc.) were included. Change of probing depth (PD) was not considered. Secondary outcome measures were only included for studies which first presented attachment level change. For radiographic bone loss, all methods (film, digital, subtraction, customized film holders) were eligible. Tooth loss data were included irrespective of whether the cause of tooth loss was reported. Clearly, tooth loss might have been related to factors other than periodontitis.

Disease determinants, risk factors, and etiologic agents

The association of attachment level progression with disease determinants was recorded where available, including gender, age, socioeconomic position, genetics, lifestyle, health behaviors, nutritional, and microbiologic factors. Wherever possible, the quality of measurement of the determinant/exposure was assessed (see below).

Study follow-up duration

Any study duration or follow-up interval of at least 12 months was included. Data were recorded for all follow-ups, and the longest follow-up available was selected.

Types of studies

The aim was to be inclusive of research, and there are many possible approaches to designing eligibility criteria for this research question. Considered as eligible was any longitudinal, prospective, observational study with a follow-up of ≥12 months that assessed changes in CAL (or variants including relative attachment level) in adult individuals (≥18 years of age). Secondary outcomes were assessed only for those studies first reporting data for CALs and comprised radiographic bone loss, tooth loss, and risk factors associated with clinical attachment loss. Intervention studies, cross-sectional studies, and reviews were excluded. Included was any prospective longitudinal study whether population- or institution-based. Studies on specific disease populations, such as diabetes, were excluded because the aim of the review was to establish evidence as far as possible for periodontitis in general populations. Clearly, within population studies, accurate general health status might not be known. In addition, studies exclusively reporting data for treated periodontitis patients would not represent overall population values.

Inclusion Criteria:

- Prospective, longitudinal studies.
- Duration of follow-up at least 12 months.
- Adults ≥18 years of age. Studies that also included younger participants within a combined data set were included although data was stratified separately.
- Study reporting progression of periodontitis using attachment level assessments.
- Periodontally healthy, untreated periodontitis or participants not part of periodontitis treatment investigations. This was set broadly as it was anticipated that population studies would not report detailed periodontal treatment status of participants.
- Tobacco use was not an eligibility criterion. Population studies would include both tobacco and non-tobacco users; it was planned to analyze the effect on periodontal health if data were available.

Exclusion Criteria:

- Studies investigating solely specific systemic disease populations, e.g., diabetes.
- Experimental studies testing the effect of interventions on periodontitis.
- Cross-sectional or retrospective studies.
- Studies only recruiting participants for periodontitis treatment or previously treated for periodontitis.

Search strategy

A highly sensitive search was conducted. Electronic databases (MEDLINE via OVID, EMBASE via OVID, LILACS) were searched using a string of medical subject headings and free-text terms (see Appendix 1 in online *Journal of Clinical Periodontology*). OpenGrey was searched for unpublished, grey literature. The search strategy was developed with author ADI, a medical librarian with extensive experience in designing searches for systematic reviews. The search strategy was first designed for the MEDLINE database and was then modified appropriately for the other databases searched. There were

no language or publication date restrictions. Reference lists of all studies included for full-text screening and previous reviews were searched for missing records. The search results were downloaded to a bibliographic database and duplicate records were removed.

Study selection

Titles and abstracts (if available) of the studies identified in the searches were screened by two of the review authors (NG and FM), in duplicate and independently. Subsequently, the full text of all publications appearing to meet the inclusion criteria or for which there was not sufficient information in the title and abstract to make a decision, were obtained. At this first stage, any study considered as potentially relevant by at least one of the reviewers was included for the next screening phase. Subsequently, the full-text publications were also evaluated in duplicate and independently by the same review examiners. The examiners were calibrated with the first 10 full-text, consecutive publications. Any disagreement on the eligibility of studies was resolved through discussion between both reviewers until consensus was reached or through arbitration by a third reviewer (IN). All potentially relevant studies that did not meet the eligibility criteria were excluded and the reasons for exclusion noted. Publications in languages other than English, Greek, Portuguese, or Spanish were sent to an interpreter with clear instructions on inclusion and exclusion criteria. Interexaminer agreement following full-text assessment was calculated via kappa statistics. In addition, the final list of eligible studies was circulated to all members of the review group and the workshop chairmen for evaluation of possibly missing studies.

There were several studies which accounted for more than one publication since it was common to find publications investigating the same population at different follow-up intervals and/or secondary analysis of the same data. For this reason, a decision was made to pool together all relevant publications for any given principal study. FM and NG assessed the pooled studies independently and included only those reporting data on the primary and/or secondary outcomes assessed in this review for the original study sample. Disagreement on the selection of the studies was resolved in the same manner as in previous stages.

Unclear or missing data

Regarding studies for which a clear decision on eligibility could not be made following full-text assessment or when there were missing data, the corresponding authors were contacted up to twice, one month apart, to seek the information needed to aid the final decision. In the absence of response, and/or if the data could not be used, these studies were excluded from the final review.

Data extraction and management

Study details were collected using a form specifically designed for data extraction for this review and which was first piloted in a small number of studies. Two of the review authors (NG and FM) independently extracted all relevant data from all included studies except publications written in any language other than English, Greek, Portuguese or Spanish. In this case, data extraction (and quality assessment) was completed by interpreters who received clear instructions on how to collect the data using the data collection form. Any disagreements were resolved through debate and consensus or through assessment of a third reviewer (IN).

The following study details were extracted:

- Type of study
- Number of centers
- Sample frame (e.g., community, university)
- Age of participants
- Periodontal status
- Definition of periodontitis cases
- Duration of follow-up
- Type of attachment level measurement (e.g., probing attachment level (PAL), CAL, Relative attachment level (RAL), etc.)
- Method of attachment level measure (e.g., manual probe, pressure sensitive probe, etc.)
- Frequency of CAL measurement
- Method for radiographic assessment of bone loss
- Cause of tooth loss reported in study (yes/no)
- Risk factors reported in study
- Number of participants (baseline/last follow-up)
- Outcomes
    - Mean attachment level change
    - Mean attachment level change stratified by subgroups
    - Mean radiographic bone loss
    - Mean radiographic bone loss stratified by subgroups
    - Mean tooth loss
    - Mean tooth loss stratified by subgroups

Quality assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale, appropriately modified (see Appendix 2 in online *Journal of Clinical Periodontology*), because it is the mostly widely used tool for epidemiologic studies.

Other domains of methodologic quality comprised:

- Security of measurement of attachment level. Studies were assessed as secure if the method involved appropriate training and calibration of examiners, insecure if training was absent or inadequate or unclear if unreported.
- Security of assessment of bone level change. Studies were assessed as secure if the method involved standardized positioning of the radiographs, e.g., cephalostat or customized film holders, insecure if standardization was absent or inadequate or unclear if unreported.

Data synthesis

Data were first entered into evidence tables stratified by study design. Decisions on which studies to include in a meta-analysis were

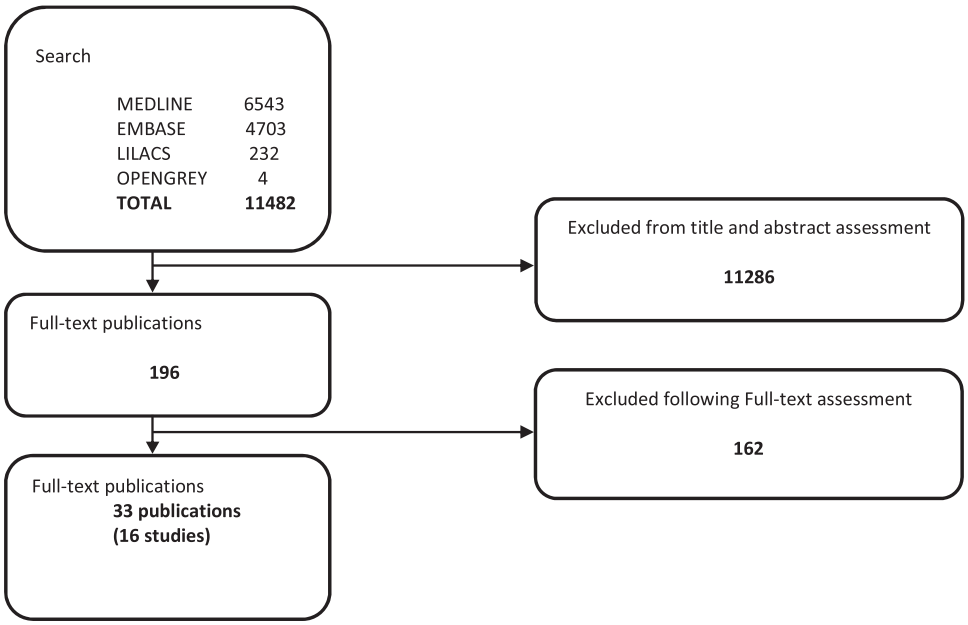

FIGURE 1 Flow chart of inclusion of studies

made depending on the similarity of chief study characteristics related to each research question, i.e., mean progression of periodontitis and association of progression with disease determinants.

When a study provided the mean progression at a known time point, it was assumed that the progression was constant with time in order to estimate the mean progression rate, i.e., the mean progression per year. When a study only provided the relevant progression information for subgroups (e.g., gender or age groups), the mean annual progression for the study was estimated as a weighted mean, with the weights being inversely proportional to the variance if the latter could be calculated or directly proportional to the frequency otherwise. The same approach was used when estimating the mean annual progression for each of the three age subgroups, namely age <30, 30–50, and >50 years. Assuming that the data were normally distributed in each study, the lowest and highest quintiles (i.e., the 20th and 80th percentiles) of annual progression were calculated for each study from its mean and standard deviation.

Statistical heterogeneity of mean annual progression between relevant studies was assessed using both the chi-square test and the I^2 measures. The I^2 was interpreted according to the guidance of the Cochrane Handbook:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

If meta-analysis appeared appropriate, it was used to provide an overall estimate of the mean annual progression, with its 95% confidence interval (CI), using a random-effects approach if there was evidence of statistical heterogeneity and a fixed-effects approach otherwise. Statistical heterogeneity was anticipated, and it was planned to investigate the contribution of risk of bias, security of disease progression method, and type of population, i.e., initially healthy or periodontitis. Similar methods were planned to assess the association between mean progression and potential modifiers. However, the available data were limited for meta-analysis, allowing only few exploratory analyses. For these analyses of association, a chi-square test of heterogeneity between the overall mean annual progression for each subgroup of the potential modifier (e.g., males and females) was performed to determine the effect of the factor (i.e., gender, geographic location, or age group) on the mean annual progression. Statistical analyses were conducted by AP, a biostatistician experienced in systematic reviews and meta-analysis. A significance level of 0.05 was used for all statistical hypothesis tests. Data were analysed using appropriate software.*

RESULTS

Search

A total of 11,482 potentially eligible records were found through the sensitive searches. A total 11,286 publications were excluded following review of the titles and abstracts and finally the full publications of 196 records were retrieved (Figure 1).

Interexaminer agreement at full-text screening was excellent (kappa score = 0.756).[20] Following careful assessment of the full papers, 116 records were excluded. Of the remaining 80 records, 4 original studies accounting for only one publication were included in the final review, while 76 publications were nested into 12 different original studies which had more than one publication (e.g., different follow-up intervals). Finally, 29 of the nested publications were also included which resulted in a total of 33 publications of 16 studies which were included for data extraction and quality assessment. The reasons for exclusion of

*Stata Statistical Software, Release 14, College Station, TX.

all studies that were not included at the stage of full-text review were recorded (see Appendix 3 in online *Journal of Clinical Periodontology*).

Study characteristics

Location

The following study geographic locations (supplementary Table 1 in *online Journal of Clinical Periodontology*) were found; two studies from Brazil,[21,22] two from China,[23–28] one from Germany,[29,30] one from Indonesia,[31,32] one from Japan,[33,34] one from New Zealand,[35] one from Norway and Sri Lanka,[36–41] and seven from the United States.[42–54]

Sample characteristics

Eight studies were epidemiologic samples,[21,23–29,33,34,45,46,49,51,55] one was a birth cohort,[35] one was a community cohort,[31,32] two were specialist periodontal clinic or practice patients,[43,44] and the status of four was unclear.[22,36,42,53,54]

The age groups of included participants varied. Five studies reported data on only participants <50 years,[23,24,31,32,35–41,43] three studies reported only ≥50 years of age,[33,34,42] seven studies included a wide age range,[21,22,25–30,44–52,55] and one study was unclear.[53,54]

Both male and female participants were included in 11 studies,[21,23–35,43–52,55] women only in two studies,[22,42] men only in one study, [36–41] and unclear in one study.[53,54]

Study duration/follow-up was ≤5 years in nine studies,[21–24,33,34,42–45,47–52] 6 to 10 years in four studies,[25–30,35–41,55] and >10 years in three studies.[31,32,46,53,54]

The completeness of follow-up of the initial sample was at least 80% in two studies,[23,24,35] 50% to 79% in five studies,[25–34,42,55] below 50% in four studies,[21,36–41,47–54] and unclear in five studies.[22,43–46]

Generally, participants of the population studies included both those with and without periodontitis as would be a normal population finding. The proportion of each within the study was not stated in most publications. Periodontitis was an inclusion criterion for two studies,[43,44] and one excluded "severe" periodontitis.[45]

CAL was measured by manual probing in most studies. Controlled force probes were employed fully or for the PD component alone in four studies.[31–34,42,45] Bone level was assessed on dental radiographs using linear measurement in both included studies.[42,45]

Risk of bias and methodologic quality

Based on the Newcastle-Ottawa Scale (Table 1), seven publications were rated 6 or 7 stars, eight were rated 4 or 5 stars, and one was at 3 stars of a maximum of 7. Security of measurement of the primary outcome, attachment level change, was graded as secure for 14 of 16 studies and insecure for the remaining two. In relation to bone level measurement of the two studies, one was assessed as secure and the other insecure.

Mean annual attachment level change

Random-effects meta-analysis of nine studies with 13 data sets showed a mean annual attachment loss (Table 2) of 0.10 mm (95% CI 0.068, 0.132) with considerable heterogeneity (I^2 = 99%) (Figure 2). When considering interproximal sites only, mean annual attachment loss was very similar to the estimate for all sites, 0.093 mm (95% CI 0.022, 0.16; I^2 = 99%) (Figure 3). The estimate for the four studies reporting data only for periodontitis was considerably higher at 0.57 mm, although with very wide uncertainty (95% CI -0.38, 1.51) and high heterogeneity (I^2 = 99%) (Figure 4). The combined estimate for the two studies reporting data for postmenopausal women was 0.052 mm (95% CI -0.084, 0.19; I^2 = 90%) (Figure 5). The small values of <1 mm change are of course not measurable but represent the effect of calculating mean change.

Exploration of subgroups

Geographic location was associated with statistically significantly greater mean annual attachment loss for Sri Lanka and China (0.20 mm, 95% CI 0.15, 0.27; I^2 = 83%) vs North America and Europe (0.056 mm, 95% CI 0.025, 0.087; I^2 = 99%) P<0.001 (Table 2, Figure 2). There was no evidence of a difference for gender; males had 0.067 mm (95% CI 0.023, 0.11; I^2 = 51%), females averaged 0.070 mm (95% CI 0.064, 0.076; I^2 = 0.0%) P = 0.89 (Figure 6). Similarly, differences between age groups were not statistically significant; age <30 years had 0.16 mm (95% CI 0.068,0.16; I^2 = 99%), age 30 to 50 years 0.074 mm (95% CI 0.052,0.096; I^2 = 96%), and age >50 years 0.13 mm (95% CI, 0.072, 0.19; I^2 = 99%) P = 0.093 (Figure 7).

For single studies where meta-analysis was not possible, additional observations were found. Overall mean annual attachment level change was greater for those with at least one site showing CAL loss of at least 3 mm compared with all participants combined (those initially 26 years old, 0.05 mm loss vs 0.02 mm gain; initially 32 years old, 0.12 mm vs 0.03 mm).[35] Selecting the 30 participants with greatest change vs the 30 people with the least change in a rural Chinese population found change of 0.14 mm compared with 0.12mm.[55]

Overall, ethnicity was associated with higher mean annual attachment loss in black (0.074 mm) than white participants (0.006 mm) in one study.[50,51] For presumed periodontitis-only data (sites which lost at least 3 mm attachment), there was little effect of gender, ethnicity, age, or education.[51] In another study, older age, being male, non-white, or from a low socioeconomic background was statistically significantly associated with greater attachment loss.[21] Age, calculus, gingival index but not smoking or plaque levels were statistically significantly associated with greater mean annual attachment loss in a secondary analysis of data from Sri Lanka.[40] Elsewhere, younger age (20 to 29 years), being male, current smokers vs never smokers, <10 years school education, and existing diabetes were all statistically significantly associated with greater attachment level change.[29,30]

TABLE 1 Risk of bias (Newcastle-Ottawa Scale [NOS]) and methodologic quality of included studies

	Selection		
Study (ID)	Representativeness of exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study
Cheng-de China Suda et al. 2000 () Pei et al. 2015 ()	1*	1*	1*
Dunedin, New Zealand Thomson et al. 2013 (35)	1*	1*	1*
Gusheng village, China Baelum et al. 1997 (25) Dahlen et al. 1995 (26)	1*	1*	1*
Java, Indonesia Timmerman et al. 2000 (31) Van der Velden et al. 2006 (32)	2*	1*	1*
Niigata, Japan Hirotomi et al. 2002, 2010 (,)	1*	1*	1*
Buffalo, NY OsteoPerio, LaMonte 2013 (42)	3	1*	1*
Piedmont, USA Brown et al. 1994 (51) Beck et al. 1997 (49) (unpublished data)	1*	1*	1*
Porto Alegre, Brazil Haas et al. 2012 ()	1*	1*2*	1*
Norway Loe et al. 1978 (38)	2*	1*	1*
West Pomerania, NE Germany SHIP Gatke et al. 2012 () Kocher et al. 2016 () (unpublished)	1*	1*	1*
Tecumseh, MI Ismail et al. 1990 ()	1*	1*	1*
Virginia Commonwealth University, VA Gunsolley et al. 1995 ()	3	1*	1*
Single publication studies			
Reno, NV Harris 2003 (44)	3	1*	1*
Erie County, USA Machtei et al. 1999 (45)	2*	1*	1*
Sao Luis, Brazil Pereira et al. 2015 (22)	3	1*	1*
Baltimore, MD Ship et al. 1996 (46)	3	4	4

*represents star(s) awarded in rating systems.

Distribution of highest and lowest mean annual attachment level change

Lowest and highest quintiles (i.e., the 20th and 80th percentiles) were calculated for each study from the mean and standard deviation assuming that the data were normally distributed in each case (Table 3, Figure 8). Caution should be exercised when interpreting these results due to the assumption of normality and also in consideration of their high between-study variability when the quintiles were combined to provide an overall estimate. However, the data overall show much different mean annual attachment level change for the lowest quintile (-0.23 mm, i.e., gain) versus highest (0.45 mm loss) (Table 3). Values were similar for interproximal sites alone; lowest quintile -0.048 mm, highest quintile 0.23 mm. The

Comparability	Outcome				
Comparability of cohorts on basis of design or analysis	Assessment of outcome	Adequacy of follow-up of cohorts	NOS total stars, maximum = 7	Security of measurement of attachment level	Security of measurement of bone level change
1*	1*	4	5	Secure	n/a
1*2*	1*	2*	7	Secure	n/a
3	1*	2*	5	Secure	n/a
2*	1*	2*	7	Secure	n/a
1*2*	1*	2	6	Secure	n/a
1*2*	1*	2	5	Secure	Secure
1*2*	1*	2*	7	Secure	n/a
n/a	1*	2*	6	Secure	n/a
n/a	1*	3	4	Secure	n/a
1*2*	1*	2*	7	Secure	n/a
3	1*	3	4	Secure	n/a
3	1*	4	3	Secure	n/a
2*	1*	1*	5	Insecure	n/a
1*2*	1*	3	6	Secure	Insecure
2*	1*	3	4	Secure	n/a
1*2*	1*	1*	4	Insecure	n/a

respective values were higher for the studies reporting on periodontitis alone; lowest quintile 0.22 mm, highest quintile 0.91 mm).

Mean annual tooth loss

Meta-analysis of included studies showed overall mean annual tooth loss was 0.20 (95% CI 0.13, 0.26, I^2 = 91%) (Table 4, Figure 9). There was no evidence of a difference comparing the geographic groupings of North America, Europe, Japan, and Oceania; mean annual tooth loss 0.21 (95% CI 0.10, 0.33; I^2 = 94%) vs South America and Asia mean annual tooth loss 0.19 (95% CI 0.11, 0.28; I^2 = 83%) P = 0.80

The data from single studies where meta-analysis was not possible showed little difference in mean annual tooth loss between males (0.17) and females (0.13) in one study.[29,30] Small differences in mean

annual tooth loss with age were also reported in a Brazilian population: age <30 years (0.02) vs age ≥50 years, 0.03.[21] Elsewhere, annual tooth loss increased with advancing age: age <30 years: 0.04 (95% CI 0.027, 0.053), 30 to 50 years: 0.13 (95% CI 0.16, 0.15), and >50 years: 0.23 (95% CI 0.21, 0.25). Similarly, annual tooth loss was more than twice the magnitude comparing severe periodontitis 0.38 (95% CI 0.34, 0.42) vs moderate periodontitis 0.17 (95% CI 0.15, 0.19).[30] In a rural Chinese population, comparing the 30 participants with the worst attachment loss at 10 years vs 30 people with the least attachment loss, annual tooth loss was 0.53 vs 0.18.[5] In another study, comparison of those with progressing disease (>one site with attachment loss of >2 mm) with non-progressing disease (all others) showed the same annual tooth loss of 0.07.[31]

Mean annual bone level change

Only two included studies also reported on bone level (Table 5). These were not comparable (general population study[45] vs postmenopausal women[42]) and therefore meta-analysis was not performed. Annual bone level loss was low with similar values in both studies 0.04 mm[5] and 0.038 mm.[42]

DISCUSSION

Key findings

Overall, in a general population including both people with and without periodontitis, mean annual attachment loss was 0.1 mm per year, and mean annual tooth loss was 0.2 teeth per year. Observational analysis of highest and lowest mean attachment change quintiles suggests substantial differences between groups with minimal annual change in the lowest quintile and a substantial average deterioration of 0.45 mm mean attachment loss per year in the highest group. This value increased to 0.6 mm per year with periodontitis alone. There was surprisingly little effect of age or gender on attachment level change. Geographic location, however, was associated with more than three times higher mean annual attachment loss in countries with developing economies (0.2 mm) compared with developed economies (0.06 mm, P <0.001).

At a first glance these low values may seem remarkable, but it has to be considered that very few sites in a subject progress beyond a 3 mm threshold of attachment level change. Thus, most sites have no or little progression with time, which may be within the range of periodontal measurement error. Furthermore, these mean values are further influenced by the observation that the periodontal attachment level change may also decrease.[29,35,50,51] To what extent remission measurements reflect biologic changes or measurement error is open to debate, but they have a big influence on these mean values.

Overall completeness and applicability of the evidence

The limited number of studies that were eligible to be included in this review might seem surprising considering the long and distinguished history of periodontal epidemiology. However, most prior studies have been either cross-sectional in design or have used relatively short follow-up periods of <1 year. The review focused on studies that could contribute to an investigation of attachment level change during a period of at least 12 months and this, in part, accounts for the limited number of eligible studies. Retrospective studies were excluded on the basis that the design of a prospective study was more likely to be robust since it was designed a priori to address the research question. The same could not be said of retrospective studies. Subject-based mean attachment level change was our primary outcome and is justified in terms of its fundamental importance to epidemiology and disease classification. Nevertheless, within the included studies, a total of 8,607 participants contributed to follow-up data. Other studies presented data in different formats such as numbers of sites (overall or per participant) with different thresholds of attachment level change. They were not included for two reasons; first, there was substantial heterogeneity in the definition of what constituted a progressing site, making statistical combination in meta-analysis not possible or highly selective. Second, the number of progressing sites would be less informative to the review aims because they depend on the number of teeth present and do not include remission. The completeness of data in this review on bone level change and tooth loss is even less as, a priori, it was planned only to include these data if presented in studies also reporting the primary outcome of attachment level change. The reason for this approach was that to include all studies on bone and tooth loss would have required additional searches resulting in a substantially increased workload for all stages of the review. It was not possible to embark on this within the available time scale. A further limitation was the difficulty in assessing the evidence for the second and third objectives, i.e., risk factors and etiologic factors. The data were analyzed as far as they allowed, but were prevented from more investigation typically by a lack of reporting or of reporting in formats that could not be combined.

Aspects of the included studies that favor applicability of the evidence are the number of large population-based surveys in both developing and developed economies, with a spread of included ages. Challenges to applicability are mainly presented by the lack of consistency as discussed below.

Overall quality, strength, and consistency of the evidence

The Newcastle-Ottawa Scale demonstrated that 11 of 16 studies received at least 5 stars of a possible 7, indicating reasonably low levels of risk of bias. Furthermore, only two studies showed an insecure method of measurement of attachment level,[44,46] and one an insecure method of bone level.[45]

The consistency of evidence is much more problematic. While the total number of included participants, 8,607, might appear to be a substantial number, the high statistical heterogeneity and the major differences in study design are troubling to the development

TABLE 2 Summary table of meta-analyses: mean annual attachment level change

Analysis	Mean annual attachment level change (mm)	95% CI	Number of data sets	I^2%
General population, including both full-mouth and partial-mouth recording	0.100	0.068, 0.13	13	99
Only interproximal sites	0.093	0.022, 0.16	6	99
Only periodontitis	0.57	−0.38, 1.51	5	99
Postmenopausal women	0.052	−0.084, 0.19	2	89
Subgroup analyses				
Effect of geographic location				
North America and Europe	0.056	0.025, 0.087	8	99
Sri Lanka and China only	0.20	0.15, 0.26	5	82
Difference between North America/Europe and Sri Lanka/China, P <0.001				
Effect of gender				
Males only	0.067	0.023, 0.11	2	50
Females only	0.070	0.064, 0.076	2	0
Difference between males and females, P = 0.893				
Effect of age				
Age <30 years	0.12	0.068, 0.16	8	99
Age 30–50 years	0.074	0.052, 0.096	5	95
Age >50 years	0.13	0.072, 0.19	4	98
Difference between age groups, P = 0.093				

of an overview of the data. Key differences in methodology include sampling frames (random or convenience population-based samples, patient populations, birth cohorts, practice samples), included ages (some studies only <50 years and others only ≥50 years), men- or women-only studies, study duration (from 2 to 28 years), full-mouth and partial-mouth recording and inclusion of only teeth present at both baseline and follow-up vs all teeth at baseline whether lost at follow-up. Remaining teeth in a mouth may represent "healthy survivor" teeth because those extracted tend to be more periodontally affected.[56] Thus, the loss of teeth due to progression of periodontitis could result in underestimation of attachment level change.[16] While some studies have shown a clear effect of this phenomenon,[49] others have reported little or no differences when modelling the analysis in different ways.[42]

The included studies might also represent the effect of period/cohort effects such as the differences between the two Chinese samples, which were recruited approximately a decade apart. The Gusheng population had a mean annual attachment loss (0.17 mm/year) almost three times that of the Cheng-de cohort (0.065 mm/year). The first cohort resembles much more that of a low-income country such as the Sri Lanka cohort from 1978, and oral health may be influenced by malnutrition and low level of personal hygiene, whereas attachment progression of the Cheng-de cohort is comparable to the European and United States cohorts. The Cheng-de cohort might reflect the dynamic change of Chinese economy, where for example malnutrition, hygiene, access to medical care, etc. have progressed. To what extent period and cohort effects influence these values cannot be explained with the available data.

The statistical heterogeneity in particular suggests that there are important differences in outcomes between studies that could not be explained. Consequently, the overall estimates from the meta-analyses, despite representing best-available evidence, should be used with caution and likely represent a low strength of evidence.

Tooth loss data are especially challenging to interpret. Tooth loss, if not exfoliation, could be due to many reasons, including but not limited to severe periodontitis. Tooth extraction will be influenced by availability of dental professionals, existing disease (including periodontitis, caries, and endodontic disease), patient preferences, financial considerations related to affordability of the treatment, professional practices, and cultural norms.[57,58] This might help to explain the lack of difference in annual tooth loss comparing studies conducted in North America, Europe, Japan, and Oceania (potentially higher economic development) with South America and Asia (lower economic development) although the heterogeneity within these two strata was very high. Only limited information was available in the reported studies to tease out if tooth loss was determined by periodontal status because tooth loss was not reported according to periodontal severity or progression. In the SHIP and Gusheng cohorts, tooth loss was much more pronounced in subjects with periodontitis in comparison with healthy subjects, whereas no such relation was found in the Java cohort. In the United States and Germany, chronic periodontitis is closely related to tooth loss in persons aged ≥40 years.[59,60]

Additional approaches to assessing progression of periodontal diseases, such as quantitative assessment of bone height and density, show promise[61] and would have been included if data

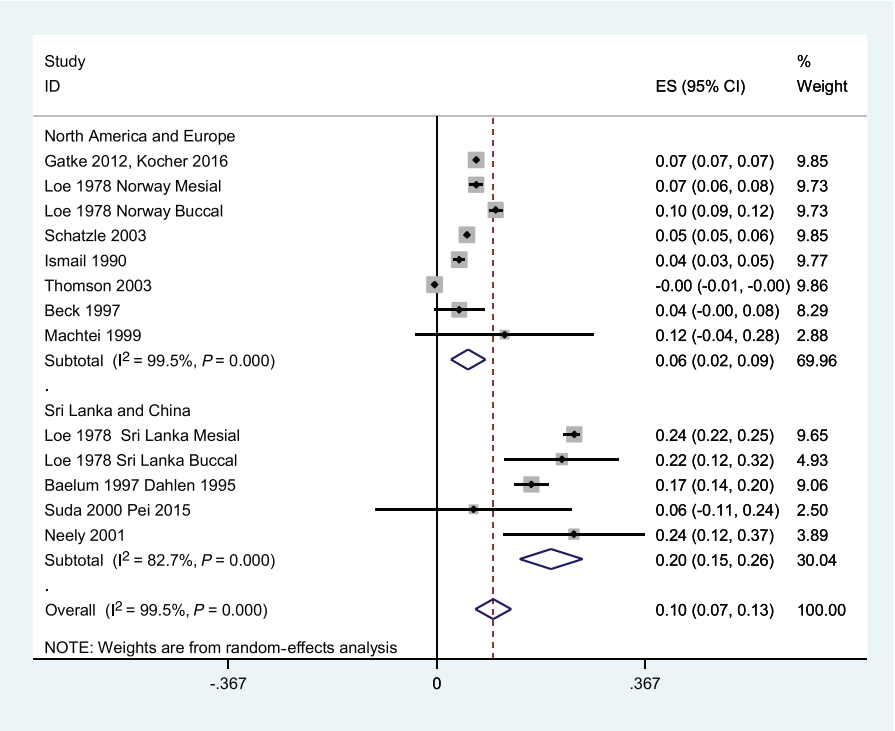

FIGURE 2 Random effects of meta-analysis: Mean annual attachment level change

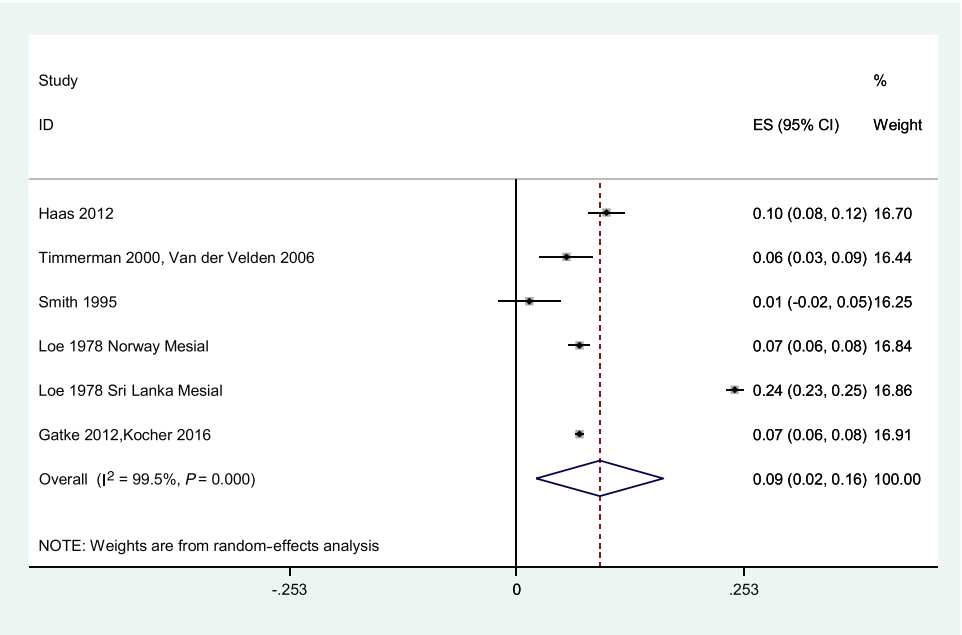

FIGURE 3 Random effects of meta-analysis: Mean annual attachment level change, interproximal sites only

had been presented in the included studies. These techniques have limited relevance to population epidemiology but could be valuable in small, more controlled institution-based studies. Interestingly, radiographic assessments did not form part of the common data set recently recommended for periodontal epidemiology.[62]

Potential biases in the review process

In order to minimize the risk of bias in the review process, the review protocol was registered a priori CRD42016035581 (www.crd.york.ac.uk/PROSPERO). Screening, eligibility decisions, and data abstraction were carried out in duplicate and independently. The

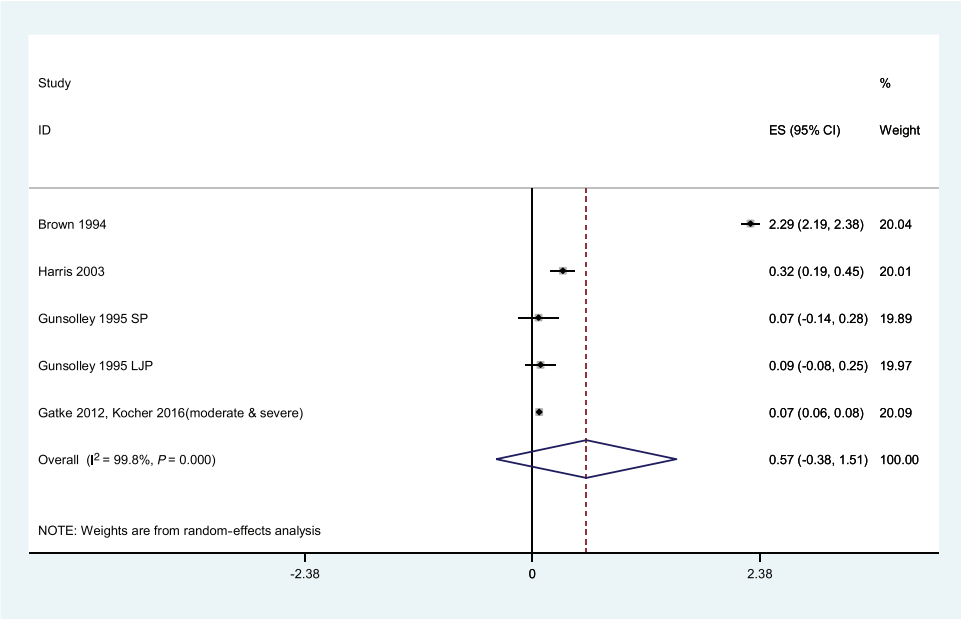

FIGURE 4 Random effects of meta-analysis: Mean annual attachment level change, periodontitis only

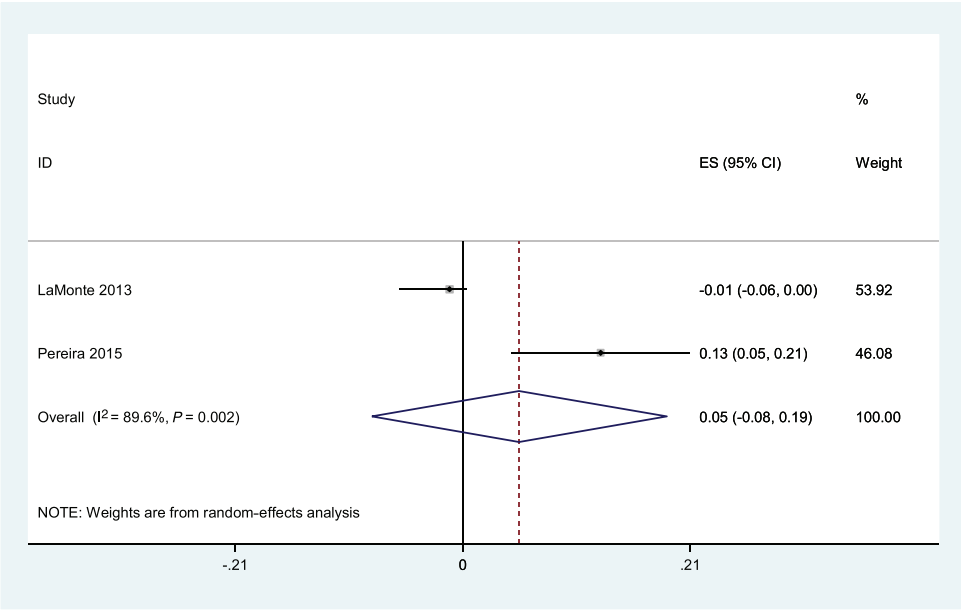

FIGURE 5 Random effects of meta-analysis: Mean annual attachment level change, postmenopausal women only

search was also designed to minimize bias, including development of a highly sensitive electronic search strategy of multiple databases, no language restrictions, and searching for grey literature. Sources of potential biases were changes to the protocol during the review process. Two post hoc analyses were included based on the data collected. These were subgrouped by geographic location and estimation of quintiles of attachment level change. Since both were treated as purely exploratory, the level of bias introduced would seem to be low.

Agreements and disagreements with other reviews

To our knowledge, there has been no systematic review of this topic. Progression of periodontitis has been considered in previous comprehensive narrative reviews.[16,63,64] These reviews report values of mean annual attachment level change ranging from 0.04 to 1.04 mm. The findings from the current systematic review are consistent with the values, although the narrative reviews included fewer studies.

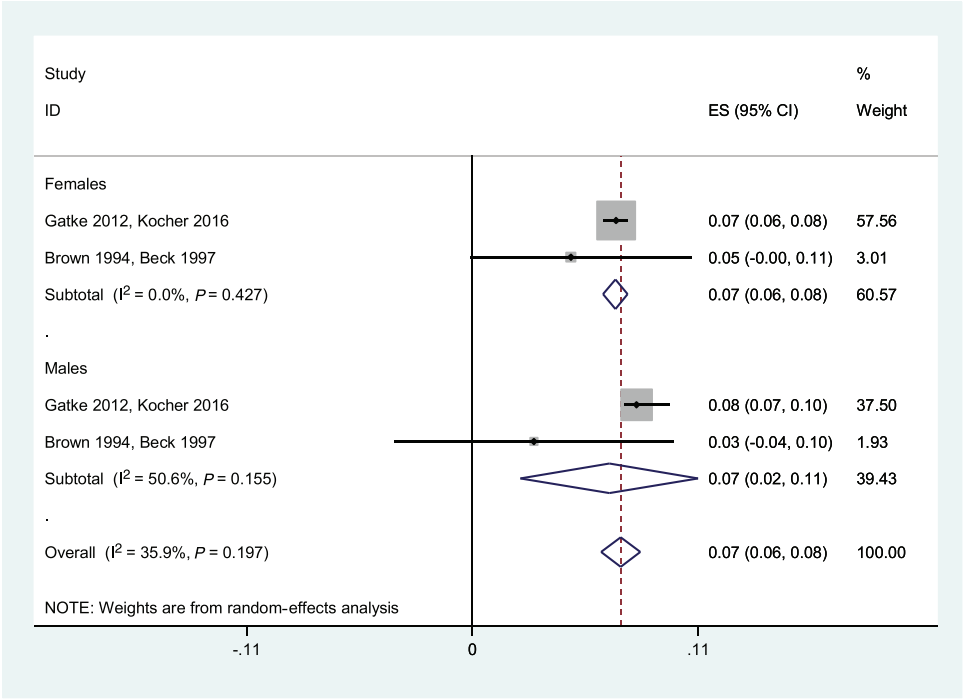

FIGURE 6 Random effects of meta-analysis: Mean annual attachment level change, subgroup analysis, effect of gender

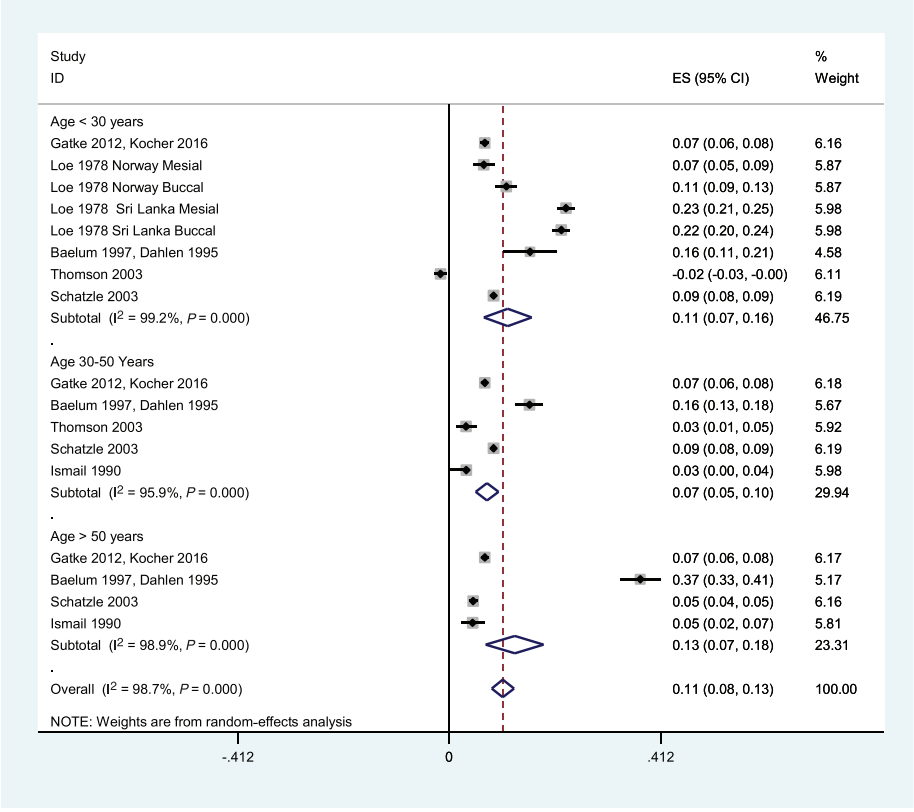

FIGURE 7 Random effects of meta-analysis: Mean annual attachment level change, subgroup analysis, effect of age

TABLE 3 Quintiles of mean annual attachment level change

Study	SD (mm)	N	Mean annual attachment level change (mm)	1st quintile (mm)	2nd quintile (mm)	3rd quintile (mm)	4th quintile (mm)
Kocher et al. 2016	0.09	1,892	0.07	−0.0058	0.047	0.093	0.15
Loe et al. 1978 Norway Mesial	0.077	167	0.07	0.0048	0.050	0.089	0.14
Loe et al. 1978 Norway Buccal	0.092	167	0.10	0.027	0.081	0.13	0.18
Loe et al. 1978 Sri Lanka Mesial	0.071	196	0.24	0.18	0.22	0.26	0.30
Loe et al. 1978 Sri Lanka Buccal	0.071	196	0.22	0.16	0.20	0.24	0.28
Schatzle et al. 2003	0.068	1,557	0.054	−0.0036	0.037	0.071	0.11
Neely et al. 2001	0.67	114	0.24	−0.32	0.072	0.41	0.81
Ismail et al. 1990	0.066	165	0.04	−0.016	0.023	0.057	0.096
Baelum et al. 1997, Dahlen et al. 1995	0.28	323	0.17	−0.067	0.097	0.24	0.40
Thomson et al. 2003	0.033	831	−0.0034	−0.031	−0.012	0.0049	0.024
Beck et al. 1997	0.39	292	0.04	−0.28	−0.058	0.14	0.36
Suda et al. 2000, Pei et al. 2015	1.79	413	0.065	−1.44	−0.39	0.52	1.57
Machtei et al. 1991	1.63	415	0.12	−1.25	−0.29	0.53	1.49
Overall mean				−0.23			0.45
Postmenopausal women							
LaMonte 2013, Osteoperio Buffalo	0.26	995	−0.012	−0.23	−0.078	0.054	0.21
Pereira 2015	0.15	15	0.13	0.0018	0.089	0.17	0.25
Overall mean				−0.11			0.23
Interproximal sites only							
Haas et al. 2012	0.26	697	0.1	−0.12	0.033	0.17	0.32
Timmerman et al. 2000, Van der Velden et al. 2006	0.19	155	0.056	−0.10	0.0086	0.10	0.21
Smith et al. 1995	0.29	264	0.014	−0.23	−0.059	0.088	0.26
Loe et al. 1978 Norway Mesial	0.077	167	0.07	0.0048	0.050	0.089	0.14
Loe et al. 1978 Sri Lanka Mesial	0.071	196	0.24	0.18	0.22	0.26	0.30
Kocher et al. 2016 (SHIP)	0.11	1,872	0.07	−0.023	0.042	0.099	0.16
Overall mean				−0.048			0.23
Periodontitis only							
Brown et al. 1994	0.79	260	2.3	1.62	2.09	2.48	2.95
Harris 2003	0.34	30	0.32	0.034	0.23	0.41	0.61
Gunsolley et al. 1995 SP	0.45	20	0.066	−0.31	−0.048	0.18	0.44
Gunsolley et al. 1995 LJP	0.36	21	0.086	−0.21	−0.0044	0.18	0.39
Kocher et al. 2016 (moderate and severe disease)	0.1	932	0.07	−0.014	0.044	0.095	0.15
Overall mean				0.22			0.91

Implications for practice and policy

Within the limitations of the research, the data show that mean annual attachment level change varies considerably both within and between populations. This finding has important implications both for classifying periodontal diseases and for the management of periodontal health.

In relation to classification, mean annual attachment level change was a challenging concept in the 1999 Workshop on Disease Classification.[9] However, rapid attachment level loss was considered a key characteristic of aggressive periodontitis,[65] whereas chronic periodontitis showed slow to moderate progression but could demonstrate periods of rapid progression.[66] Therefore, while it was accepted that the use of progression thresholds was

problematic to defining different types of disease, the final classification incorporated such elements. Previous workshops have also struggled with such issues and accepted the substantial variability of presentation of periodontitis, including progression of attachment level change.[11,67] Furthermore, severity of attachment loss at initial assessment (and by implication annual attachment loss at that point) can be a poor predictor of trajectory.[11,68] A recent review of aggressive periodontitis highlighted the variability in mean annual attachment level progression, although the values cited are within those found in the present systematic review. Despite the variability, one of the distinctive criteria recommended for case definition was "relatively high progression rate of periodontal tissues loss".[69] The operationalization of such a characteristic is unclear. Also, the data in the incorporated studies represent "progression" of disease based on mean values of all sites and do not inform the behavior or biologic mechanisms of attachment level change at individual sites. This is a significant limitation of the current research base.

The 2015 Task Force Update to the 1999 classification enlarged on this issue.[10] In relation to chronic periodontitis, they acknowledged a spectrum of annual attachment level change, including a slow, continuous pattern of disease progression, bursts of periodontal destruction around certain teeth in relatively short periods (random burst pattern), and many bursts of destructive periodontal disease activity at a high frequency during certain periods (multiple burst pattern). Age of onset (detection) was recommended as the general guideline to distinguish aggressive from chronic periodontitis and not annual attachment level change, although this could provide supportive evidence. Overall, the results of this new systematic review do not support or refute the continuing differentiation between forms of periodontal diseases based upon progression of attachment level change.

Prevention of periodontitis includes both prevention of gingivitis or if already established, treatment of gingivitis.[1] This review has not sought to ask whether preventive outcomes are different across people who will go on to follow low or high trajectories of mean annual attachment loss. Since it is not currently possible to screen for such tendencies, a universal approach to prevention is indicated rather than attempting to identify individuals at high risk.[70] However, management of periodontal health should also be conceived broadly to include healthy lifestyle promotion and risk factor reduction through the combined engagement of policy makers, health professionals, and empowered individuals[1] and with an understanding of the impact of social inequalities.[71]

Implications for further research

The unexplained high levels of statistical heterogeneity point to a need for future studies to investigate attachment level change. Many population-based studies collect data from six sites per tooth and from all teeth other than third molars. This is recommended as part of developing a standardized data set as proposed for reporting periodontitis prevalence.[62] Standardized statistical analysis will be equally important. Important key limitations of the existing data are the presentation chiefly of the difference in full-mouth mean attachment level between baseline and final evaluations. Even though some studies report little impact on the method of analysis,[42] it is recommended instead data analysis based on the change in attachment level for each site at each time point still present.[29,49,72] This would reduce the tendency to underestimate change from the loss of teeth due to periodontitis. Employing repeated follow-up, perhaps annually, rather than one final assessment after several years might also help to prevent this effect, although this would be impractical for large epidemiologic studies.

However, since many sites will show no or minimal change, calculating a full-mouth mean value will both lose information and not adequately characterize periodontal health. A consensus on more meaningful data presentations is urgently required and could include separate estimation of change for regressing and

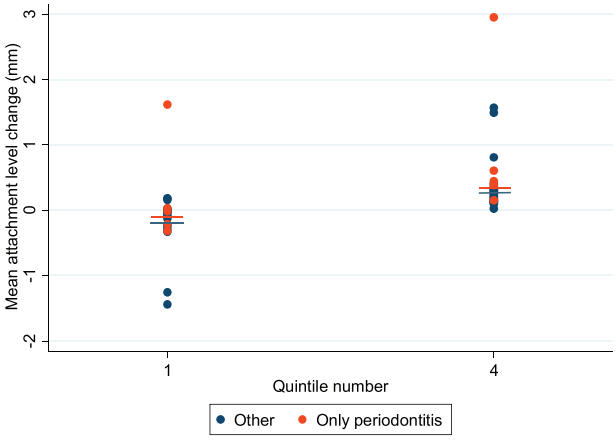

FIGURE 8 Distribution (with means) of highest and lowest quintiles, mean annual attachment level change (mm)

TABLE 4 Summary of meta-analyses: mean annual tooth loss

Analysis	Mean annual tooth loss	95% CI	Number of data sets	I^2%
General population. studies	0.20	0.13, 0.26	10	91
Subgroup analyses				
North America, Europe, Japan, Oceania	0.21	0.10, 0.33	6	94
South America and Asia	0.19	0.11, 0.28	4	82
Difference between groups $P = 0.80$				

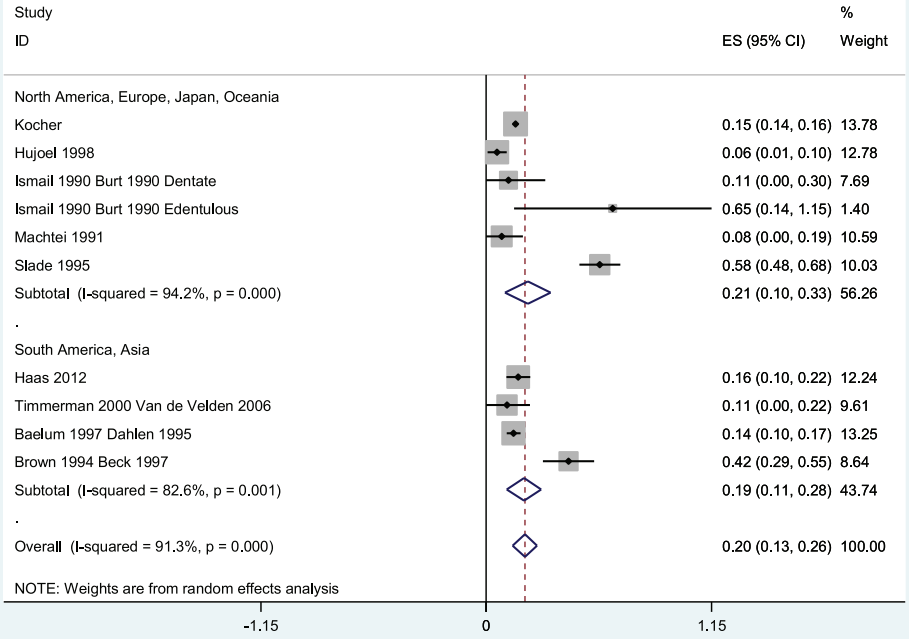

FIGURE 9 Random effects meta-analysis: Mean annual tooth loss

TABLE 5 Mean annual bone level change (mm): single studies (no meta-analysis)

Study	n	SD	Mean	95% CI LL	95% CI UL
General population excluding severe periodontitis					
Machtei et al. 1999	415	.002[a]	.04	.04	.04
Postmenopausal women					
LaMonte et al. 2013	1025	.219	.038	.025	.051

[a]SE given as 0.00, taken as 0.0001.
LL, lower limit; UL, upper limit.

progressing sites (above an arbitrary threshold of for instance 3 mm) as well as the proportion of sites affected or, if the data are normally distributed, mean values percentile. A percentile-based analysis (on tertiles, quartiles, quintiles, etc.) might help to dissect the within-population variation of periodontal disease as well to understand if there is a link between periodontal health and tooth loss.

Characterizing participants at baseline by diagnosis, i.e., periodontitis and non-periodontitis is challenging. First, gingivitis and periodontitis are increasingly viewed as part of a continuum,[1] and therefore an arbitrary threshold for diagnosis might lack validity. This is highlighted by the high prevalence values of at least mild forms of periodontitis which typically affect almost half of most populations.[6–8] Similar difficulties exist with case definitions for other chronic conditions such as hypertension, diabetes, etc. For these conditions, case definitions are based on natural history/treatment studies, where subjects beyond a certain threshold have different health/treatment outcomes. As an analogy for periodontitis, a starting point might be to look across cohorts to determine whether there are subjects with a certain baseline periodontal status, who go on to lose more attachment and teeth and then define them as periodontally "healthy" or "severe."

In addition to periodontal data, a consensus is required for a standardized data set of potential modifiers of attachment level change including certain oral microbiomes, genetic factors, lifestyle, general health, and socioeconomic measures.[62]

Finally, tooth loss, as a measure of periodontitis progression requires further research. Prevention of tooth loss is arguably the chief objective of prevention and treatment of periodontitis and is implicit in definitions of oral health.[73] Although this parameter would potentially seem to be ideal in terms of being an objective measure and a true endpoint for assessing the impact of periodontal diseases,[74] the many contributors to tooth loss/retention (e.g., patient preference, caries, dental professional treatment planning) complicate the interpretation of the data currently beyond very general observations. Further modelling in both existing data

sets and in future research studies might help to unravel the associations between periodontal health and tooth loss.

CONCLUSIONS

Within the many limitations of the data, it is possible to conclude that mean annual attachment level change is highly variable both within and between populations. The differences in magnitude of mean annual change are clinically important, representing progression values potentially commensurate with tooth retention during a lifetime to tooth loss within three decades. Only geographic location or ethnic status, a likely proxy for socioeconomic position (and its associated risk determinants), showed evidence of a statistically significant effect on mean change. Most of the substantial statistical heterogeneity between studies could not be explained from available data. Overall, the evidence does not support or refute the differentiation between forms of periodontal diseases based upon progression of attachment level change in adults ≥18 years of age.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

Age-dependent distribution of periodontitis in two countries: Findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objective: We used epidemiologic data of clinical periodontal status from two population-based samples in two countries, United States and Germany, to examine 1) the impact of age on the relative contribution of recession and pocketing on the distribution of clinical attachment loss, and 2) whether it is feasible to define age-dependent thresholds for severe periodontitis.

Methods: The analytical sample was based on persons aged ≥30 and included 10,713 individuals in the United States, participants in NHANES 2009 to 2014, and 3,071 individuals in Pomerania, Germany, participants in the SHIP-Trend 2008 to 2012. NHANES used a full-mouth examination protocol to collect data on recession (R), pocket depth (PD) and clinical attachment loss (CAL) for six sites/tooth on a maximum of 28 teeth; SHIP-Trend used a half-mouth examination at four sites/tooth. In both samples, percentile distributions of mean CAL/person were generated for each 5-year age interval. Age-dependent thresholds defining the upper quintile of mean CAL were calculated for both samples. The topographic intraoral distribution of CAL and the relative contribution of R and PD on CAL was assessed.

Results: Mean CAL increased linearly with age in both samples and was higher in SHIP-Trend than NHANES across the age spectrum. In contrast, mean PD was constant across age groups in both populations. R contributed increasingly to CAL with age, especially after 45 to 49 years. Upper quintile mean CAL thresholds in NHANES were < 3 mm for ages up to 39 years, and under 3.58 mm in all other age groups. Corresponding values in SHIP-Trend were also < 3 mm in ages up to 39 years but increased linearly with age up to 7.21 mm for ages ≥75 years.

Conclusions: Despite substantial differences in the overall severity of attachment loss between the two samples, common patterns of CAL and of the relative contribution of R and PD to CAL with increasing age were identified. Although periodontitis severity may vary in different populations, empirical evidence-driven definitions of CAL thresholds signifying disproportionate severity of periodontitis by age are feasible.

KEYWORDS

classification, clinical attachment loss, epidemiology, periodontitis, pocket depth, recession

INTRODUCTION

It is estimated that severe periodontitis affects 11% of the world population with prevalence increasing by age.[1,2] There has been considerable discussion over the years regarding the role of age as a risk factor or risk indicator for periodontitis. A risk factor is an attribute or exposure that increases the likelihood of developing a disease or injury in an individual. Conceptually, risk factors are part of the causal chain with exposure to the risk factor occurring before the outcome, and can be modifiable (e.g., lifestyle factors) or non-modifiable (e.g., genetic factors). In contrast, risk indicators are characteristics that are associated with a disease or condition without being etiologically related, and for which temporality or direction of the observed relationship remains unclear.[3] The influence of age on periodontitis is complex. While the likelihood of developing periodontitis increases with age in populations across the globe, suggesting that age is an important risk indicator,[4] aging *per se* is not necessarily a risk factor,[5,6] but likely a health determinant, or the underlying characteristic of a group that shapes the health of individuals and populations.[20] As such, aging can account for a substantial part of the variance of periodontitis in the population and can influence incidence rates.

Although severe periodontitis can occur throughout the life span, it is estimated that the global incidence of severe periodontitis peaks around the age of 38 years.[1] Because age may increase susceptibility to the onset of periodontal disease and its progression, there have been many attempts to incorporate age—as a risk factor/indicator or determinant—into risk assessment tools for the prevention of periodontal disease progression.[7] A high-utility risk assessment tool can improve screening for disease and may improve diagnostic decision-making for clinicians. However, understanding the distinction between the cause of disease in individuals and the cause of patterns of incidence in a population is important because effective disease mitigation may require distinct prevention strategies.[8] More importantly, recognizing the role of a characteristic as a risk factor or health determinant informs the diagnostic process.

A disease is diagnosed in a patient based on a constellation of signs, symptoms, clinical and/or laboratory tests. Such criteria used by clinicians in the diagnosis and treatment planning are commonly known as diagnostic criteria. However, diagnostic criteria and classification criteria are not synonymous. Classification criteria are developed with the goal of utilizing standardized case definitions, facilitating comparability between studies and consequently generating uniformity in interpretation of study results. Classification criteria are not designed to characterize every single patient with a unique set of disease manifestations but rather to set a foundation to aggregate a majority of patients with specific phenotypes into a category. The main attribute of a classification scheme is to have high specificity, that is, to ensure that healthy people are not misclassified as having disease. However, if both the sensitivity and the specificity of a classification system approach 100%, then these classification criteria may also serve as diagnostic criteria. Nevertheless, given that classification criteria are not designed to have an accuracy of 100%, it is inevitable that a certain proportion of patients will be misclassified, hence why classification criteria are not meant to be used to diagnose disease in a particular patient or to guide treatment planning. To avoid introducing error in study design that can compromise validity, classification criteria for diseases must be developed utilizing empirical evidence-driven methodologies and should not be based on expert opinion alone.

The evolution of classification criteria for periodontal diseases over the years has been shaped by a rich discussion in the scientific community. Our understanding of the pathobiology of periodontitis has changed over these years and the expansion of new knowledge is generating the need to revisit the existing classification criteria. In view of the upcoming World Workshop for a revised classification of periodontal and peri-implant diseases and conditions organized by the American Academy Periodontology (AAP) and the European Federation Periodontology (EFP), and given the ubiquity and state of equipoise over elements of the classification system, the purpose of this study was to critically ascertain the association between age and periodontitis in an empirical evidence-driven manner. Specifically, our objectives were to address the following questions: 1) how does age affect the distribution of periodontitis in the general population, and 2) is it feasible to define age-dependent thresholds for severe periodontitis. Epidemiologic data from two population-based samples in two countries, United States and Germany, were used to address these questions.

METHODS

Study Populations

We used data from the National Health and Nutrition Examination Survey (NHANES), for years 2009 to 2014 and from the Study of Health in Pomerania (SHIP-Trend) for years 2008 to 2012.

NHANES is a population-based cross-sectional survey conducted in the United States by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC).[19] The survey uses a stratified, multistage, cluster sampling design with the non-institutionalized civilian resident population of the United States as the target population. Approximately 5,000 sampled participants of all ages are interviewed in their homes and undergo a health examination in Mobile Examination Centers (MEC). Dental examinations, including full-mouth periodontal examinations involving participants aged ≥30 years, were conducted by trained dental examiners on the MEC. Details on NHANES methodology, the oral health component, and related data quality assurance may be found elsewhere.[9,10] The NHANES 2009 to 2014 interviewed 30,468 people, of which, 9,667 were edentulous, and 9,393 did not have a periodontal examination and were therefore excluded, resulting in a total of 10,713 participants for analysis in this study (see Fig. L, supplementary Appendix in online *Journal of Clinical Periodontology*).

SHIP-Trend is a large population-based longitudinal survey conducted in Germany. SHIP uses a stratified, random sampling

design with a target population for community dwelling persons between ages 20 and 79 years in Pomerania, a region in northeast Germany. The survey uses interviews, questionnaires, and a physical examination to collect a broad range of health data, including oral health data. Details on SHIP-Trend methodology may be found elsewhere.[11] SHIP-Trend examined a total of 4,420 people during 2008 to 2012. After excluding the edentulous individuals and those without a periodontal examination, a total of 3,071 participants remained for inclusion in the analysis of this study (Fig. Y, Appendix).

Periodontal examination

Between 2009 to 2014, NHANES conducted a full-mouth periodontal examination (FMPE) among those ≥30 years who did not have a health condition that required antibiotic prophylaxis prior to periodontal probing. The FMPE was undertaken with the intent to produce gold standard assessments for clinical attachment loss (CAL). Direct measurements of the distance between the cemento-enamel junction and the free gingival margin (CEJ-FGM) and the pocket depth (PD) at six sites (mesio-buccal, mid-buccal disto-buccal, mesio-lingual, mid-lingual and disto-lingual) for each tooth (excluding third molars) were made. All measurements were rounded to the lower whole millimeter. CAL was calculated based on these two measurements.

SHIP-Trend involved a partial-mouth periodontal examination (PMPE) randomly selecting the right or left side and carried out probing assessments at only four sites per tooth (the disto-lingual and mesio-lingual sites were not assessed).[12] The assessment of PD employed direct measurements. However, for the assessment of CAL, either direct or indirect measurements were used, depending on the position of the CEJ relative to the FGM. If the FGM was located coronal to the CEJ, CAL was calculated as the difference between PD and the distance between FGM and CEJ. If the FGM was located apical to the CEJ indicating clinical recession, CAL was directly measured as the distance between CEJ and the base of the pocket.

In both studies, where the determination of the CEJ was indistinct (wedge-shaped defects, fillings, and crown margins), CAL was not recorded.

Study variables

Age in years was categorized into 10 groups: 30 to 34, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74 and ≥75 years. When participants were initially selected for the SHIP study, the age target was 20–79 years. Because some individuals participated at later stage, the age range at time of examination extended to 83 years. Age eligibility for a periodontal examination began at age 30 for NHANES and there was no maximum age, but individuals aged ≥80 years were top-coded at 80 years of age for public data use. In all subsequent figures and tables, "clinical recession" refers to the clinical presentation where the FGM was located either at (clinical recession of 0) or apical to the CEJ (clinical recession > 0). All figures presented as stacked histograms convey two conditions: CAL (the entire length of the bar) and clinical recession (the portion of CAL attributed to clinical recession; blue portion).

Statistical analysis

Exploratory data analysis was performed to ascertain the relationship between age and the three clinical measures of periodontitis, namely recession (R), pocket depth and CAL. Analyses were conducted using survey weights and design variables to account for the sampling design to produce representative estimates for both United States and Pomerania, Germany. Analytical datasets included those dentate, with tooth count ≥2, and age ≥30 years. Mean R, PD, and CAL across 28 teeth, for each individual and the total sample were computed. Percentiles with a step of 5 for mean R, PD and CAL were computed to arrive at cumulative distributions for the total sample and each age category, with the contribution of R to CAL plotted in stacked histograms. Mean number of sites (each individual could have maximum of $6 \times 28 = 168$ sites affected) with CAL ≥4 mm, PD ≥5 mm and R ≥3 mm was computed for each age category. In addition, data of the top 20% (upper quintile) of mean CAL were analyzed separately for the total sample and each age category. Stacked histograms of these upper quintiles were generated to indicate the distribution of the contribution of R to CAL by site. Finally, the linear relationship between mean R, mean PD, mean CAL and age were explored and linear regression lines were fitted. All analyses were undertaken using Stata/SE 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and SAS (SAS Institute Inc, Cary, North Carolina version 9.4).

RESULTS

Findings from NHANES 2009 to 2014

The mean age of the study population was 50.9 years (SE: 0.25), with the majority falling within the age range of 30 to 59 years (Table 1). Within this age range, the population was fairly equally distributed among each of the six 5-year age categories (~12%). Age categories within the age range of ≥60 years constituted ~27% of the total sample. The majority of the population was non-Hispanic Whites (68.4%), had some education beyond high school (63.8%).

Figure 1A shows the mean CAL, PD, and clinical recession for each age group. Mean CAL ranged from 1.3 mm in the youngest age group (aged 30 to 34 years) to 2.3 mm in the oldest age group (aged ≥75 years). Average mean clinical recession steadily increased with age and was lowest in the age group of 30 to 34 years (Average: 0.1, SE: 0.2) and highest in the age group of ≥75 years (Average: 1.0, SE: 0.9). Unlike mean CAL and mean recession, the mean PD was fairly constant across age groups; thus, the 30- to 34-year age group had a mean pocket depth of 1.5 mm (SE: 0.5) and the ≥75-year age

TABLE 1 Demographic characteristics of total population – aged ≥30 years

Characteristics	NHANES 2009 to 2014 (n = 10,713)	SHIP-Trend 2008 to 2012 (n = 3,071)
Age (years)		
Average age in years (SE)	50.86 (0.25)	51.94 (0.23)
	n (%)	n (%)
Age 30 to 34	1,298 (12.26)	297 (10.28)
Age 35 to 39	1,253 (12.22)	320 (8.89)
Age 40 to 44	1,304 (12.85)	383 (12.49)
Age 45 to 49	1,198 (12.55)	409 (16.03)
Age 50 to 54	1,196 (12.27)	369 (13.59)
Age 55 to 59	989 (11.12)	371 (11.70)
Age 60 to 64	1,157 (9.15)	314 (7.30)
Age 65 to 69	795 (6.55)	282 (7.72)
Age 70 to 74	604 (4.53)	188 (6.97)
Age ≥75*	919 (6.48)	138 (5.03)
Race/ethnicity*		
Non-Hispanic white	4,594 (68.43)	3,071 (100.00)
Non-Hispanic black	2,229 (10.68)	–
Hispanic	2,588 (13.51)	–
Other	1,302 (7.38)	–
Education*		
Less than high school	2,511 (15.36)	560 (19.16)
High school grad/GED or equivalent	2,307 (20.81)	1,683 (54.76)
More than high school	5,882 (63.75)	821 (26.09)
Smoking		
Current smoker	2,015(17.42)	1,158 (37.23)
Former smoker	2,680(26.17)	1,151 (37.56)
Never smoked	6,013(56.41)	755 (25.21)

NHANES – National Health and Nutrition Examination Survey; SHIP – Study of Health in Pomerania | GED – General Equivalency Diploma | *In SHIP-Trend last age category is 75 to 83 years; Race is categorized as European Caucasian; Education is categorized as < 10 years of schooling, 10 years of schooling and > 10 years of schooling | All percentages are weighted.

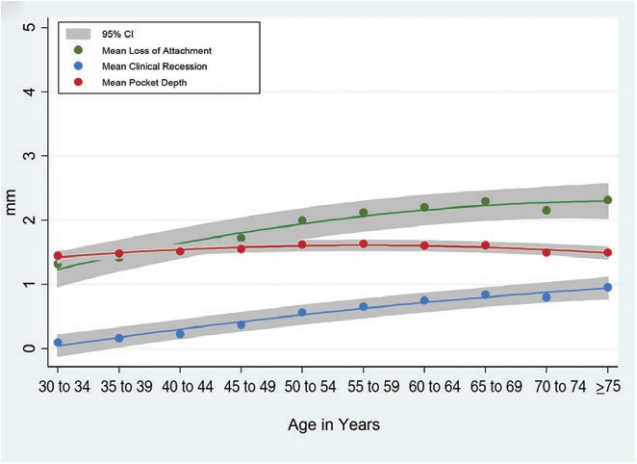

FIGURE 1A Trend in mean loss of attachment, clinical recession and pocket depth by age group, National Health and Nutrition Examination Survey (NHANES), 2009 to 2014. Lines show quadratic fits to averages (points)

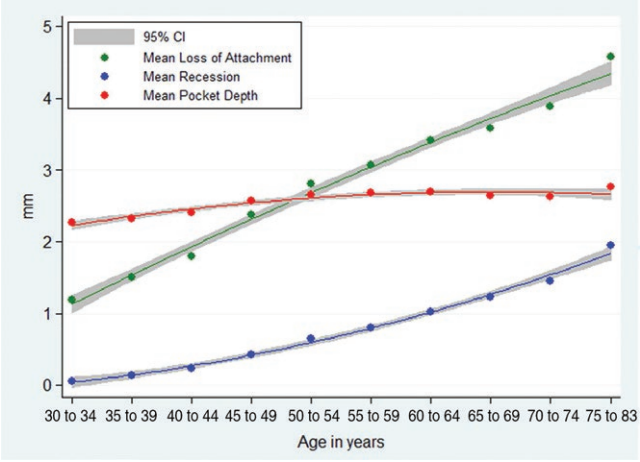

FIGURE 1B Trend in mean loss of attachment, clinical recession and pocket depth by age group, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012. Lines show quadratic fits to averages (points)

group had a mean PD of 1.50 mm (SE: 0.5). Thus, it appears that the observed increase in mean CAL with age was primarily driven by increased recession.

The pattern of mean recession, pocket depth and clinical attachment loss per participant is investigated in greater detail in Figure 2A, which presents boxplots of their distribution across age groups. The box boundaries identify the 25th and 75th percentiles, the horizontal line within the box represent median value, the whiskers define the interval between the 25th percentile minus 1.5 times the interquartile distance and the 75th percentile plus 1.5 times the interquartile distance, and the dots depict the outliers. When evaluating clinical recession by age group, the median value of subject-based mean recession gradually increased with age as did the interquartile range. Unlike recession, the interquartile range and median value for subject-based mean PD remained relatively stable across all age groups, as illustrated by the minimal difference in the size of the boxes across the age groups. For CAL, the increase in the median value of subject-based average attachment loss was minimal across the age groups, but the interquartile range increased with age, especially in ages between 45 to 64 years where this increase appeared to be more dependent on the third and fourth quartiles.

When the cumulative distribution of the entire sample with respect to mean CAL was analyzed (Figure 3A), it was observed that 95% of the sample had a mean CAL of ≤4.2 mm and a mean clinical recession of ≤2 mm. In contrast, persons in the top 5% of the

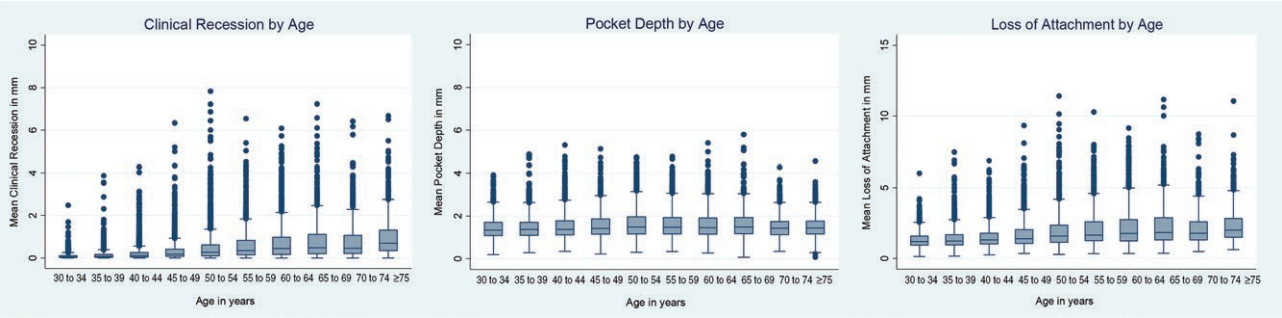

FIGURE 2A Boxplots of mean clinical recession, mean pocket depth and mean loss of attachment by age groups, National Health and Nutrition Examination Survey (NHANES), 2009 to 2014

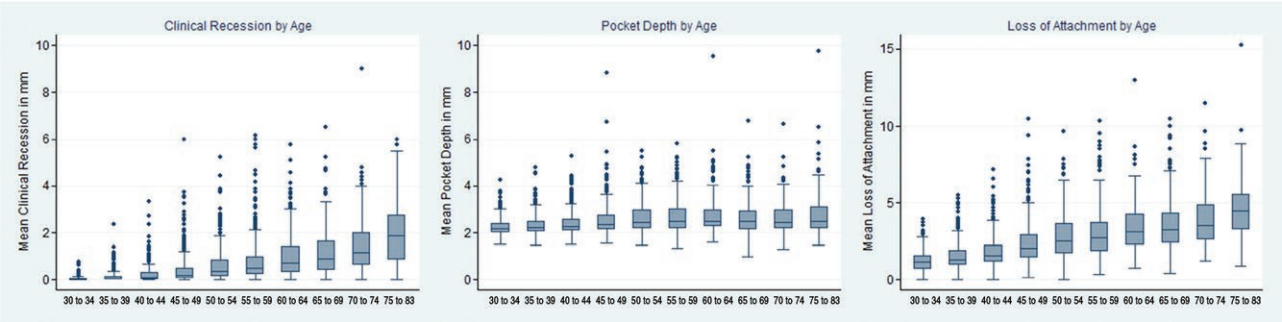

FIGURE 2B Boxplots of mean clinical recession, mean pocket depth and mean loss of attachment by age groups, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

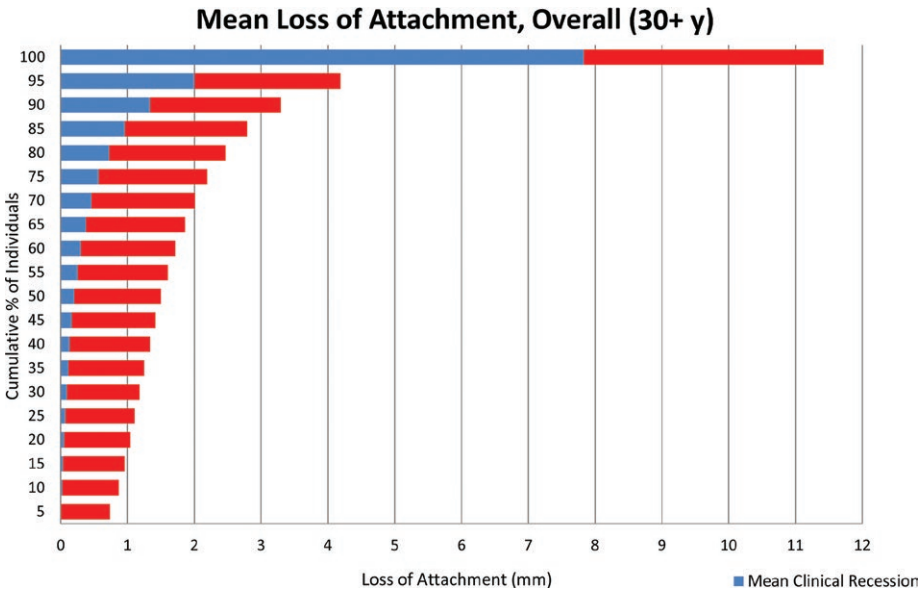

FIGURE 3A Mean loss of attachment in total population, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

population had a mean CAL of 11.4 mm and a mean clinical recession of 7.8 mm. In 75% of the sample, the mean CAL did not exceed 2.2 mm. When stratified by age (Figures 3B through 3K), 95% of the 30- to 34-year olds had a mean CAL of ≤2.5 mm and a mean clinical recession of ≤0.3 mm while the top 5% reached a mean CAL of 6.0 mm and a mean clinical recession of 2.5 mm. In contrast, 95% of the oldest participants (Figure 3K) had a mean CAL ≤4.5 mm and a mean clinical recession of < 2.7 mm, whereas the top 5% had a mean CAL of 11.1 mm and a mean clinical recession of 6.7 mm. When comparing across the lifespan by age group, the contribution of recession

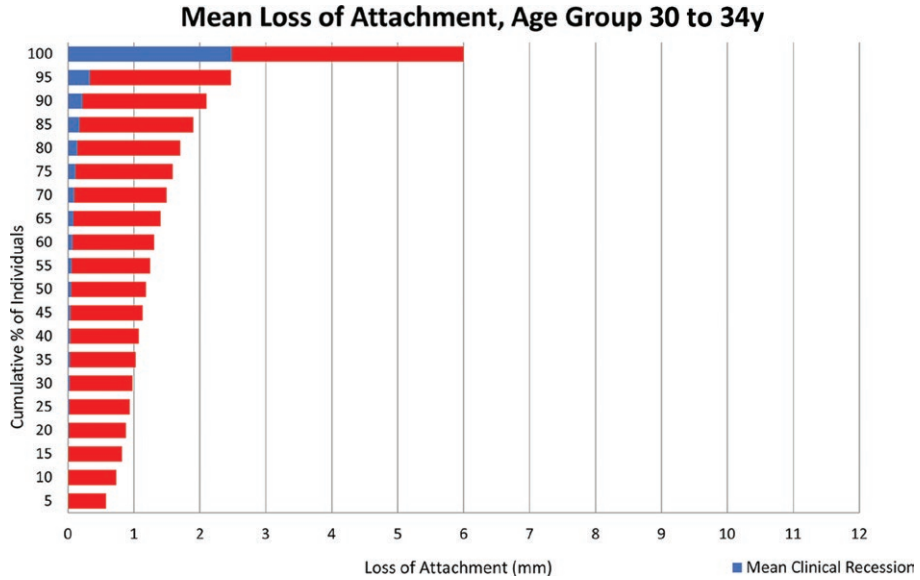

FIGURE 3B Mean loss of attachment in age group 30 to 34 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

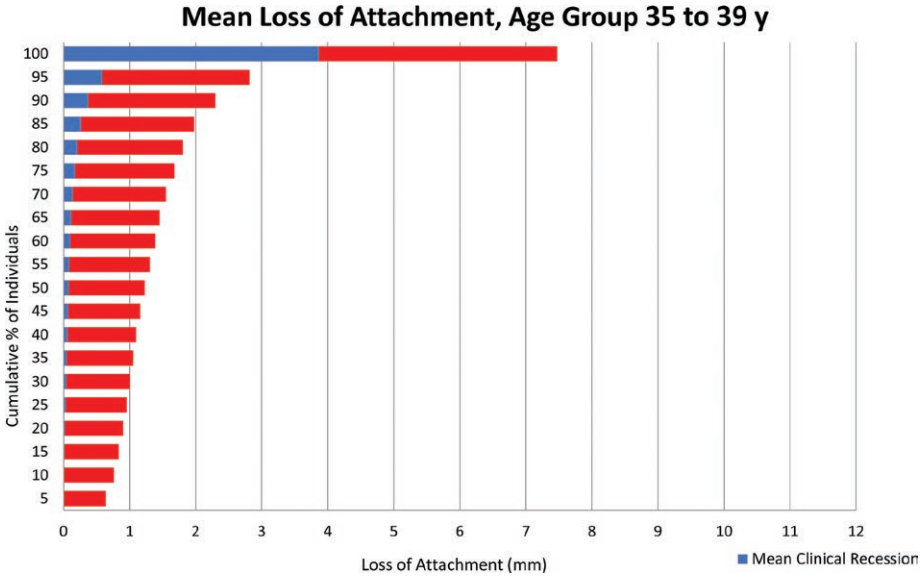

FIGURE 3C Mean loss of attachment in age group 35 to 39 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

to CAL appeared to increase substantially between 35 and 54 years with the mean recession increasing from 3.9 mm (aged 35 to 39 years, Figure 3C) to 7.8 mm (aged 50 to 54 years, Figure 3F) for the top 5% of the sample.

Table 2A shows the mean CAL, average number of sites with CAL ≥4 mm, average number of sites with PD ≥5 mm, average number of sites with clinical recession ≥3 mm, and mean number of missing teeth for all participants in the sample, as well as those in the upper quintile of mean CAL by age group. For example, in the 30- to 34-year old age group the upper quintile of CAL had a mean CAL of 2.6 mm and an average of 25 sites per person with CAL ≥4 mm, whereas in the overall sample the mean CAL was 1.3 mm and the number of sites affected by CAL ≥4 mm was 4. In ages 55 to 59 years, individuals in the upper quintile had a mean CAL of 3.5 mm and an average of 38 sites with CAL ≥4 mm, versus a mean CAL of 2.1 mm and 16 sites with CAL ≥4 mm among similarly aged individuals in the total sample. Persons in the youngest age group averaged about one missing tooth and this number increased to nine for persons in the oldest age group. In contrast, those aged 30 to 34 years in the upper quintile group averaged about two missing teeth whereas those aged ≥75 years were missing an average of 12 teeth.

When we further analyzed the distribution of average CAL in the upper quintile by tooth type and site location (disto-facial, mid-facial,

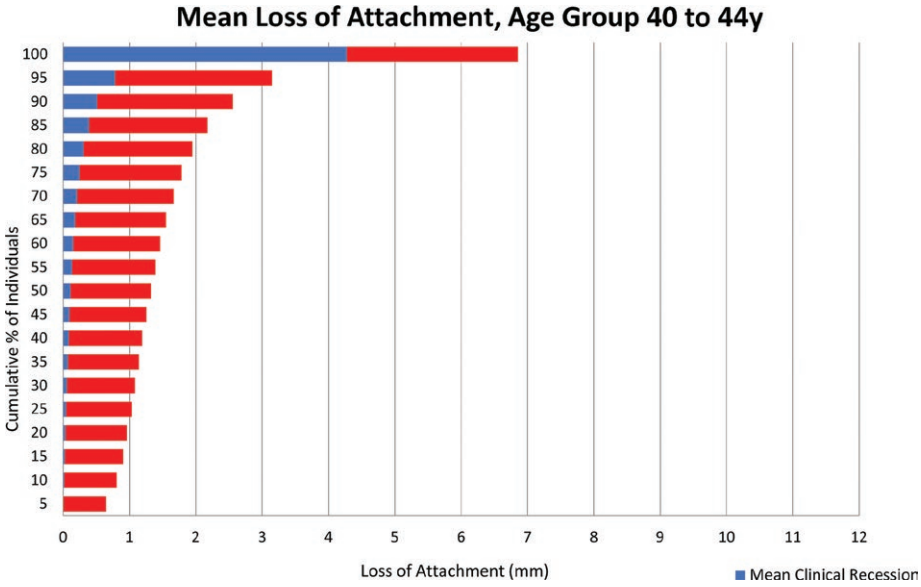

FIGURE 3D Mean loss of attachment in age group 40 to 44 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

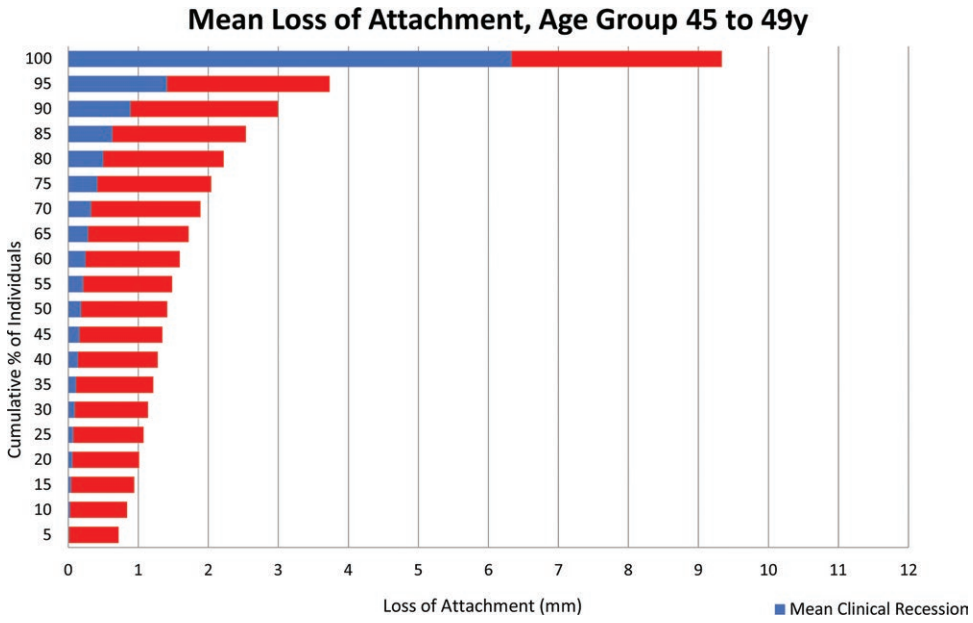

FIGURE 3E Mean loss of attachment in age group 45 to 49 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

mesio-facial, disto-lingual, mid-lingual and mesio-lingual), it was observed that across all six sites, the average CAL was generally lower for maxillary anterior teeth compared to the remaining dentition (Fig. A, Appendix). Average CAL was notably higher in the mid-lingual and mesio-lingual sites of lower anterior teeth. Clinical recession showed a variable pattern, but was more pronounced across most of the mid-facial sites and mid-lingual (predominantly among anterior teeth) sites.

When similar analyses were undertaken for individuals in the upper quintile in each age group separately (Figs. B through K, Appendix), it was observed that, in the youngest age group, predominantly mid-facial and mid-lingual sites were affected by recession. However, as age increased, interproximal sites were increasingly affected by recession, although the portion of CAL attributed to PD was relatively stable across age groups.

Findings from SHIP-Trend 2008 to 2012

SHIP-Trend participants were on average 51.9 years old (SE: 0.23), with the majority falling within the age range of 40 to 59 years (Table 1). Within this age range, proportions peaked at 45–49 years (16%). Subjects aged ≥60 years constituted ~27% of the total

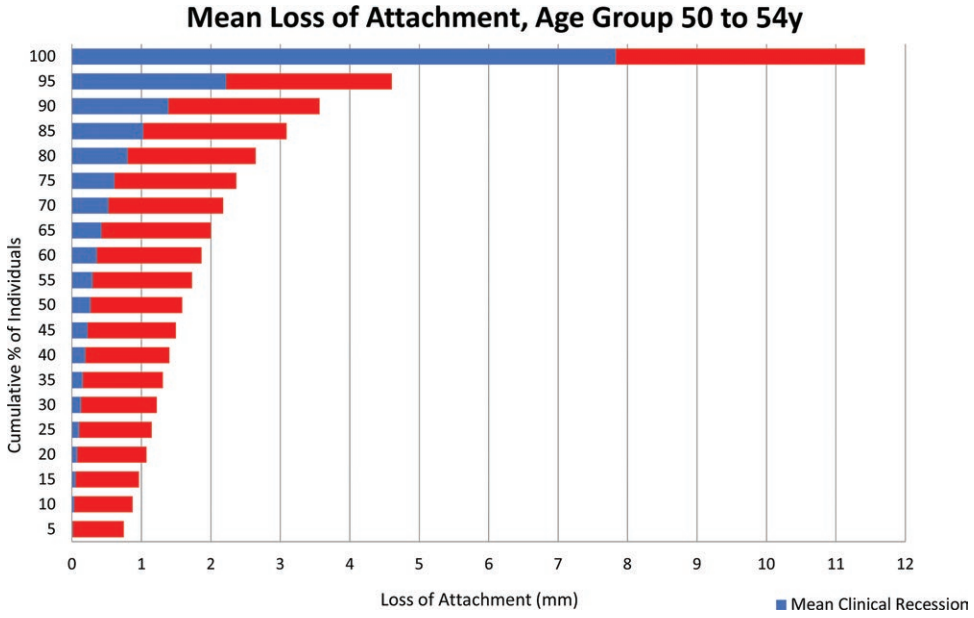

FIGURE 3F Mean loss of attachment in age group 50 to 54 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

sample. Ethnicity of the study population was European Caucasian. The majority had 10 years of schooling (54.8%).

Figure 1B shows mean CAL, mean PD, and mean clinical recession across age groups. For mean CAL, averages ranged from 1.2 mm in the youngest age group (aged 30 to 34 years) to 4.6 mm in the oldest age group (aged 75 to 83 years). Mean recession steadily increased with age and was lowest in the age group of 30 to 34 years (mean: 0.05, SE: 0.1) and highest in the age group of 75 to 83 years (mean: 1.9, SE: 1.3). In contrast, mean PD was fairly constant across age groups, with the 30- to 34-year age group having a mean PD of 2.3 mm (SE: 0.4) and the 75- to 83-year age group having a mean PD of 2.8 mm (SE: 1.0). Consistent with NHANES findings, the observed increase in mean CAL with age was primarily driven by increased recession.

Distributions of mean recession, mean PD, and mean CAL per participant were more closely investigated in boxplots of their distribution across age groups (Figure 2B). The median of subject-based mean recession steadily increased with age as did the interquartile range (i.e., the box height). Unlike recession, the median value for subject-based mean PD increased up to ages 45 to 49 years and then remained relatively stable across the older age strata. Also, interquartile ranges doubled between the youngest and the 45- to 49-year age group and remained constant thereafter. For CAL, the median value of subject-based mean CAL increased substantially across the age groups as did the interquartile range.

When subjects were grouped according to 5%-percentiles of the entire sample with respect to mean CAL (Figure 3L), it was observed that 95% of the sample had a mean CAL of < 5.5 mm and a mean clinical recession of < 2.1 mm. In contrast, for people in the top 5% of the sample, a mean CAL of 7.2 mm and a mean recession of 3.3 mm was observed. In 75% of the sample, the mean CAL did not exceed 3.4 mm. When stratified by age (Figures 3M through 3V), 95% of the 30- to 34-year olds had a mean CAL of < 2.3 mm and a mean recession of < 0.1 mm. In the top 5% group, mean CAL was 2.9 mm and mean recession was 0.2 mm. In contrast, 95% of the oldest participants (26) had a mean CAL < 7.2 mm and mean recession of < 3.6 mm. In contrast, the top 5% mean CAL was 9.5 mm and the mean recession was 4.3 mm. Thus, the contribution of recession to CAL appeared to increase dramatically over the whole age range with the mean recession increasing from 0.2 mm to 4.3 mm, respectively, for the top 5% of each age-stratified sample.

Table 2B lists additional clinical characteristics of individuals in the entire sample as well as in the upper quintile of mean CAL stratified by age group. For example, the youngest age group of the entire sample had a mean CAL of 1.19 mm, an average of 1.2 sites per person with CAL ≥4 mm, an average of 0.7 sites per person with PD ≥5 mm, an average of 0.1 sites per person with recession ≥3 mm, and an average of 1.5 missing teeth. Corresponding figures for the upper quintile in the same age group were 2.26 mm, 4.4 sites, 2.6 sites, 0.1 sites, and 2.3 missing teeth, respectively. In the 55- to 59-year old group, individuals in the entire sample had a mean CAL of 3.09 mm, 9.8 sites with CAL ≥4 mm, 2.3 sites with PD ≥5 mm, 2.5 sites with recession ≥3 mm and 7.2 missing teeth, versus a mean CAL of 5.72 mm, 19.7 sites with CAL ≥4 mm, 6.8 sites with PD ≥5 mm, 6.7 sites with recession ≥3 mm and 11.9 missing teeth in the upper quintile of the corresponding age group.

We further analyzed average CAL levels in the upper quintile group by tooth type and site location (disto-facial, mid-facial, mesio-facial and mid-lingual). Across all four sites, the average CAL was generally higher for posterior than anterior teeth, except for anterior mandibular teeth (Fig. M, Appendix). Average recession varied

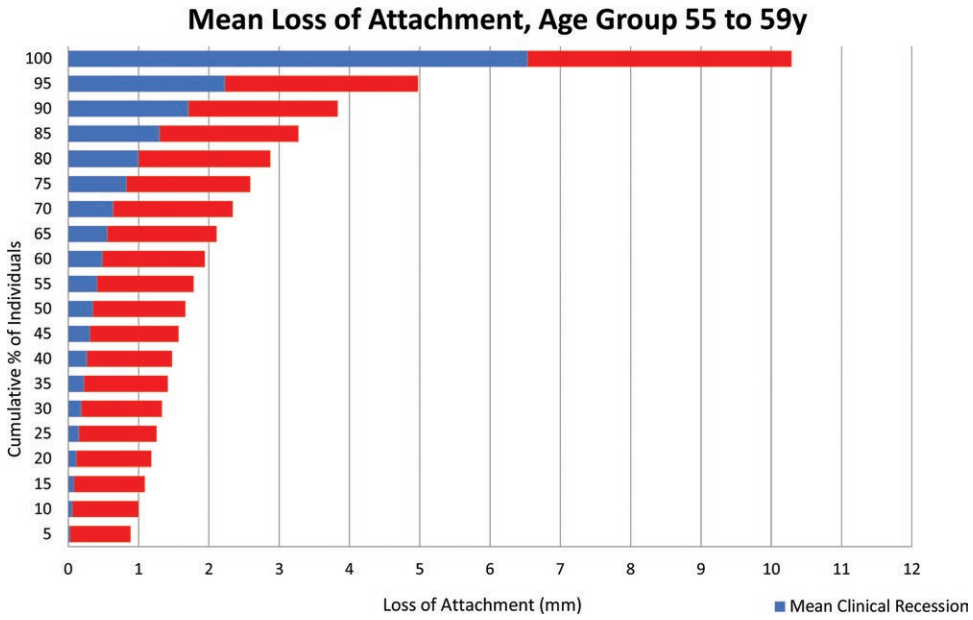

FIGURE 3G Mean loss of attachment in age group 55 to 59 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

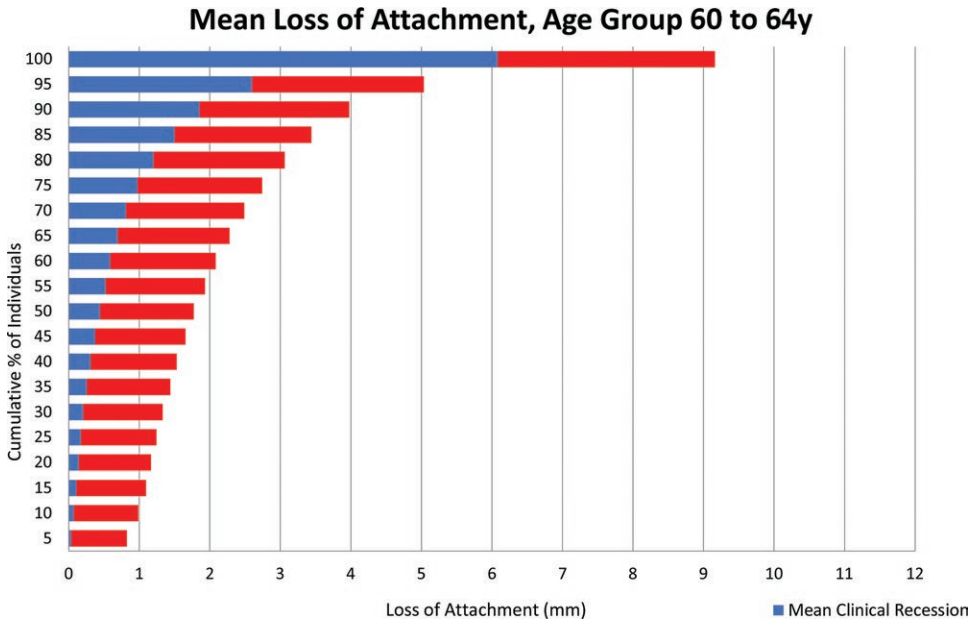

FIGURE 3H Mean loss of attachment in age group 60 to 64 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

among sites and teeth, with more pronounced recession occurring at mid-facial and mid-lingual (predominantly among posterior maxillary and anterior mandibular teeth) sites. The average contribution of PD to CAL was lowest at mid-facial sites, followed by mid-lingual sites, and highest at interproximal sites.

When similar analyses were repeated for the upper quintile within each age group, (Figs. N through X, Appendix), primarily mid-facial and mid-lingual sites were affected by recession in the youngest age groups. As age increased, interproximal sites were equally affected by recession. Across all age groups, in participants in the upper quintile of attachment loss, the contribution of PD to CAL was lower at facial and lingual sites as compared to interproximal sites.

DISCUSSION

Our primary aim with this study was to attempt to generate age-dependent thresholds of periodontitis severity, using an empirical evidence-driven epidemiologic approach derived from two population-based studies of clinical periodontal status. To provide

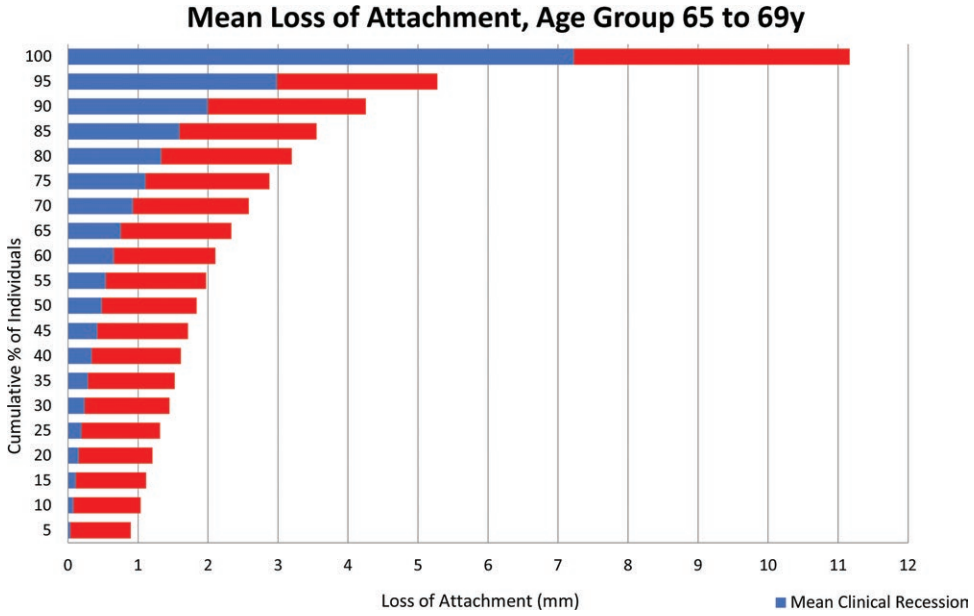

FIGURE 3I Mean loss of attachment in age group 65 to 69 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

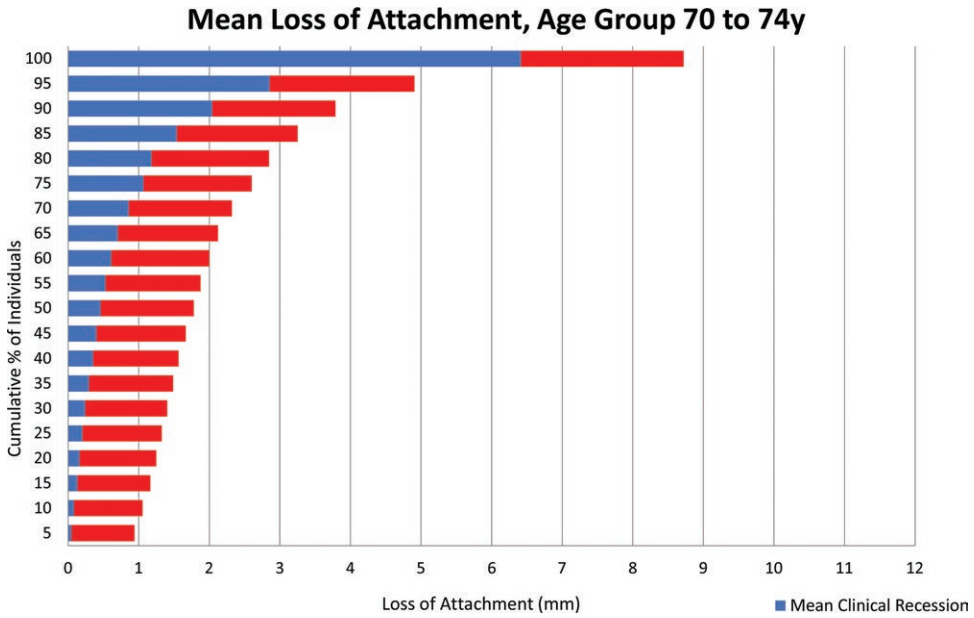

FIGURE 3J Mean loss of attachment in age group 70 to 74 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

some context, one currently adopted definition of "severe periodontitis" is based on a specific threshold of linear clinical attachment loss (> 5 mm).[13] An alternative commonly used definition of "severe periodontitis", developed by the American Academy of Periodontology and the Centers of Disease Control calls for presence of ≥2 interproximal sites with ≥6 mm CAL (not on the same tooth) and ≥1 interproximal sites with ≥5 mm PD.[22] Neither approach is ideal because the same level of attachment loss or pocket depth at different ages can signify vastly different levels of risk for disease progression and tooth loss.[14] Moreover, use of the above definitions in epidemiologic studies has resulted in questionably high estimates of the prevalence of severe periodontitis, especially in older age groups.[15] Therefore, the alternative strategy adopted in this study was to 1) examine in detail the cumulative distribution of attachment loss in two different population samples across the age spectrum, 2) identify within each age group subsets of individuals mostly affected by attachment loss, and 3) quantify thresholds of mean attachment loss which, if exceeded, identify individuals whose periodontitis severity is disproportionate to their age.

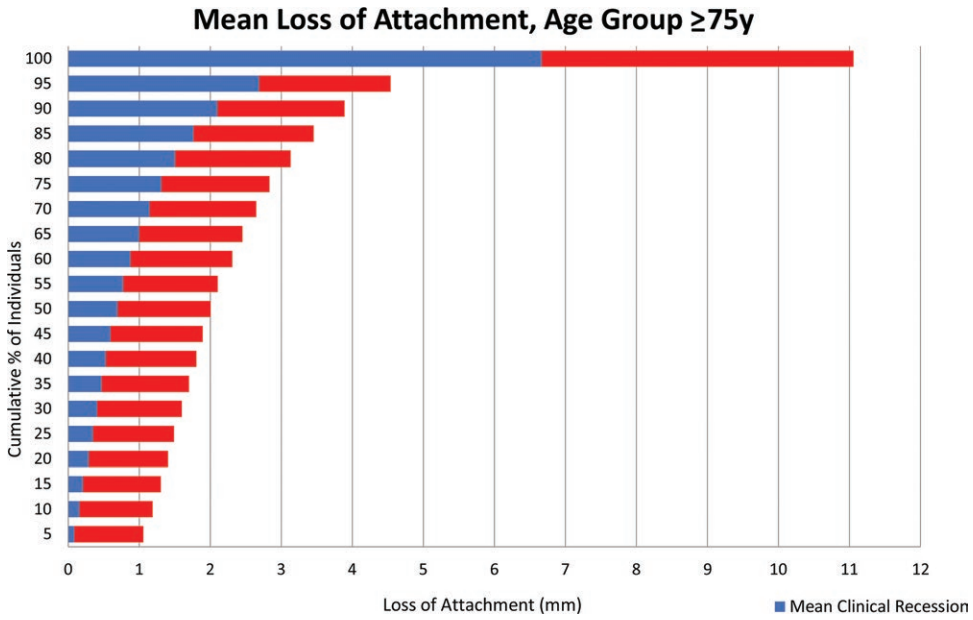

FIGURE 3K Mean loss of attachment in age group ≥75 years, full-mouth exam, National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

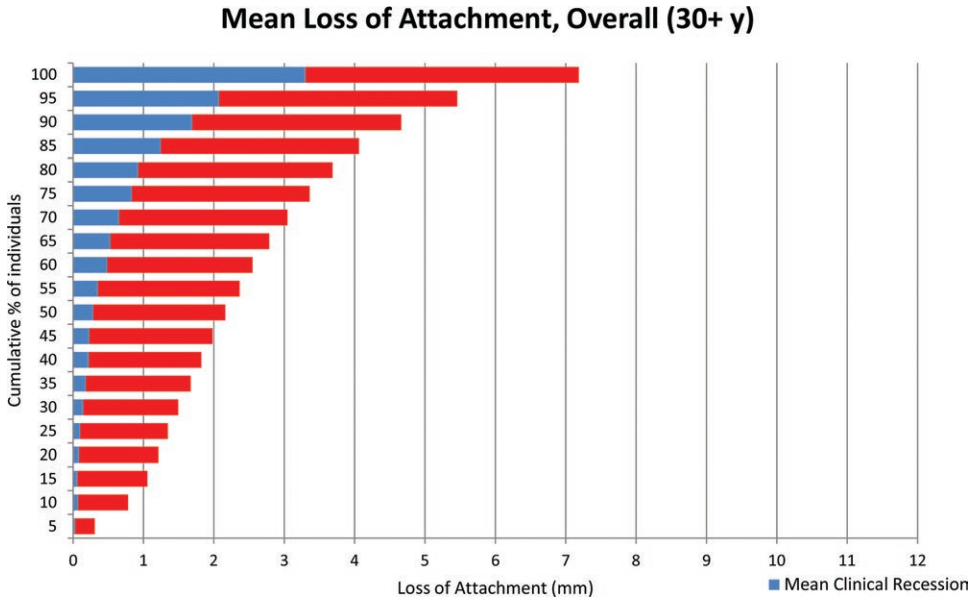

FIGURE 3L Mean loss of attachment in total population, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

Overall, mean attachment loss was higher in the Pomeranian than in the US sample across all age groups (Figures 1A and 1B), although individuals in the upper 5% of the NHANES sample displayed substantially higher average mean CAL than their SHIP-Trend counterparts (Figures 3A and 3L). However, common patterns were identified in the two populations, including a linear association of CAL with age. Interestingly, PD appeared to be the main contributor to CAL in ages up to 44 years, but in the older ages the contribution of recession to CAL increased substantially. As demonstrated by the cumulative distributions of CAL by age, for every 5-year age group in the US sample, there was a subset of the sample (at least half), where the mean attachment loss did not exceed 2 mm in each age cohort. In Pomerania, approximately a quarter of the sample had a mean attachment loss of approximately ≥3 mm. Importantly, in these cohorts, attachment loss was mostly a result of pocket depth. However, on the other end of the continuum, the slope of the percentile distribution curve changed dramatically and the upper 10% to 20% subset of the sample showed substantially higher mean CAL. In this group, the mean CAL exceeded 2 mm in both the United States and Pomerania across all age groups.

A steeper increase in average CAL in percentiles above the median was noticeable in ages over 45 to 49 years, where recession,

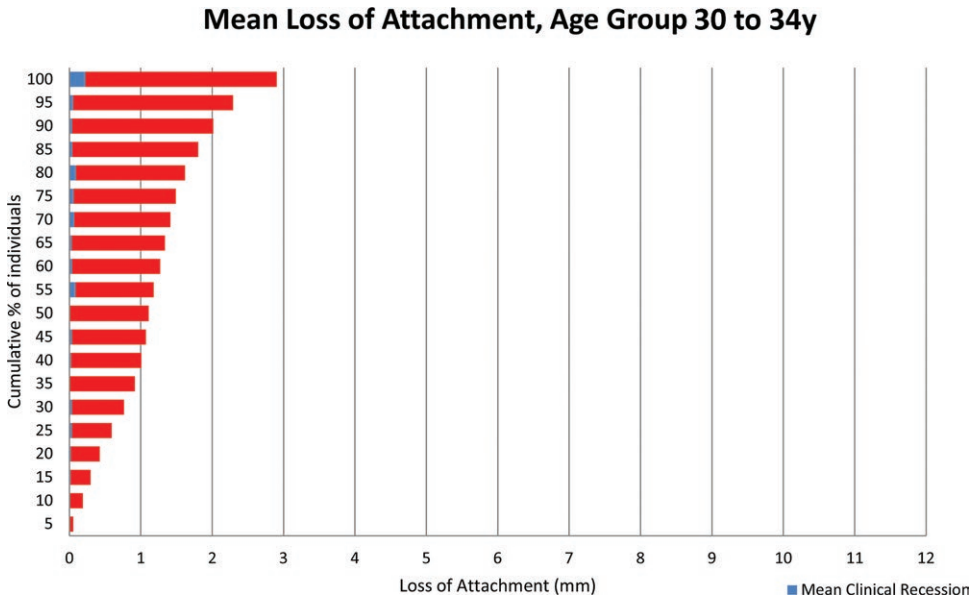

FIGURE 3M Mean loss of attachment in age group 30 to 34 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

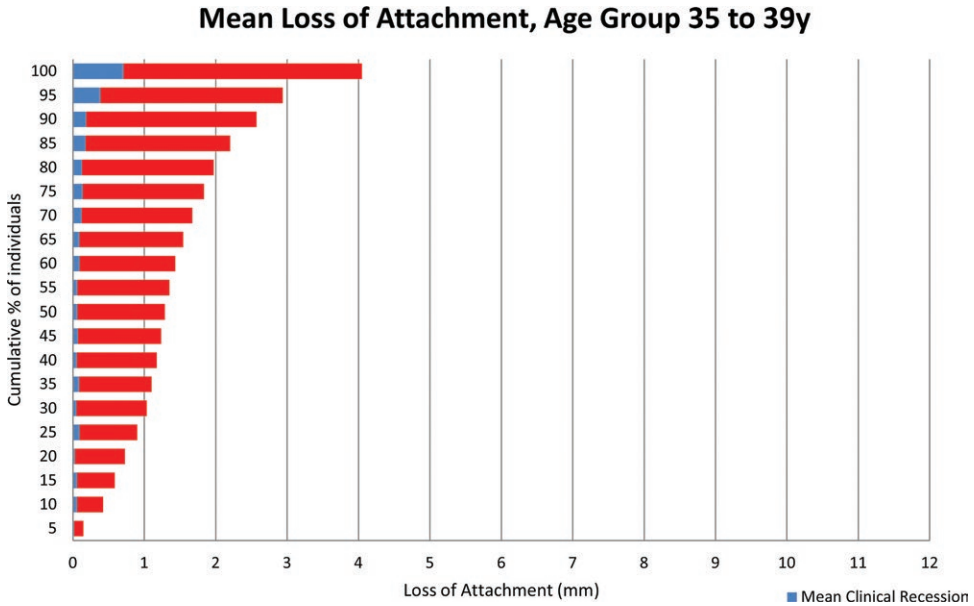

FIGURE 3N Mean loss of attachment in age group 35 to 39 years, half-mouth exam, Study of Health in Pomerania (ship)-trend 2008 to 2012

rather than pocket depth, gradually accounted for an increasing portion of clinical attachment loss. Although the median scores of the mean CAL increased with each age group in both the United States and Pomeranian population, the rate of increase was higher in the SHIP-Trend sample (Figures 2A and 2B). In both populations, the rate of increase of CAL by age was mirrored by a similar trend in recession. In nearly all age groups from both populations, adults in percentiles below the median had PD accounting for more than half of their mean CAL.

Interestingly, our data demonstrate that the mean PD remains fairly consistent across the lifespan. Furthermore, as illustrated by the boxplots, the median scores of mean PD showed little variation across age groups. Equally important, the interquartile range remained consistent across age groups, suggesting no differential change in PD by increasing age in the majority of the participants in both the United States and Pomeranian samples.

Since the NHANES and SHIP-Trend populations displayed significantly different levels of periodontitis, thresholds for mean attachment loss based on population percentiles were obviously different in the two samples. Although the threshold values for mean CAL in the upper quintile in NHANES and SHIP-Trend were very close to each other in the two youngest age groups (2.58 mm and 2.98 mm

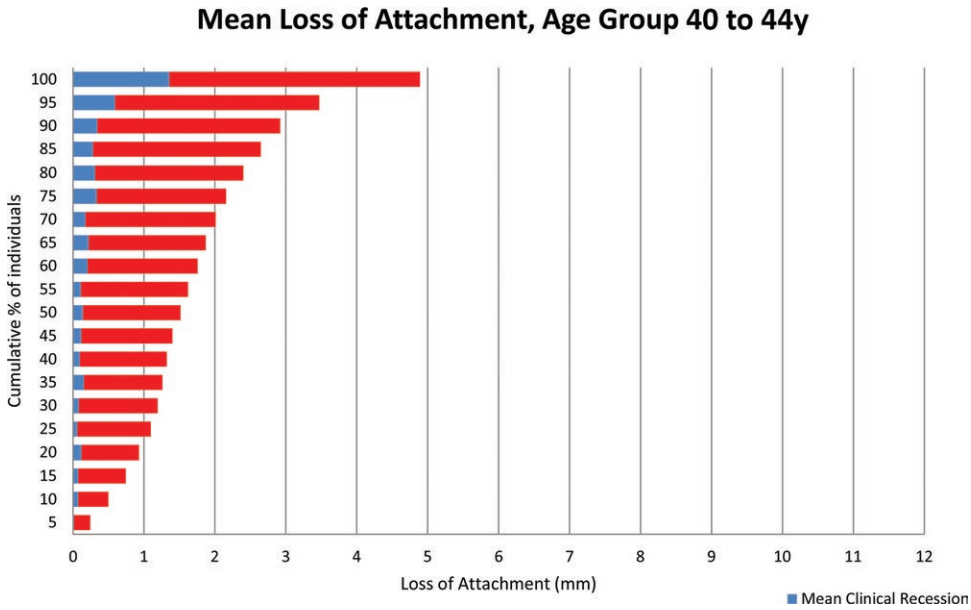

FIGURE 3O Mean loss of attachment in age group 40 to 44 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

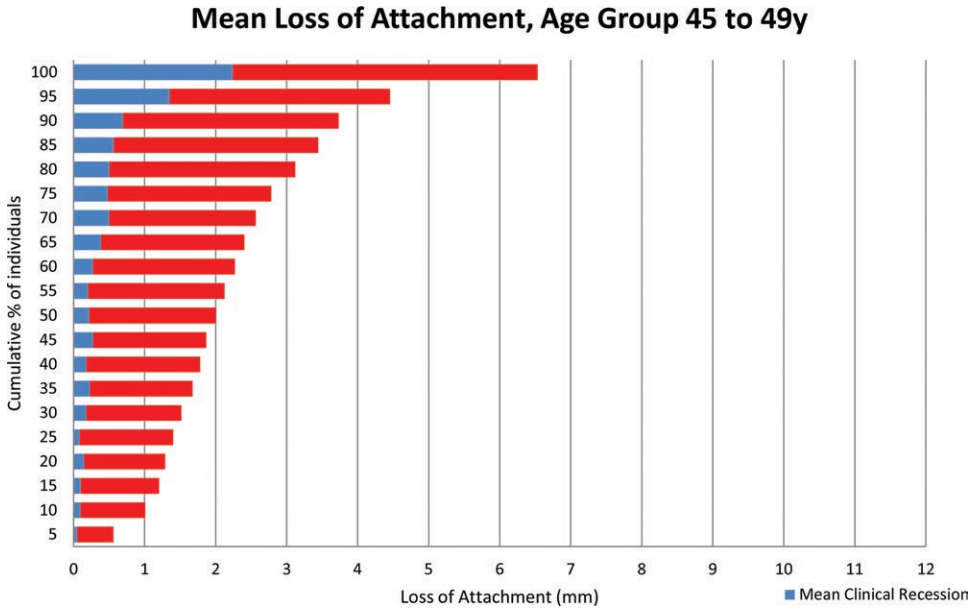

FIGURE 3P Mean loss of attachment in age group 45 to 49 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

vs. 2.26 and 2.94 mm), these thresholds diverged substantially in older ages. In NHANES, the upper quintile CAL threshold values increased gradually after the age of 40 to 44 years, peaked at 3.58 mm at age 65 to 69 years, and were somewhat lower in the two older age groups (3.40 and 3.25 mm), partly also because of an increasing number of missing teeth. In contrast, in SHIP-Trend, the upper quintile mean CAL values increased linearly and more steeply with age and peaked at 7.20 mm at the oldest age group. Thus, "universal" age-dependent thresholds of periodontitis severity by age may be better defined by the magnitude of the attachment loss *per se* rather than by a specific percentile distribution cut-off.

Nevertheless, it must be realized that utilization of such thresholds obviously requires full-mouth assessments of clinical attachment loss which is time consuming and relatively uncommon in everyday clinical practice. We therefore sought to examine in more detail the clinical periodontal characteristics of those individuals who were identified as belonging to the upper quintile of their age group with respect to mean CAL. Thus, the value of the data presented in Tables 2A and 2B, as well as in the Appendix graphs that visualize the tooth- and site-specific patterns of CAL, lies with their potential to provide surrogate markers that can be employed in the identification of individuals in the upper quintile of mean CAL, in

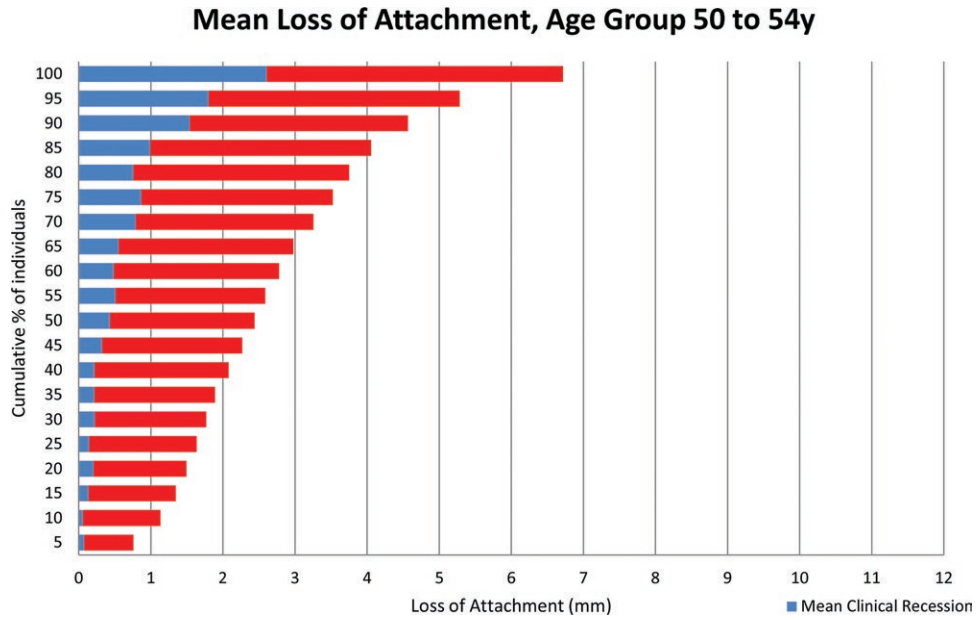

FIGURE 3Q Mean loss of attachment in age group 50 to 54 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

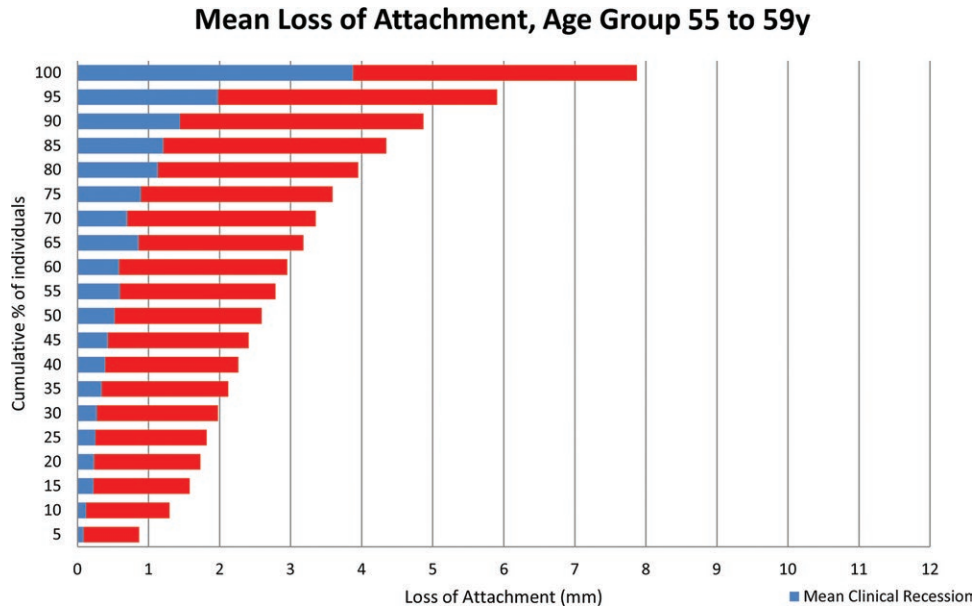

FIGURE 3R Mean loss of attachment in age group 55 to 59 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

the absence of full mouth CAL. For example, it would be useful to attempt to employ easily assessable measures of periodontal status, such as number of missing teeth, number of pockets beyond a certain depth, or number of sites with visible recession exceeding a defined threshold to identify individuals in the upper quintile of CAL. Obviously, the development of such a predictive tool has to undergo a formal validation process before it can be implemented, and is beyond the scope of the current work.

Alternatively, validation of these thresholds should include a longitudinal assessment examining whether identified individuals ran a higher risk of tooth loss due to periodontitis, in a manner analogous to the utility of hypertension thresholds generated in the Framingham Studies to predict incident cardiovascular disease or mortality.[16] These subsequent analyses should be carried out in existing longitudinal data sets from different population samples to examine whether there are "inherent" age-dependent thresholds of periodontitis severity, beyond which tooth loss is inevitable.

Furthermore, the Appendix graphs provide a clear illustration of the commonalities in the relationship between recession and CAL in specific teeth and periodontal sites in NHANES and SHIP-Trend. In

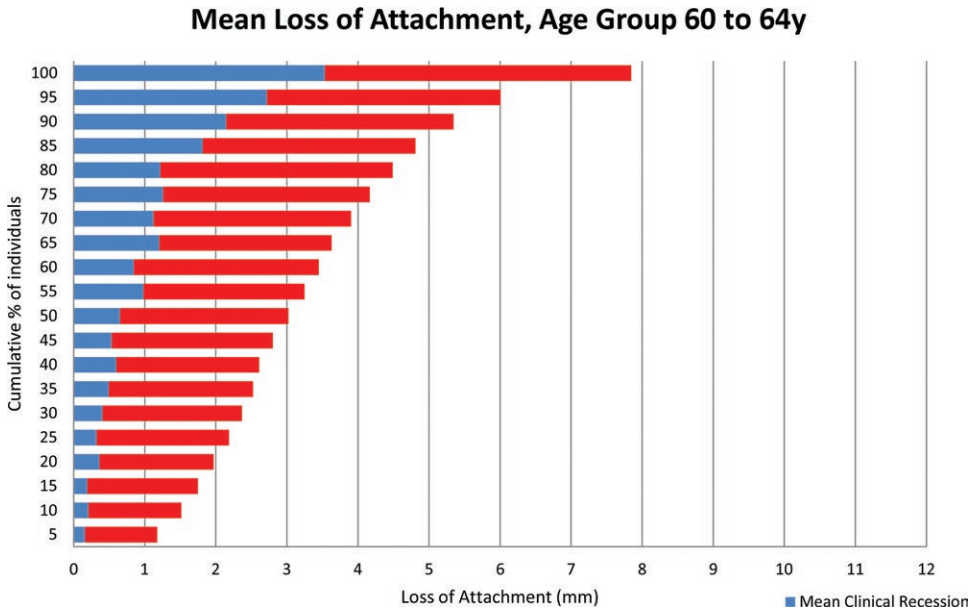

FIGURE 3S Mean loss of attachment in age group 60 to 64 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

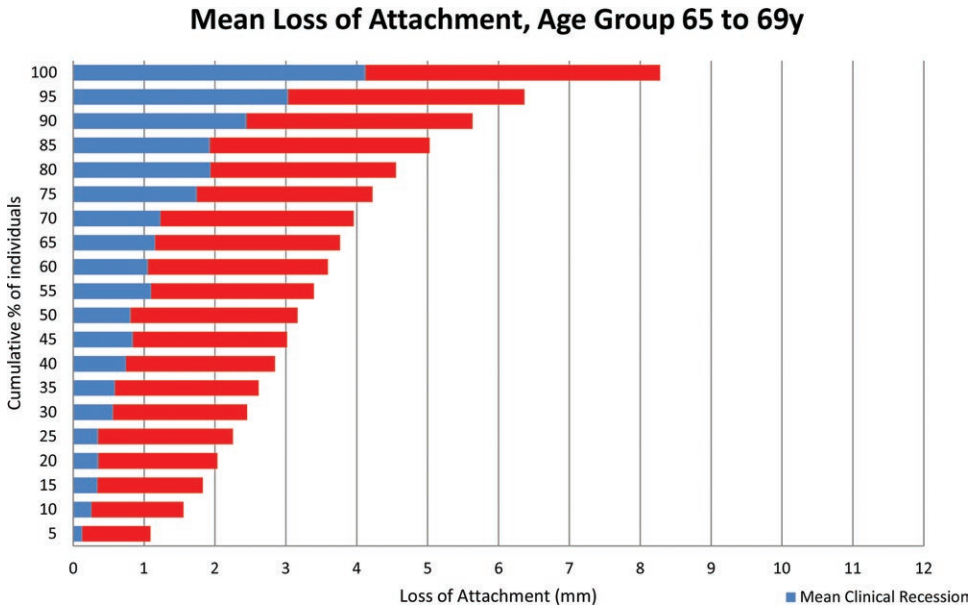

FIGURE 3T Mean loss of attachment in age group 65 to 69 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

both populations, individuals in the upper quintile of CAL showed highest average CAL and recession at the lower anterior teeth and posterior molars. In both populations, the disto-facial aspect of the upper first molar and the mesio-facial of the upper second molar showed the highest average CAL. Lower anterior teeth consistently presented with high levels of clinical recession.

Our study has important strengths, notably the fact that it is based on two large population-based national surveys from two developed countries. Although NHANES is based on a FMPE assessing 28 teeth at six sites per tooth, thereby providing an accurate estimation of the prevalence of periodontitis in the US population, SHIP-Trend is based on a PMPE assessing four sites per tooth, which may have resulted in underestimation of prevalence. However, given that the focus of our study was the age-dependent distribution of CAL and related periodontal measures rather than assessment of prevalence of periodontitis within the respective populations, it is unlikely that this methodological limitation has had any substantial impact on our findings. Moreover, the study does not attempt to make any causal inferences on the role of age on periodontal status due to its cross-sectional design. The study samples were limited

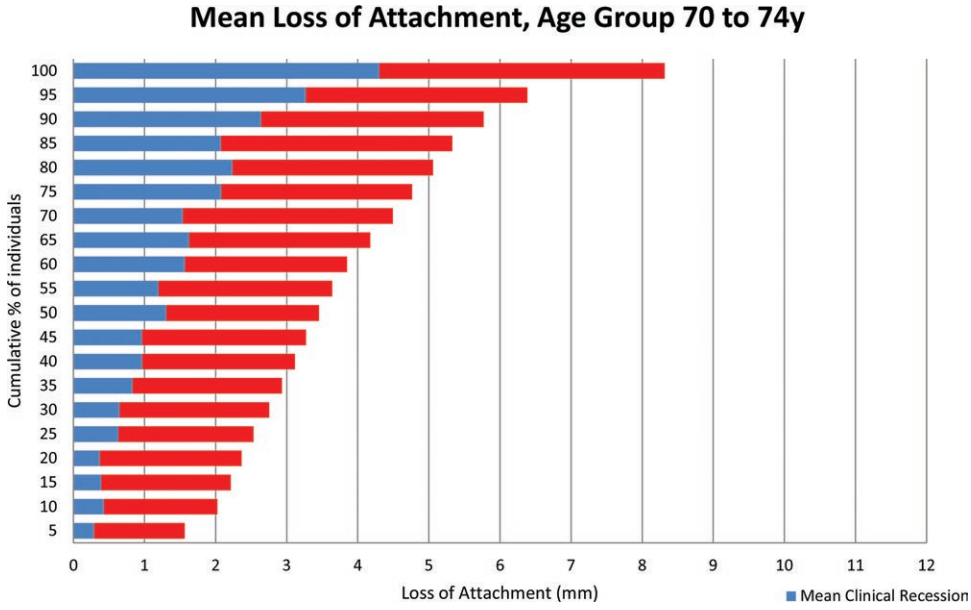

FIGURE 3U Mean loss of attachment in age group 70 to 74 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

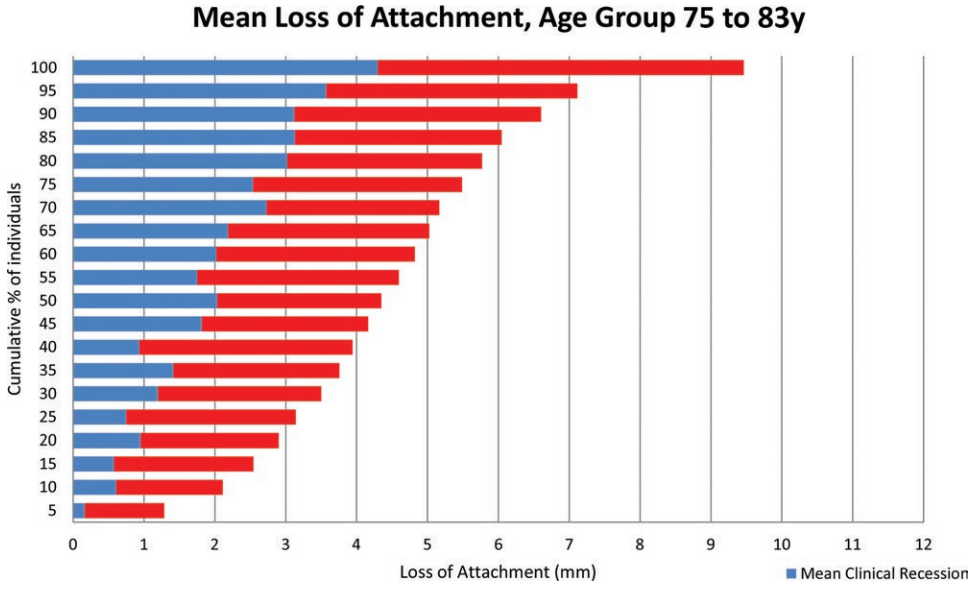

FIGURE 3V Mean loss of attachment in age group 75 to 83 years, half-mouth exam, Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

to adults aged ≥30 years, consequently, age-dependent patterns of CAL in younger individuals were unascertainable. Both studies excluded those with a medical condition that would require antibiotic prophylaxis prior to probing and institutionalized individuals, therefore, a segment of the population with potentially more severe periodontitis may have not been assessed. Nevertheless, it is unlikely that the age-dependent distributions of CAL generated in the study would be substantially different, had these individuals been included in the samples examined.

Lastly, we note that the NHANES and SHIP-Trend populations showed substantially different levels of periodontitis severity, a finding that is likely attributed to cohort effects. Typically, cohort effects are driven by age, as age and related period effects can be a strongly associated, resulting in confounding. However, the mean age of both populations did not differ substantially (51 vs. 52 years) and the sample sizes among the analyzed age groups were similar. Additional attributes, rather than age, that were unique to each population and are more

TABLE 2A Comparison of participants in the upper quintile of mean clinical attachment levels (CAL) with the entire sample, by age. National Health and Nutrition Examination Survey (NHANES) 2009 to 2014

	Total population[a]						Upper quintile group (top 20%)[a]					
Age	n	Mean CAL	Mean no. of sites with CAL ≥4 mm	Mean no. of sites with PD ≥5 mm	Mean no. of sites with recession ≥3 mm	Mean no. of teeth missing [b]	n	Mean CAL	Mean no. of sites with CAL ≥4 mm	Mean no. of sites with PD ≥5 mm	Mean no. of sites with recession ≥3 mm	Mean no. of teeth missing [b]
30–34	1,298	1.32	3.7	0.8	0.7	1.3	139	2.58	24.7	5.9	2.9	1.7
35–39	1,253	1.42	5.6	1.2	1.5	1.9	154	2.98	33.5	7.8	7.4	3.2
40–44	1,303	1.54	8.0	1.8	2.4	2.4	215	3.04	37.0	9.1	9.3	3.7
45–49	1,195	1.72	10.5	1.9	4.0	3.4	281	3.16	35.9	6.9	12.2	5.9
50–54	1,195	2.00	13.9	2.0	6.3	4.8	389	3.43	36.3	5.6	15.6	7.8
55–59	986	2.13	15.8	2.2	7.6	5.4	355	3.46	37.7	5.7	17.1	8.5
60–64	1,150	2.20	16.7	1.9	8.5	6.7	459	3.47	36.5	4.5	17.6	9.7
65–69	790	2.30	16.3	1.5	8.9	7.6	325	3.58	34.0	3.2	18.0	11.6
70–74	598	2.15	12.5	0.8	7.6	8.4	217	3.40	28.2	1.7	16.7	12.3
≥75	902	2.32	16.5	0.7	9.9	9.3	417	3.25	30.3	1.3	17.5	11.6

[a]Based on full-mouth examination.
[b]Based on a 28-tooth dentition.

TABLE 2B Comparison of participants in the upper quintile of mean clinical attachment levels (CAL) with the entire sample, by age. Study of Health in Pomerania (SHIP)-Trend 2008 to 2012

	Total population[a]						Upper quintile group (top 20%)[a]					
Age	n	Mean CAL	Mean no. of sites with CAL ≥4 mm	Mean no. of sites with PD ≥5 mm	Mean no. of sites with recession ≥3 mm	Mean no. of teeth missing[b]	n	Mean CAL	Mean no. of sites with CAL ≥4 mm	Mean no. of sites with PD ≥5 mm	Mean no. of sites with recession ≥3 mm	Mean no. of teeth missing[b]
30 to 34	297	1.19	1.2	0.7	0.1	1.5	59	2.26	4.4	2.6	0.1	2.3
35 to 39	320	1.52	3.1	1.2	0.3	2.5	64	2.94	11.1	4.1	1.1	4.0
40 to 44	383	1.83	4.9	1.6	0.8	3.1	75	3.52	16.0	5.6	2.5	4.9
45 to 49	409	2.41	6.9	2.1	1.4	4.6	78	4.58	18.3	6.4	4.3	8.0
50 to 54	369	2.80	8.6	2.2	2.0	6.5	73	5.17	19.0	6.4	5.8	11.6
55 to 59	371	3.09	9.8	2.3	2.5	7.2	73	5.72	19.7	6.8	6.7	11.9
60 to 64	314	3.43	10.6	2.0	3.3	8.5	59	5.93	16.2	4.1	7.3	14.7
65 to 69	282	3.61	11.3	1.6	4.1	9.4	56	6.30	17.4	4.0	9.2	15.5
70 to 74	188	3.84	11.3	1.4	4.7	11.1	36	6.40	17.7	3.3	9.7	16.1
75 to 83	138	4.54	11.5	1.4	4.8	14.3	27	7.20	9.8	3.1	5.7	20.7

[a]Based on half-mouth examination.
[b]Based on a 28-tooth dentition.

likely underlying the cohort effect include social/political/economic conditions, access to care, and exposure to important risk factors such as cigarette smoking. In the United States, cigarette smoking has been declining and only 18% of the NHANES sample analyzed in this study were current smokers. In contrast, smoking was more prevalent in the SHIP-Trend cohort, with > 35% of the participants being current smokers. Because the population attributable risk for periodontitis due to smoking is high, the differences seen in periodontitis severity between the two countries can be attributed to a large extent to differences in smoking. Tooth loss was also different between the two populations and could have contributed to a cohort effect as well. Although loss of periodontitis-affected teeth can conceivably result in "healthy tooth survivor" effects, it has been shown that individuals with fewer remaining teeth have higher mean CAL and PD measures.[17,18] However, the reasons underlying the observed differences in periodontitis severity between NHANES and SHIP-Trend was not the main purpose of this report which rather focused on illustrating patterns of attachment loss by age.

Our study is an exploratory, initial step towards introducing empirical evidence-driven, age-dependent thresholds for severe periodontitis. It provides detailed evidence that age is a significant determinant of the clinical presentation of periodontitis, and demonstrates that the relative contribution of pocketing and recession to total attachment loss differs with age. At the same time, the substantial phenotypic variability within each age group strongly suggests that exposures other than age are pivotal in determining susceptibility to periodontitis. Additional data from other populations must be used to augment the generalizability of the present findings.

ACKNOWLEDGMENTS AND DISCLOSURES

All study participants gave informed consent in accordance with the respective research ethics review boards for both the NHANES and SHIP-Trend studies. SHIP is part of the Community Medicine Research (CMR) program of the University Medicine Greifswald, Germany, which is funded by the Federal Ministry of Education and Research, the Ministry of Cultural Affairs, as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania. The CMR encompasses several research projects, which are sharing data of population-based studies SHIP (http://ship.community-medicine.de). The National Health and Nutrition Examination Survey (NHANES) is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention and receives additional funding from various agencies of the US Government. This research was partially supported by the National Institute of Dental and Craniofacial Research (NIDCR), and some authors were paid a salary by the NIH. The views expressed in this article are those of the authors and do not necessarily represent the views of the National Institutes of Health or the US Government. The authors do not have any financial or other competing interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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2017 WORLD WORKSHOP

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Staging and grading of periodontitis: Framework and proposal of a new classification and case definition

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Background: Authors were assigned the task to develop case definitions for periodontitis in the context of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. The aim of this manuscript is to review evidence and rationale for a revision of the current classification, to provide a framework for case definition that fully implicates state-of-the-art knowledge and can be adapted as new evidence emerges, and to suggest a case definition system that can be implemented in clinical practice, research and epidemiologic surveillance.

Methods: Evidence gathered in four commissioned reviews was analyzed and interpreted with special emphasis to changes with regards to the understanding available prior to the 1999 classification. Authors analyzed case definition systems employed for a variety of chronic diseases and identified key criteria for a classification/case definition of periodontitis.

Results: The manuscript discusses the merits of a periodontitis case definition system based on Staging and Grading and proposes a case definition framework. Stage I to IV of periodontitis is defined based on severity (primarily periodontal breakdown with reference to root length and periodontitis-associated tooth loss), complexity of management (pocket depth, infrabony defects, furcation involvement, tooth hypermobility, masticatory dysfunction) and additionally described as extent (localized or generalized). Grade of periodontitis is estimated with direct or indirect evidence of progression rate in three categories: slow, moderate and rapid progression (Grade A-C). Risk factor analysis is used as grade modifier.

Conclusions: The paper describes a simple matrix based on stage and grade to appropriately define periodontitis in an individual patient. The proposed case definition extends beyond description based on severity to include characterization of biological features of the disease and represents a first step towards adoption of precision medicine concepts to the management of periodontitis. It also provides the necessary framework for introduction of biomarkers in diagnosis and prognosis.

KEYWORDS

aggressive periodontitis, biomarkers, case definition, chronic periodontitis, classification, clinical attachment loss, diagnosis, furcation involvement, grade A periodontitis, grade B

periodontitis, grade C periodontitis, inflammatory burden, infrabony defect, masticatory dysfunction, necrotizing periodontitis, periodontal pocket, periodontitis, periodontitis as manifestation of systemic disease, periodontitis/grade, periodontitis/stage, radiographic bone loss, risk factors, stage I periodontitis, stage II periodontitis, stage III periodontitis, stage IV periodontitis, standard of care, tooth hypermobility, tooth loss

INTRODUCTION: THE 1999 CLASSIFICATION OF PERIODONTITIS

Periodontitis is characterized by microbially-associated, host-mediated inflammation that results in loss of periodontal attachment. The pathophysiology of the disease has been characterized in its key molecular pathways, and ultimately leads to activation of host-derived proteinases that enable loss of marginal periodontal ligament fibers, apical migration of the junctional epithelium, and allows apical spread of the bacterial biofilm along the root surface. The bacterial biofilm formation initiates gingival inflammation; however, periodontitis initiation and progression depend on dysbiotic ecological changes in the microbiome in response to nutrients from gingival inflammatory and tissue breakdown products that enrich some species and anti-bacterial mechanisms that attempt to contain the microbial challenge within the gingival sulcus area once inflammation has initiated. Current evidence supports multifactorial disease influences, such as smoking, on multiple immunoinflammatory responses that make the dysbiotic microbiome changes more likely for some patients than others and likely influence severity of disease for such individuals.

Marginal alveolar bone loss – a key secondary feature of periodontitis – is coupled with loss of attachment by inflammatory mediators. Clinical presentation differs based on age of patient and lesion number, distribution, severity, and location within the dental arch. The level of oral biofilm contamination of the dentition also influences the clinical presentation.

In recent decades, attempts to classify periodontitis have centered on a dilemma represented by whether phenotypically different case presentations represent different diseases or just variations of a single disease. Lack of ability to resolve the issue is illustrated in the changes to the classification system that progressively emphasized either differences or commonalities.[1,2] Shortly before the 1999 International Workshop on Classification of Periodontal Diseases, research in the field emphasized individual features of periodontitis and thus differences in phenotype. These emerged from the identification of specific bacteria or bacterial complexes as etiologic agents of periodontitis,[3] the recognition of the existence of multiple modifiable risk factors,[4] and the identification of the relevance of genetic susceptibility[5,6] and specific polymorphisms associated with disease severity.[7] The research perspective on the disease impacted the 1999 classification system that emphasized perceived unique features of different periodontitis phenotypes and led to the recognition of four different forms of periodontitis:

1. Necrotizing periodontitis
2. Chronic periodontitis
3. Aggressive periodontitis
4. Periodontitis as a manifestation of systemic diseases

The overall classification system aimed to differentiate the more common forms of periodontitis, i.e. chronic and aggressive periodontitis, from the unusual necrotizing form of the disease (characterized by a unique pathophysiology, distinct clinical presentation and treatment), and the rare major genetic defects or acquired deficiencies in components of host defense (characterized by a primary systemic disorder that also expresses itself by premature tooth exfoliation).

The 1999 group consensus report on aggressive periodontitis identified specific features of this form of disease and proposed the existence of major and minor criteria for case definition as well as distribution features to differentiate localized from generalized forms of periodontitis.[8] By default, cases of periodontitis that would not satisfy the "aggressive" phenotype definition would be classified as "chronic" with the implication that latter cases could be managed more easily and, with appropriate therapy and maintenance care, would rarely jeopardize the retention of a functional dentition.[9] The rationale for differentiating between chronic and aggressive periodontitis included the ability to identify and focus on the more problematic cases: presenting with greater severity earlier in life, at higher risk of progression and/or in need of specific treatment approaches.

The 1999 workshop addressed a host of concerns with the clinical applicability and pathophysiologic rationale of previous classification systems (see Armitage 1999[10] for discussion), emphasized the need to capture differences between forms of the disease able to lead to edentulism, but did not clearly communicate differences between chronic and aggressive periodontitis. While the consensus report of the aggressive periodontitis working group articulated major and minor criteria required for the aggressive periodontitis diagnosis as well as specific definitions to identify patterns of distribution of lesions within the dentition (localized molar incisor versus generalized, see Lang et al. 1999[8] for detailed discussion), the difficulty in applying the stipulated criteria in the everyday clinical practice and the substantial overlap between the diagnostic categories provided a barrier to clinicians in the application of the classification system. Furthermore, the validity of many of the criteria for aggressive periodontitis has not been confirmed in adequately designed studies.

Over the past 2 decades clinicians, educators, researchers and epidemiologists have voiced concern about their ability to correctly

differentiate between aggressive and chronic periodontitis cases, and these difficulties have been a major rationale for a new classification workshop.[11]

SUMMARY AND INTERPRETATION OF EVIDENCE FROM CURRENT WORKSHOP POSITION PAPERS

To update evidence that has accumulated since the latest classification workshop, the organizing committee commissioned a review on acute periodontal lesions including necrotizing periodontitis,[12] a review of manifestations of systemic diseases that affect the periodontal attachment apparatus,[13] and three position papers that are relevant to the discussion of aggressive and chronic periodontitis.[14–16]

The position papers that addressed aggressive and chronic periodontitis reached the following overarching conclusions relative to periodontitis:

1. There is no evidence of specific pathophysiology that enables differentiation of cases that would currently be classified as aggressive and chronic periodontitis or provides guidance for different interventions.
2. There is little consistent evidence that aggressive and chronic periodontitis are different diseases, but there is evidence of multiple factors, and interactions among them, that influence clinically observable disease outcomes (phenotypes) at the individual level. This seems to be true for both aggressive and chronic phenotypes.
3. On a population basis, the mean rates of periodontitis progression are consistent across all observed populations throughout the world.
4. There is evidence, however, that specific segments of the population exhibit different levels of disease progression, as indicated by greater severity of clinical attachment loss (CAL) in subsets of each age cohort relative to the majority of individuals in the age cohort.
5. A classification system based only on disease severity fails to capture important dimensions of an individual's disease, including the complexity that influences approach to therapy, the risk factors that influence likely outcomes, and level of knowledge and training required for managing the individual case.

Authors' interpretation of current evidence reviews

There is sufficient evidence to consider necrotizing periodontitis as a separate disease entity. Evidence comes from: i) a distinct pathophysiology characterized by prominent bacterial invasion and ulceration of epithelium; ii) rapid and full thickness destruction of the marginal soft tissue resulting in characteristic soft and hard tissue defects; iii) prominent symptoms; and iv) rapid resolution in response to specific antimicrobial treatment.

There is sufficient evidence to consider that periodontitis observed in the context of systemic diseases that severely impair host response should be considered a periodontal manifestation of the systemic disease and that the primary diagnosis should be the systemic disease according to International Statistical Classification of Disease (ICD).[13,17] Many of these diseases are characterized by major functional impairment of host defenses and have multiple non-oral sequelae. At the moment there is insufficient evidence to consider that periodontitis observed in poorly controlled diabetes is characterized by unique pathophysiology and/or requires specific periodontal treatment other than the control of both co-morbidities.[18]

Despite substantial research on aggressive periodontitis since the 1999 workshop,[14] there is currently insufficient evidence to consider aggressive and chronic periodontitis as two pathophysiologically distinct diseases.

Current multifactorial models of disease applied to periodontitis appear to account for a substantial part of the phenotypic variation observed across cases as defined by clinical parameters. Multiple observational studies in populations with long-term exposure to microbial biofilms on the teeth have shown that a small segment of the adult population expresses severe generalized periodontitis and most express mild to moderate periodontitis.[19,20] It is also well documented using twin studies that a large portion of the variance in clinical severity of periodontitis is attributable to genetics.[5,6,21,22]

It is reasonable to expect that future research advances will increase our knowledge of disease-specific mechanisms in the context of the multifactorial biological interactions involved in specific phenotypes. That pursuit may be valuable in guiding better management of complex cases and may lead to novel approaches that enhance periodontitis prevention, control, and regeneration. Multi-dimensional profiles that combine biological and clinical parameters are emerging that better define phenotypes and may guide deeper understanding of the mechanisms that lead to differences in phenotypes.[23–26]

There is clinical value in individualizing the diagnosis and the case definition of a periodontitis patient to take into account the known dimension of the multifactorial etiology to improve prognosis, account for complexity and risk, and provide an appropriate level of care for the individual.

INTEGRATING CURRENT KNOWLEDGE TO ADVANCE CLASSIFICATION OF PERIODONTITIS

Clinical definition of periodontitis

Periodontitis is characterized by microbially-associated, host-mediated inflammation that results in loss of periodontal attachment. This is detected as clinical attachment loss (CAL) by circumferential assessment of the erupted dentition with a standardized periodontal probe with reference to the cemento-enamel junction (CEJ).

It is important to note:

1. Some clinical conditions other than periodontitis present with clinical attachment loss.
2. Periodontitis definitions based on marginal radiographic bone loss suffer from severe limitations as they are not specific enough and miss detection of mild to moderate periodontitis.[27] Periodontitis definitions based on radiographic bone loss should be limited to the stages of mixed dentition and tooth eruption when clinical attachment level measurement with reference to the CEJ are impractical.[28] In such cases periodontitis assessments based on marginal radiographic bone loss may use bitewing radiographs taken for caries detection.

Objectives of a periodontitis case definition system

A case definition system should facilitate the identification, treatment and prevention of periodontitis in individual patients. Given current knowledge, a periodontitis case definition system should include three components:

1. Identification of a patient as a periodontitis case,
2. Identification of the specific form of periodontitis, and
3. Description of the clinical presentation and other elements that affect clinical management, prognosis, and potentially broader influences on both oral and systemic health.

Furthermore, case definitions may be applied in different contexts: patient care, epidemiological surveys and research on disease mechanisms or therapeutic outcomes, as discussed in Appendix A in the online *Journal of Clinical Periodontology*. In the various contexts, case definitions may require different diagnostic characteristics based on the objectives of the specific application, as is discussed below.

Definition of a patient as a periodontitis case

Given the measurement error of clinical attachment level with a standard periodontal probe, a degree of misclassification of the initial stage of periodontitis is inevitable and this affects diagnostic accuracy. As disease severity increases, CAL is more firmly established, and a periodontitis case can be identified with greater accuracy. Decreasing the threshold of CAL increases sensitivity. Increasing the threshold, requiring CAL at ≥1 site, and excluding causes of CAL, other than periodontitis, increases specificity.

We should anticipate that until more robust methods are validated, potentially salivary biomarkers or novel soft-tissue imaging technologies, the level of training and experience with periodontal probing will greatly influence the identification of a case of initial periodontitis.

It should be noted that periodontal inflammation, generally measured as bleeding on probing (BOP), is an important clinical parameter relative to assessment of periodontitis treatment outcomes and residual disease risk post-treatment.[29–32] However BOP itself, or as a secondary parameter with CAL, does not change the initial case definition as defined by CAL or change the classification of periodontitis severity.

Multiple periodontitis case definitions have been proposed in recent years. The AAP/Centers for Disease Control (CDC) case definition for epidemiologic surveillance and the EFP case definition for the purpose of risk factors research have been widely utilized.[33,34] Although the AAP/CDC and the sensitive EFP definition share similarities there are some important differences.

In the context of the 2017 World Workshop, it is suggested that a single definition be adopted.

A patient is a periodontitis case in the context of clinical care if:

1. Interdental CAL is detectable at ≥2 non-adjacent teeth, or
2. Buccal or oral CAL ≥3 mm with pocketing >3 mm is detectable at ≥2 teeth

and the observed CAL cannot be ascribed to non-periodontal causes such as: 1) gingival recession of traumatic origin; 2) dental caries extending in the cervical area of the tooth; 3) the presence of CAL on the distal aspect of a second molar and associated with malposition or extraction of a third molar, 4) an endodontic lesion draining through the marginal periodontium; and 5) the occurrence of a vertical root fracture.

Key to periodontitis case definition is the notion of "detectable" interdental CAL: the clinician being able to specifically identify areas of attachment loss during periodontal probing or direct visual detection of the interdental CEJ during examination, taking measurement error and local factors into account.

It is recognized that "detectable" interdental attachment loss may represent different magnitudes of CAL based upon the skills of the operator (e.g. specialist or general practitioner) and local conditions that may facilitate or impair detection of the CEJ, most notably the position of the gingival margin with respect to the CEJ, the presence of calculus or restorative margins. The proposed case definition does not stipulate a specific threshold of detectable CAL to avoid misclassification of initial periodontitis cases as gingivitis and maintain consistency of histological and clinical definitions. There is also a need to increase specificity of the definition and this is accomplished requiring detection of CAL at two non-adjacent teeth. Setting a specific threshold of CAL for periodontitis definition (e.g. 2 mm) to address measurement error with CAL detection with a periodontal probe would result in misclassification of initial periodontitis cases as gingivitis. Specific considerations are needed for epidemiological surveys where threshold definition is likely to be based on numerical values dependent on measurement errors.

Identification of the form of periodontitis

Based on pathophysiology, three clearly different forms of periodontitis have been identified:

1. Necrotizing periodontitis
2. Periodontitis as a direct manifestation of systemic diseases
3. Periodontitis

Differential diagnosis is based on history and the specific signs and symptoms of necrotizing periodontitis and the presence or absence of an uncommon systemic disease that definitively alters the host immune response. Necrotizing periodontitis is characterized by history of pain, presence of ulceration of the gingival margin and/or fibrin deposits at sites with characteristically decapitated gingival papillae, and, in some cases, exposure of the marginal alveolar bone. With regard to periodontitis as a direct manifestation of systemic disease, the recommendation is to follow the classification of the primary disease according to the respective International Statistical Classification of Diseases and Related Health Problems (ICD) codes.

The vast majority of clinical cases of periodontitis do not have the local characteristics of necrotizing periodontitis or the systemic characteristics of a rare immune disorder with a secondary manifestation of periodontitis. The majority of clinical cases of periodontitis present with a range of phenotypes that require different approaches to clinical management and offer different complexities that define the knowledge and experience necessary to successfully manage various cases.

Additional elements proposed for inclusion in the classification of periodontitis

Since the 1999 International Classification Workshop, it has become apparent that additional information beyond the specific form of periodontitis and the severity and extent of periodontal breakdown is necessary to more specifically characterize the impact of past disease on an individual patient's dentition and on treatment approaches needed to manage the case. Clinical diagnosis needs to be more all-encompassing in expressing the effects of periodontitis and should account not only for the oral effects but also for potential systemic implications of the disease.

Severity

The degree of periodontal breakdown present at diagnosis has long been used as the key descriptor of the individual case of periodontitis. The 1999 case definition system is also based on severity. Rationale of classification according to severity encompasses at least two important dimensions: complexity of management and extent of disease. Important limitations of severity definitions are worth discussing also in the context of recent therapeutic improvements that have enabled successful management of progressively more severe periodontitis.[35] Conventional definitions of severe periodontitis need to be revised to better discriminate the more severe forms of periodontitis. Another important limitation of current definitions of severe periodontitis is a paradox: whenever the worst affected teeth in the dentition are lost, severity may actually decrease. Tooth loss attributable to periodontitis needs to be incorporated in the definition of severity.

Complexity of management

Factors such as probing depths,[36] type of bone loss (vertical and/or horizontal),[37] furcation status,[38] tooth mobility,[39–41] missing teeth, bite collapse,[42] and residual ridge defect size increase treatment complexity and need to be considered and should ultimately influence diagnostic classification. Explicit designation of case complexity factors helps to define levels of competence and experience that a case is likely to require for optimal outcomes.

Extent

The number and the distribution of teeth with detectable periodontal breakdown has been part of current classification systems. The number of affected teeth (as a percentage of teeth present) has been used to define cases of chronic periodontitis in the 1999 classification[9,10] while the distribution of lesions (molar incisor versus generalized pattern of breakdown) has been used as a primary descriptor for aggressive periodontitis.[8,28] Rationale for keeping this information in the classification system comes from the fact that specific patterns of periodontitis (e.g. the molar-incisor pattern of younger subjects presenting with what was formerly called localized juvenile periodontitis) provide indirect information about the specific host-biofilm interaction.

Rate of progression

One of the most important aspects for a classification system is to properly account for variability in the rate of progression of periodontitis. The importance of this criteria has been well recognized in the 1989 AAP classification that identified a rapidly progressing form of periodontitis.[43] Concern about this criterion has been mostly on how to assess the rate of progression at initial examination in the absence of direct evidence (e.g. an older diagnostic quality radiograph allowing comparison of marginal bone loss over time).

Risk factors

Recognized risk factors have not been previously included formally in the classification system of periodontitis but have been used as a descriptor to qualify the specific patient as a smoker or a patient with diabetes mellitus. Improved knowledge of how risk factors affect periodontitis (higher severity and extent at an earlier age) and treatment response (smaller degrees of improvements in surrogate outcomes and higher rates of tooth loss during supportive periodontal therapy[40,41,44]) indicate that risk factors should be considered in the classification of periodontitis.

Interrelationship with general health

Since the 1999 workshop considerable evidence has emerged concerning potential effects of periodontitis on systemic diseases. Various mechanisms linking periodontitis to multiple systemic diseases have been proposed.[45,46] Specific oral bacteria in the periodontal pocket may gain bloodstream access through ulcerated pocket epithelium. Inflammatory mediators from the periodontium may enter the bloodstream and activate liver acute phase proteins, such as C-reactive protein (CRP), which further amplify systemic

inflammation levels. Case-control[47–50] and pilot intervention studies[51,52] show that periodontitis contributes to the overall inflammatory burden of the individual which is strongly implicated in coronary artery disease, stroke, and Type II diabetes.[53–58] Initial evidence also supports the potential role of the overall systemic inflammatory burden on the risk for periodontitis.[59]

Modestly sized periodontitis treatment studies of uncontrolled Type II diabetes have shown value in reducing hyperglycemia, although reductions in hyperglycemia have not been supported in some larger studies where the periodontal treatment outcomes were less clear.[18,60,61] Although intriguing health economics analyses have shown a reduction in cost of care for multiple medical conditions following treatment for periodontitis,[62] little direct periodontitis intervention evidence, beyond the diabetes experience, has convincingly demonstrated the potential value of effectively treating periodontitis relative to overall health benefits. **Current evidence that effective treatment of certain cases of periodontitis can favorably influence systemic diseases or their surrogates, although limited, is intriguing and should definitively be assessed**.

Other factors that need to be considered in formulating a diagnostic classification include the medical status of the patient and the level of expertise needed to provide appropriate care. If the patient has severe systemic disease, as indicated by their American Society of Anesthesiologists (ASA) status, this can seriously affect the clinician's ability to control disease progression due to the patient's inability to withstand proper treatment or their inability to attend necessary maintenance care.

FRAMEWORK FOR DEVELOPING A PERIODONTITIS STAGING AND GRADING SYSTEM

New technologies and therapeutic approaches to periodontitis management are now available such that clinicians with advanced training can manage patients with moderate and severe periodontitis to achieve clinical outcomes that were not previously possible.

The other dimension not previously available in our classification is the directed identification of individual patients who are more likely to require greater effort to prevent or control their chronic disease long-term. This explicitly acknowledges the evidence that most individuals and patients respond predictably to conventional approaches to prevent periodontitis and conventional therapeutic approaches and maintenance, while others may require more intensive and more frequent preventive care or therapeutic interventions, monitoring, and maintenance.[19,20,63–65]

Staging, an approach used for many years in oncology, has been recently discussed relative to periodontal disease[66] and affords an opportunity to move beyond the one-dimensional approach of using past destruction alone and furnishes a platform on which a multidimensional diagnostic classification can be built. Furthermore, a uniform staging system should provide a way of defining the state of periodontitis at various points in time, can be readily communicated to others to assist in treatment, and may be a factor in assessing prognosis. Periodontitis staging should assist clinicians in considering all relevant dimensions that help optimize individual patient management and thus represents a critical step towards personalized care (or precision medicine).

Staging relies on the standard dimensions of severity and extent of periodontitis at presentation but introduces the dimension of complexity of managing the individual patient.

As it is recognized that individuals presenting with different severity/extent and resulting complexity of management may present different rates of progression of the disease and/or risk factors, the information derived from the staging of periodontitis should be supplemented by information on the inherent biological grade of the disease. This relies on three sets of parameters: 1) rate of periodontitis progression; 2) recognized risk factors for periodontitis progression; and 3) risk of an individual's case affecting the systemic health of the subject.

The concept and value of "staging" has been extensively developed in the oncology field. Staging of tumors is based on current observable clinical presentation including size or extent and whether it has metastasized. This may be an example of how one might communicate current severity and extent of a disease, as well as the clinical complexities of managing the case. To supplement staging, which provides a summary of clinical presentation, grade has been used as an assessment of the potential for a specific tumor to progress, i.e. to grow and spread, based on microscopic appearance of tumor cells. In addition, current molecular markers often guide selection of specific drug therapies, and thereby incorporate biological targets that increase the granularity of the grade and thus may increase the probability of a favorable clinical outcome. These concepts have been adapted to periodontitis, as summarized in Table 1, and as described in detail below.

While devising a general framework, it seems relevant from a patient management standpoint to differentiate four stages of periodontitis. Each of these stages is defined by unique disease presentation in terms of disease severity and complexity of management. In each stage of severity, it may be useful to identify subjects with

TABLE 1 Primary goals in staging and grading a patient with periodontitis

Staging a Periodontitis Patient
• **Goals** ◦ **Classify Severity and Extent** of an individual based on currently measurable extent of destroyed and damaged tissue attributable to periodontitis ◦ **Assess Complexity**. Assess specific factors that may determine complexity of controlling current disease and managing long-term function and esthetics of the patient's dentition
Grading a Periodontitis Patient
• **Goals** ◦ **Estimate Future Risk** of periodontitis progression and responsiveness to standard therapeutic principles, to guide intensity of therapy and monitoring ◦ **Estimate Potential Health Impact of Periodontitis** on systemic disease and the reverse, to guide systemic monitoring and co-therapy with medical colleagues

TABLE 2 Framework for staging and grading of periodontitis

		Disease Severity and Complexity of Management			
		Stage I: Initial periodontitis	Stage II: Moderate periodontitis	Stage III: Severe periodontitis with potential for additional tooth loss	Stage IV: Advanced periodontitis with extensive tooth loss and potential for loss of dentition
Evidence or risk of rapid progression, anticipated treatment response, and effects on systemic health	Grade A Grade B Grade C	**Individual Stage and Grade Assignment**			

different rates of disease progression and it is foreseen that, in the future, stage definition will be enriched by diagnostic tests enabling definition of the biological "grade" and/or susceptibility of periodontitis progression in the individual patient. The addition of grade may be achieved by refining each individual's stage definition with a grade A, B, or C, in which increasing grades will refer to those with direct or indirect evidence of different rates of periodontal breakdown and presence and level of control of risk factors.

An individual case may thus be defined by a simple matrix of stage at presentation (severity and complexity of management) and grade (evidence or risk of progression and potential risk of systemic impact of the patient's periodontitis; these also influence the complexity of management of the case). Table 2 illustrates this concept and provides a general framework that will allow updates and revisions over time as specific evidence becomes available to better define individual components, particularly in the biological grade dimension of the disease and the systemic implications of periodontitis.

Stage I periodontitis

Stage I periodontitis is the borderland between gingivitis and periodontitis and represents the early stages of attachment loss. As such, patients with stage I periodontitis have developed periodontitis in response to persistence of gingival inflammation and biofilm dysbiosis. They represent more than just an early diagnosis: if they show a degree of clinical attachment loss at a relatively early age, these patients may have heightened susceptibility to disease onset. Early diagnosis and definition of a population of susceptible individuals offers opportunities for early intervention and monitoring that may prove more cost-effective at the population level as shallow lesions may provide specific options for both conventional mechanical biofilm removal and pharmacological agents delivered in oral hygiene aids. It is recognized that early diagnosis may be a formidable challenge in general dental practice: periodontal probing to estimate early clinical attachment loss – the current gold standard for defining periodontitis – may be inaccurate. Assessment of salivary biomarkers and/or new imaging technologies may increase early detection of stage I periodontitis in a variety of settings.

Stage II periodontitis

Stage II represents established periodontitis in which a carefully performed clinical periodontal examination identifies the characteristic damages that periodontitis has caused to tooth support. At this stage of the disease process, however, management remains relatively simple for many cases as application of standard treatment principles involving regular personal and professional bacterial removal and monitoring is expected to arrest disease progression. Careful evaluation of the stage II patient's response to standard treatment principles is essential, and the case grade plus treatment response may guide more intensive management for specific patients.

Stage III periodontitis

At stage III, periodontitis has produced significant damage to the attachment apparatus and, in the absence of advanced treatment, tooth loss may occur. The stage is characterized by the presence of deep periodontal lesions that extend to the middle portion of the root and whose management is complicated by the presence of deep intrabony defects, furcation involvement, history of periodontal tooth loss/exfoliation, and presence of localized ridge defects that complicate implant tooth replacement. In spite of the possibility of tooth loss, masticatory function is preserved, and treatment of periodontitis does not require complex rehabilitation of function.

Stage IV periodontitis

At the more advanced stage IV, periodontitis causes considerable damage to the periodontal support and may cause significant tooth loss, and this translates to loss of masticatory function. In the absence of proper control of the periodontitis and adequate rehabilitation, the dentition is at risk of being lost.

This stage is characterized by the presence of deep periodontal lesions that extend to the apical portion of the root and/or history of multiple tooth loss; it is frequently complicated by tooth hypermobility due to secondary occlusal trauma and the sequelae of tooth loss: posterior bite collapse and drifting. Frequently, case management requires stabilization/restoration of masticatory function.

Grade of periodontitis

Irrespective of the stage at diagnosis, periodontitis may progress with different rates in individuals, may respond less predictably to treatment in some patients, and may or may not influence general health or systemic disease. This information is critical for precision medicine but has been an elusive objective to achieve in clinical practice. In recent years, validated risk assessment tools[25,67] and presence of individually validated risk factors[65] have been associated with tooth loss, indicating that it is possible to estimate risk of periodontitis progression and tooth loss.

In the past, grade of periodontitis progression has been incorporated into the classification system by defining specific forms of periodontitis with high(er) rates of progression or presenting with more severe destruction relatively early in life.[28] One major limitation in the implementation of this knowledge has been the assumption that such forms of periodontitis represent different entities and thus focus has been placed on identification of the form rather than the factors contributing to progression. The reviews commissioned for this workshop[13–16] have indicated that there is no evidence to suggest that such forms of periodontitis have a unique pathophysiology, rather the complex interplay of risk factors in a multifactorial disease model may explain the phenotypes of periodontitis in exposed patients. In this context, it seems useful to provide a framework for implementation of biological grade (risk or actual evidence of progression) of periodontitis.

Recognized risk factors, such as cigarette smoking or metabolic control of diabetes, affect the rate of progression of periodontitis and, consequently, may increase the conversion from one stage to the next. Emerging risk factors like obesity, specific genetic factors, physical activity, or nutrition may one day contribute to assessment, and a flexible approach needs to be devised to ensure that the case-definition system will adapt to the emerging evidence.

Disease severity at presentation/diagnosis as a function of patient age has also been an important indirect assessment of the level of individual susceptibility. While not ideal – as it requires significant disease at an early age or minimal disease at advanced age – this concept has been used in clinical practice and risk assessment tools to identify highly susceptible or relatively resistant individuals. One approach has been the assessment of bone loss in relation to patient age by measuring radiographic bone loss in percentage of root length divided by the age of the patient. This approach was originally applied in a longitudinal assessment of disease progression assessed in intraoral radiographs[68,69] and was later incorporated in the theoretical concept that led to development of the periodontal risk assessment (PRA) system.[31,70] More recently, an individual's severity of CAL has been compared to his/her age cohort.[16] This information from large and diverse populations could be considered an age standard for CAL, with the assumption that individuals who exceed the mean CAL threshold for a high percentile in the age cohort would be one additional piece of objective information that may represent increased risk for future progression. The CAL must be adjusted in some way based on number of missing teeth to avoid biasing the CAL based on measuring only remaining teeth after extraction of the teeth with the most severe periodontitis. Such challenges again require a framework that will adapt to change as more precise ways to estimate individual susceptibility become available.

Integrating biomarkers in a case definition system

Clinical parameters are very effective tools for monitoring the health-disease states in most patients, likely because they respond favorably to the key principles of periodontal care, which include regular disruption, and reduction of the gingival and subgingival microbiota. Current evidence suggests, however, that some individuals are more susceptible to develop periodontitis, more susceptible to develop progressive severe generalized periodontitis, less responsive to standard bacterial control principles for preventing and treating periodontitis, and theoretically more likely to have periodontitis adversely impact systemic diseases.

If, due to multiple factors, such individuals are more likely than others to develop and maintain a dysbiotic microbiota in concert with chronic periodontal inflammation; it is unclear whether current clinical parameters are sufficient to monitor disease development and treatment responses in such patients. For those individuals, biomarkers, some of which are currently available, may be valuable to augment information provided by standard clinical parameters.

Biomarkers may contribute to improved diagnostic accuracy in the early detection of periodontitis and are likely to provide decisive contributions to a better assessment of the grade of periodontitis. They may assist both in staging and grading of periodontitis. The proposed framework allows introduction of validated biomarkers in the case definition system.

Integrating knowledge of the interrelationship between periodontal health and general health in a case definition system

At present there is only emerging evidence to identify specific periodontitis cases in which periodontal treatment produces general health benefits. it is important to identify approaches to capture some dimensions of the potential systemic impact of a specific periodontitis case and its treatment to provide the basis for focusing attention on this issue and beginning to collect evidence necessary to assess whether effective treatment of certain cases of periodontitis truly influence systemic disease in a meaningful way.

Specific considerations for use of the staging and grading of periodontitis with epidemiological and research applications are discussed in Appendix B in the online *Journal of Clinical Periodontology*.

INCORPORATION OF STAGING AND GRADING IN THE CASE DEFINITION SYSTEM OF PERIODONTITIS

A case definition system needs to be a dynamic process that will require revisions over time in much the same way the tumor, node,

TABLE 3 Periodontitis stage – Please see text and appendix A (in online *Journal of Clinical Periodontology*) for explanation

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1 to 2 mm	3 to 4 mm	≥5 mm	≥5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to middle or apical third of the root	Extending to middle or apical third of the root
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥6 mm Vertical bone loss ≥3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

The initial stage should be determined using CAL; if not available then RBL should be used. Information on tooth loss that can be attributed primarily to periodontitis – if available – may modify stage definition. This is the case even in the absence of complexity factors. Complexity factors may shift the stage to a higher level, for example furcation II or III would shift to either stage III or IV irrespective of CAL. The distinction between stage III and stage IV is primarily based on complexity factors. For example, a high level of tooth mobility and/or posterior bite collapse would indicate a stage IV diagnosis. For any given case only some, not all, complexity factors may be present, however, in general it only takes one complexity factor to shift the diagnosis to a higher stage. It should be emphasized that these case definitions are guidelines that should be applied using sound clinical judgment to arrive at the most appropriate clinical diagnosis.

For post-treatment patients CAL and RBL are still the primary stage determinants. If a stage-shifting complexity factor(s) is eliminated by treatment, the stage should not retrogress to a lower stage since the original stage complexity factor should always be considered in maintenance phase management.

CAL = clinical attachment loss; RBL = radiographic bone loss.

metastasis (TNM) staging system for cancer has been shaped over many decades. It needs to be:

1. Simple enough to be clinically applicable but not simplistic: additional knowledge has distinguished dimensions of periodontitis, such as complexity of managing the case to provide the best level of care
2. Standardized to be able to support effective communication among all stakeholders
3. Accessible to a wide range of people in training and understood by members of the oral health care team around the world

It is suggested that a case definition based on a matrix of periodontitis stage and periodontitis grade be adopted. Such multidimensional view of periodontitis would create the potential to transform our view of periodontitis. And the powerful outcome of that multidimensional view is the ability to communicate better with patients, other professionals, and third parties.

Stage of periodontitis (Table 3)

At present, relevant data are available to assess the two dimensions of the staging process: severity and complexity. These can be assessed in each individual case at diagnosis by appropriate anamnestic, clinical, and imaging data.

The severity score is primarily based on interdental CAL in recognition of low specificity of both pocketing and marginal bone loss, although marginal bone loss is also included as an additional descriptor. It follows the general frame of previous severity-based scores and is assigned based on the worst affected tooth in the dentition. Only attachment loss attributable to periodontitis is used for the score.

The complexity score is based on the local treatment complexity assuming the wish/need to eliminate local factors and takes into account factors like presence of vertical defects, furcation involvement, tooth hypermobility, drifting and/or flaring of teeth, tooth loss, ridge deficiency and loss of masticatory

function. Besides the local complexity, it is recognized that individual case management may be complicated by medical factors or comorbidities.

The diagnostic classification presented in Table 3 provides definitions for four stages of periodontitis. In using the table, it is important to use CAL as the initial stage determinant in the severity dimension. It is recognized that in clinical practice application some clinicians may prefer to use diagnostic quality radiographic imaging as an indirect and somehow less sensitive assessment of periodontal breakdown. This may be all that is necessary to establish the stage. However, if other factors are present in the complexity dimension that influence the disease then modification of the initial stage assignment may be required. For example, in case of very short common root trunk a CAL of 4 mm may have resulted in class II furcation involvement, hence shifting the diagnosis from stage II to stage III periodontitis. Likewise, if posterior bite collapse is present then the stage IV would be the appropriate stage diagnosis since the complexity is on the stage IV level.

Evidence for defining different stages based on CAL/bone loss in relation to root length is somewhat arbitrary.

Patients who have been treated for periodontitis may be periodically staged to monitor them. In most of successfully treated patients, complexity factors that might have contributed to baseline staging will have been resolved through treatment. In such patients CAL and radiographic bone loss (RBL) will be the primary stage determinants. If a stage shifting complexity factor(s) were eliminated by treatment, the stage should not retrogress to a lower stage since the original stage complexity factor should always be considered in maintenance phase management. A notable exception is successful periodontal regeneration that may, through improvement of tooth support, effectively improve CAL and RBL of the specific tooth.

Grade of periodontitis (Table 4)

Grading adds another dimension and allows rate of progression to be considered. Table 4 illustrates periodontitis grading based on primary criteria represented by the availability of direct or indirect evidence of periodontitis progression. Direct evidence is based on longitudinal observation available for example in the form of older diagnostic quality radiographs. Indirect evidence is based on the assessment of bone loss at the worst affected tooth in the dentition as a function of age (measured as radiographic bone loss in percentage of root length divided by the age of the subject). Periodontitis grade can then be modified by the presence of risk factors.

The objective of grading is to use whatever information is available to determine the likelihood of the case progressing at a greater rate than is typical for the majority of the population or responding less predictably to standard therapy.

Clinicians should approach grading by assuming a moderate rate of progression (grade B) and look for direct and indirect measures of actual progression in the past as a means of improving the establishment of prognosis for the individual patient. If the patient has risk factors that have been associated with more disease progression or less responsiveness to bacterial reduction therapies, the risk factor information can be used to modify the estimate of the patient's future course of disease. A risk factor, should therefore shift the grade score to a higher value independently of the primary criterion represented by the rate of progression. For example, a stage and grade case definition could be characterized by moderate attachment loss (stage II), the assumption of moderate rate of progression (grade B) modified by the presence of poorly controlled Type II diabetes (a risk factor that is able to shift the grade definition to rapid progression or grade C).

In summary, a periodontitis diagnosis for an individual patient should encompass three dimensions:

1. Definition of a periodontitis case based on detectable CAL loss at two non-adjacent teeth
2. Identification of the form of periodontitis: necrotizing periodontitis, periodontitis as a manifestation of systemic disease or periodontitis
3. Description of the presentation and aggressiveness of the disease by stage and grade (see Appendix B in online *Journal of Clinical Periodontology*)

CONCLUSIONS

The proposed staging and grading of periodontitis provides an individual patient assessment that classifies patients by two dimensions beyond severity and extent of disease that identify patients as to **complexity** of managing the case and **risk** of the case exhibiting more progression and/or responding less predictably to standard periodontal therapy. The proposed risk stratification is based on well-validated risk factors including smoking, uncontrolled Type II diabetes, clinical evidence of progression or disease diagnosis at an early age, and severity of bone loss relative to patient age.

The proposed staging and grading explicitly acknowledges the potential for some cases of periodontitis to influence systemic disease. The current proposal does not intend to minimize the importance or extent of evidence supporting direct distal effects of periodontal bacteremia on adverse pregnancy outcomes and potentially other systemic conditions; but focuses on the role of periodontitis as the second most frequent factor (obesity being the most frequent) that is well-documented as a modifiable contributor to systemic inflammatory burden.

The proposed staging and grading is designed to avoid the paradox of improvement of disease severity observed after loss/extraction of the more compromised teeth. This is achieved by incorporating, whenever available, knowledge about periodontitis being the predominant reason for loss of one or more teeth.

Finally, one of the strong benefits of the staging and grading of periodontitis is that it is designed to accommodate regular review

TABLE 4 Periodontitis grade – Please see text and appendix A (in online *Journal of Clinical Periodontology*) for explanation

Periodontitis grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic / no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes
Risk of systemic impact of periodontitis[a]	Inflammatory burden	High sensitivity CRP (hsCRP)	<1 mg/L	1 to 3 mg/L	>3 mg/L
Biomarkers	Indicators of CAL/bone loss	Saliva, gingival crevicular fluid, serum	?	?	?

Grade should be used as an indicator of the rate of periodontitis progression. The primary criteria are either direct or indirect evidence of progression. Whenever available, direct evidence is used; in its absence indirect estimation is made using bone loss as a function of age at the most affected tooth or case presentation (radiographic bone loss expressed as percentage of root length divided by the age of the subject, RBL/age). Clinicians should initially assume grade B disease and seek specific evidence to shift towards grade A or C, if available. Once grade is established based on evidence of progression, it can be modified based on the presence of risk factors.

[a]Refers to increased risk that periodontitis may be an inflammatory comorbidity for the specific patient. CRP values represent a summation of the patient's overall systemic inflammation, which may be in part influenced by periodontitis, but otherwise is an "unexplained" inflammatory burden that be valuable to assess in collaboration with the patient's physicians. The grey color of the table cells refers to the need to substantiate with specific evidence. This element is placed in the table to draw attention to this dimension of the biology of periodontitis. It is envisaged that in the future it will be possible to integrate the information into periodontitis grade to highlight the potential of systemic impact of the disease in the specific case. Question marks in the last row indicate that specific biomarkers and their thresholds may be incorporated in the table as evidence will become avaialble.

HbA1c, glycated hemoglobin; hsCRP, high sensitivity C-reactive protein; PA, periapical; CAL, clinical attachment loss.

by an ad hoc international task force to ensure that the framework incorporates relevant new knowledge within an already functioning clinical application.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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2017 WORLD WORKSHOP

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Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

A new periodontitis classification scheme has been adopted, in which forms of the disease previously recognized as "chronic" or "aggressive" are now grouped under a single category ("periodontitis") and are further characterized based on a multi-dimensional *staging* and *grading* system. S*taging* is largely dependent upon the severity of disease at presentation as well as on the complexity of disease management, while *grading* provides supplemental information about biological features of the disease including a history-based analysis of the rate of periodontitis progression; assessment of the risk for further progression; analysis of possible poor outcomes of treatment; and assessment of the risk that the disease or its treatment may negatively affect the general health of the patient.

Necrotizing periodontal diseases, whose characteristic clinical phenotype includes typical features (papilla necrosis, bleeding, and pain) and are associated with host immune response impairments, remain a distinct periodontitis category.

Endodontic-periodontal lesions, defined by a pathological communication between the pulpal and periodontal tissues at a given tooth, occur in either an acute or a chronic form, and are classified according to signs and symptoms that have direct impact on their prognosis and treatment.

Periodontal abscesses are defined as acute lesions characterized by localized accumulation of pus within the gingival wall of the periodontal pocket/sulcus, rapid tissue destruction and are associated with risk for systemic dissemination.

KEYWORDS
acute periodontal conditions, endo-periodontal lesion, necrotizing gingivitis, necrotizing periodontitis, periodontal abscess, periodontal disease, periodontitis

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss (CAL) and radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding. Periodontitis is a major public health problem due to its high prevalence, as well as because it may lead to tooth loss and disability, negatively affect chewing function and aesthetics, be a source of social inequality, and impair quality of life. Periodontitis accounts for a substantial proportion of edentulism and masticatory dysfunction, results in significant dental care costs and has a plausible negative impact on general health.

According to the latest internationally accepted classification scheme (Armitage[1] 1999), *periodontitis* is further subdivided as follows:

- *Chronic periodontitis*, representing the forms of destructive periodontal disease that are generally characterized by slow progression
- *Aggressive periodontitis*, a diverse group of highly destructive forms of periodontitis affecting primarily young individuals, including conditions formerly classified as "early-onset periodontitis" and "rapidly progressing periodontitis"
- *Periodontitis as a manifestation of systemic disease*, a heterogeneous group of systemic pathological conditions that include periodontitis as a manifestation
- *Necrotizing periodontal diseases*, a group of conditions that share a characteristic phenotype where necrosis of the gingival or periodontal tissues is a prominent feature
- *Periodontal abscesses*, a clinical entity with distinct diagnostic features and treatment requirements

Although the above classification has provided a workable framework that has been used extensively in both clinical practice and scientific investigation in periodontology during the past 17 years, the system suffers from several important shortcomings, including substantial overlap and lack of clear pathobiology-based distinction between the stipulated categories, diagnostic imprecision, and implementation difficulties. The objectives of workgroup 2 were to revisit the current classification system of periodontitis, incorporate new knowledge relevant to its epidemiology, etiology and pathogenesis that has accumulated since the current classification's inception, and propose a

new classification framework along with case definitions. To this end, five position papers were commissioned, authored, peer-reviewed, and accepted. The first reviewed the classification and diagnosis of aggressive periodontitis (Fine et al.[2] 2018); the second focused on the age-dependent distribution of clinical attachment loss in two population-representative, cross-sectional studies (Billings et al.[3] 2018); the third reviewed progression data of clinical attachment loss from existing prospective, longitudinal studies (Needleman at al.[4] 2018); the fourth reviewed the diagnosis, pathobiology, and clinical presentation of acute periodontal lesions (periodontal abscesses, necrotizing periodontal diseases and endo-periodontal lesions; Herrera et al.[5] 2018); lastly, the fifth focused on periodontitis case definitions (Tonetti et al.[6] 2018), Table 1.

The workgroup reviewed, debated and agreed by consensus on the overall conclusions of the five position papers, that can be largely summarized as follows:

1. The conflicting literature findings on aggressive periodontitis are primarily due to the fact that (i) the currently adopted classification is too broad, (ii) the disease has not been studied from its inception, and (iii) there is paucity of longitudinal studies including multiple time points and different populations. The position paper argued that a more restrictive definition might be better suited to take advantage of modern methodologies to enhance knowledge on the diagnosis, pathogenesis, and management of this form of periodontitis.

TABLE 1A Classification of periodontitis based on stages defined by severity (according to the level of interdental clinical attachment loss, radiographic bone loss and tooth loss), complexity and extent and distribution

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1 to 2 mm	3 to 4 mm	≥5 mm	≥5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to middle or apical third of the root	Extending to middle or apical third of the root
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥6 mm Vertical bone loss ≥3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

The initial stage should be determined using clinical attachment loss (CAL); if not available then radiographic bone loss (RBL) should be used. Information on tooth loss that can be attributed primarily to periodontitis – if available – may modify stage definition. This is the case even in the absence of complexity factors. Complexity factors may shift the stage to a higher level, for example furcation II or III would shift to either stage III or IV irrespective of CAL. The distinction between stage III and stage IV is primarily based on complexity factors. For example, a high level of tooth mobility and/or posterior bite collapse would indicate a stage IV diagnosis. For any given case only some, not all, complexity factors may be present, however, in general it only takes one complexity factor to shift the diagnosis to a higher stage. It should be emphasized that these case definitions are guidelines that should be applied using sound clinical judgment to arrive at the most appropriate clinical diagnosis.

For post-treatment patients, CAL and RBL are still the primary stage determinants. If a stage-shifting complexity factor(s) is eliminated by treatment, the stage should not retrogress to a lower stage since the original stage complexity factor should always be considered in maintenance phase management.

TABLE 1B Classification of periodontitis based on grades that reflect biologic features of the disease including evidence of, or risk for, rapid progression, anticipated treatment response, and effects on systemic health

Periodontitis grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic / no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes

Grade should be used as an indicator of the rate of periodontitis progression. The primary criteria are either direct or indirect evidence of progression. Whenever available, direct evidence is used; in its absence indirect estimation is made using bone loss as a function of age at the most affected tooth or case presentation (radiographic bone loss expressed as percentage of root length divided by the age of the subject, RBL/age). Clinicians should initially assume grade B disease and seek specific evidence to shift towards grade A or C, if available. Once grade is established based on evidence of progression, it can be modified based on the presence of risk factors. CAL = clinical attachment loss; HbA1c = glycated hemoglobin A1c; RBL = radiographic bone loss.

2. Despite substantial differences in the overall severity of attachment loss between the two population samples analyzed by Billings et al.[3], suggesting presence of cohort effects, common patterns of CAL were identified across different ages, along with consistencies in the relative contribution of recession and pocket depth to CAL. The findings suggest that it is feasible to introduce empirical evidence-driven thresholds of attachment loss that signify disproportionate severity of periodontitis with respect to age.
3. Longitudinal mean annual attachment level change was found to vary considerably both within and between populations. Surprisingly, neither age nor sex had any discernible effects on CAL change, but geographic location was associated with differences. Overall, the position paper argued that the existing evidence neither supports nor refutes the differentiation between forms of periodontal diseases based upon progression of attachment level change.
4. Necrotizing periodontal diseases are characterized by three typical clinical features (papilla necrosis, bleeding, and pain) and are associated with host immune response impairments, which should be considered in the classification of these conditions (Table 2).

   Endodontic-periodontal lesions are defined by a pathological communication between the pulpal and periodontal tissues at a given tooth, occur in either an acute or a chronic form, and should be classified according to signs and symptoms that have direct impact on their prognosis and treatment (i.e., presence or absence of fractures and perforations, and presence or absence of periodontitis) (Table 3).

   Periodontal abscesses most frequently occur in pre-existing periodontal pockets and should be classified according to their etiology. They are characterized by localized accumulation of pus within the gingival wall of the periodontal pocket/sulcus, cause rapid tissue destruction which may compromise tooth prognosis, and are associated with risk for systemic dissemination (Table 4).
5. A periodontitis case definition system should include three components: (a) identification of a patient as a periodontitis case, (b) identification of the specific type of periodontitis, and (c) description of

TABLE 2 Classification of necrotizing periodontal diseases (NPD)

Category	Patients	Predisposing conditions	Clinical condition
Necrotizing periodontal diseases in chronically, severely compromised patients	In adults	HIV+/AIDS with CD4 counts < 200 and detectable viral load	NG, NP, NS, Noma. Possible progression
		Other severe systemic conditions (immunosuppression)	
	In children	Severe malnourishments[a]	
		Extreme living conditions[b]	
		Severe (viral) infections[c]	
Necrotizing periodontal diseases in temporarily and/or moderately compromised patients	In gingivitis patients	Uncontrolled factors: stress, nutrition, smoking, habits	Generalized NG. Possible progression to NP
		Previous NPD: residual craters	
		Local factors: root proximity, tooth malposition	Localized NG. Possible progression to NP
		Common predisposing factors for NPD (see paper)	NG. Infrequent progression
	In periodontitis patients		NP. Infrequent progression

NG, necrotizing gingivitis; NP, necrotizing periodontitis; NS, necrotizing stomatitis.
[a]Mean plasma and serum concentrations of retinol, total ascorbic acid, zinc, and albumin markedly reduced, or very marked depletion of plasma retinol, zinc, and ascorbate; and saliva levels of albumin and cortisol, as well as plasma cortisol concentrations, significantly increased.
[b]Living in substandard accommodations, exposure to debilitating childhood diseases, living near livestock, poor oral hygiene, limited access to potable water and poor sanitary disposal of human and animal fecal waste.
[c]Measles, herpes viruses (cytomegalovirus, Epstein-Barr virus-1, herpes simplex virus), chicken pox, malaria, febrile illness.

TABLE 3 Classification of endo-periodontal lesions

Endo-periodontal lesion with root damage	Root fracture or cracking	
	Root canal or pulp chamber perforation	
	External root resorption	
Endo-periodontal lesion without root damage	Endo-periodontal lesion in periodontitis patients	*Grade 1* – narrow deep periodontal pocket in 1 tooth surface
		Grade 2 – wide deep periodontal pocket in 1 tooth surface
		Grade 3 – deep periodontal pockets in > 1 tooth surface
	Endo-periodontal lesion in non-periodontitis patients	*Grade 1* – narrow deep periodontal pocket in 1 tooth surface
		Grade 2 – wide deep periodontal pocket in 1 tooth surface
		Grade 3 – deep periodontal pockets in > 1 tooth surface

the clinical presentation and other elements that affect clinical management, prognosis, and potentially broader influences on both oral and systemic health. A framework for developing a multi-dimensional periodontitis *staging* and *grading* system was proposed, in which *staging* (Table 1A) is largely dependent upon the severity of disease at presentation as well as on the complexity of disease management, while *grading* (Table 1B) provides supplemental information about biological features of the disease including a history-based analysis of the rate of periodontitis progression; assessment of the risk for further progression; analysis of possible poor outcomes of treatment; and assessment of the risk that the disease or its treatment may negatively affect the general health of the patient.

During the workgroup deliberations, the following questions were formulated and addressed in order to clarify and substantiate the need for a new classification system for periodontitis:

TABLE 4 Classification of periodontal abscesses based on the etiologic factors involved

Periodontal abscess in periodontitis patients (in a pre-existing periodontal pocket)	Acute exacerbation	Untreated periodontitis	
		Non-responsive to therapy periodontitis	
		Supportive periodontal therapy	
	After treatment	Post-scaling	
		Post-surgery	
		Post-medication	Systemic antimicrobials
			Other drugs: nifedipine
Periodontal abscess in non-periodontitis patients (not mandatory to have a pre-existing periodontal pocket)	Impaction		Dental floss, orthodontic elastic, toothpick, rubber dam, or popcorn hulls
	Harmful habits		Wire or nail biting and clenching
	Orthodontic factors		Orthodontic forces or a cross-bite
	Gingival overgrowth		
	Alteration of root surface	Severe anatomic alterations	Invaginated tooth, dens evaginatus or odontodysplasia
		Minor anatomic alterations	Cemental tears, enamel pearls or developmental grooves
		Iatrogenic conditions	Perforations
		Severe root damage	Fissure or fracture, cracked tooth syndrome
		External root resorption	

Which are the main features that identify periodontitis?

Loss of periodontal tissue support due to inflammation is the primary feature of periodontitis. A threshold of interproximal, CAL of ≥2 mm or ≥3 mm at ≥2 non-adjacent teeth is commonly used. Clinicians typically confirm presence of interproximal tissue loss through radiographic assessments of bone loss. Clinically meaningful descriptions of periodontitis should include the proportion of sites that bleed on probing, and the number and proportion of teeth with probing depth over certain thresholds (commonly ≥4 mm and ≥6 mm) and of teeth with CAL of ≥3 mm and ≥5 mm (Holtfreter et al.[7]).

Which criteria would need to be fulfilled to support the contention that chronic and aggressive periodontitis are indeed different diseases? (e.g., etiology, histology, pathophysiology, clinical presentation, other)

Differences in etiology and pathophysiology are required to indicate presence of distinct periodontitis entities; variations in clinical presentation *per se*, i.e. extent and severity, do not support the concept of different diseases.

Does current evidence suggest that we should continue to differentiate between "aggressive" and "chronic" periodontitis as two different diseases?

Current evidence does not support the distinction between chronic and aggressive periodontitis, as defined by the 1999 Classification Workshop, as two separate diseases; however, a substantial variation in clinical presentation exists with respect to extent and severity throughout the age spectrum, suggesting that there are population subsets with distinct disease trajectories due to differences in exposure and/or susceptibility.

Is there evidence suggesting that early-onset forms of periodontitis (currently classified under "aggressive periodontitis") have a distinct pathophysiology (e.g., genetic background, microbiology, host-response) compared to later-onset forms?

Although localized early onset periodontitis has a distinct, well-recognized clinical presentation (early onset, molar/incisor distribution, progression of attachment loss), the specific etiologic or pathological elements that account for this distinct presentation are insufficiently

defined. Likewise, mechanisms accounting for the development of generalized periodontitis in young individuals are poorly understood.

What are the determinants for the mean annual attachment loss based on existing longitudinal studies in adults?

A meta-analysis included in the position paper documented differences in mean annual attachment loss between studies originating from different geographic regions but did not reveal an association with age or sex. It should be emphasized that meta-analysis of mean data may fail to identify associations due to the loss of information and the lack of accounting for both disease progression and regression. However, approaches that have modelled both progression and regression of CAL have also reported no effect of age or smoking on progression, although age and smoking reduced disease regression (e.g., Faddy et al.[8]). Individual studies that could not be included in the meta-analysis have shown effects of smoking, socioeconomic status, previous attachment loss, ethnicity, age, sex, and calculus on mean annual attachment loss.

How do we define a patient as a periodontitis case?

In the context of clinical care, a patient is a "periodontitis case" if:

1. Interdental CAL is detectable at ≥2 non-adjacent teeth, or
2. Buccal or oral CAL ≥3 mm with pocketing ≥3 mm is detectable at ≥2 teeth but the observed CAL cannot be ascribed to non-periodontitis-related causes such as: 1) gingival recession of traumatic origin; 2) dental caries extending in the cervical area of the tooth; 3) the presence of CAL on the distal aspect of a second molar and associated with malposition or extraction of a third molar, 4) an endodontic lesion draining through the marginal periodontium; and 5) the occurrence of a vertical root fracture.

Which different forms of periodontitis are recognized in the present revised classification system?

Based on pathophysiology, three clearly different forms of periodontitis have been identified:

(A) Necrotizing periodontitis
(B) Periodontitis as a direct manifestation of systemic diseases
(C) Periodontitis

Differential diagnosis is based on history and the specific signs and symptoms of necrotizing periodontitis, or the presence or absence of an uncommon systemic disease that alters the host immune response. Periodontitis as a direct manifestation of systemic disease (Albandar et al.[9], Jepsen et al.[10]) should follow the classification of the primary disease according to the respective International Statistical Classification of Diseases and Related Health Problems (ICD) codes.

The remaining clinical cases of periodontitis which do not have the local characteristics of necrotizing periodontitis or the systemic characteristics of a rare immune disorder with a secondary manifestation of periodontitis should be diagnosed as "periodontitis" and be further characterized using a staging and grading system that describes clinical presentation as well as other elements that affect clinical management, prognosis, and potentially broader influences on both oral and systemic health.

How is a periodontitis case further characterized by stage and grade?

An individual case of periodontitis should be further characterized using a simple matrix that describes the *stage* and *grade* of the disease. Stage is largely dependent upon the severity of disease at presentation, as well as on the anticipated complexity of disease management, and further includes a description of extent and distribution of the disease in the dentition. Grade provides supplemental information about biological features of the disease including a history-based analysis of the rate of periodontitis progression; assessment of the risk for further progression; analysis of possible poor outcomes of treatment; and assessment of the risk that the disease or its treatment may negatively affect the general health of the patient. For a complete description of the rationale, determinants, and practical implementation of the staging and grading system, refer to Tonetti et al.[6] Tables 1 and 2 list the framework of the staging and grading system.

Do the acute periodontal lesions have distinct features when compared with other forms of periodontitis?

Periodontal abscesses, lesions from necrotizing periodontal diseases and acute presentations of endo-periodontal lesions, share the following features that differentiate them from periodontitis lesions: (1) rapid-onset, (2) rapid destruction of periodontal tissues, underscoring the importance of prompt treatment, and (3) pain or discomfort, prompting patients to seek urgent care.

Do periodontal abscesses have a distinct pathophysiology when compared to other periodontitis lesions?

The first step in the development of a periodontal abscess is bacterial invasion or foreign body impaction in the soft tissues surrounding the periodontal pocket, which develops into an inflammatory process that attracts polymorphonuclear neutrophils (PMNs) and low numbers of other immune cells. If the neutrophil-mediated defense process fails to control the local bacterial invasion or clear the foreign body, degranulation, necrosis and further neutrophilic influx may occur, leading to the formation of pus which, if not drained, results in an abscess. Pathophysiologically, this lesion differs in that the low pH within an abscess leads to rapid enzymatic disruption

of the surrounding connective tissues and, in contrast to a chronic inflammatory lesion, has a greater potential for resolution if quickly managed.

What is the case definition of a periodontal abscess?

Periodontal abscess is a localized accumulation of pus located within the gingival wall of the periodontal pocket/sulcus, resulting in a significant tissue breakdown. The primary detectable signs/symptoms associated with a periodontal abscess may involve ovoid elevation in the gingiva along the lateral part of the root and bleeding on probing. Other signs/symptoms that may also be observed include pain, suppuration on probing, deep periodontal pocket, and increased tooth mobility.

A periodontal abscess may develop in a pre-existing periodontal pocket, e.g., in patients with untreated periodontitis, under supportive therapy or after scaling and root planing or systemic antimicrobial therapy. A periodontal abscess occurring at a previously periodontally healthy site is commonly associated with a history of impaction or harmful habits.

Do necrotizing periodontal diseases have a distinct pathophysiology when compared to other periodontitis lesions?

Yes. Necrotizing gingivitis lesions are characterized by the presence of ulcers within the stratified squamous epithelium and the superficial layer of the gingival connective tissue, surrounded by a non-specific acute inflammatory infiltrate. Four zones have been described: (1) superficial bacterial zone, (2) neutrophil-rich zone, (3) necrotic zone and (4) a spirochetal/bacterial infiltration zone.

Necrotizing periodontal diseases are strongly associated with impairment of the host immune system, as follows: (1) in chronically, severely compromised patients (e.g., AIDS patients, children suffering from severe malnourishment, extreme living conditions, or severe infections) and may constitute a severe or even life-threating condition; and (2) in temporarily and/or moderately compromised patients (e.g., in smokers or psycho-socially stressed adult patients).

What are the case definitions of necrotizing periodontal diseases?

Necrotizing gingivitis is an acute inflammatory process of the gingival tissues characterized by presence of necrosis/ulcer of the interdental papillae, gingival bleeding, and pain. Other signs/symptoms associated with this condition may include halitosis, pseudomembranes, regional lymphadenopathy, fever, and sialorrhea (in children).

Necrotizing periodontitis is an inflammatory process of the periodontium characterized by presence of necrosis/ulcer of the interdental papillae, gingival bleeding, halitosis, pain, and rapid bone loss. Other signs/symptoms associated with this condition may include pseudomembrane formation, lymphadenopathy, and fever.

Necrotizing stomatitis is a severe inflammatory condition of the periodontium and the oral cavity in which soft tissue necrosis extends beyond the gingiva and bone denudation may occur through the alveolar mucosa, with larger areas of osteitis and formation of bone sequestrum. It typically occurs in severely systemically compromised patients. Atypical cases have also been reported, in which necrotizing stomatitis may develop without prior appearance of necrotizing gingivitis/periodontitis lesions.

Do endo-periodontal lesions have a distinct pathophysiology when compared to other periodontitis or endodontic lesions?

The term endo-periodontal lesion describes a pathologic communication between the pulpal and periodontal tissues at a given tooth that may be triggered by a carious or traumatic lesion that affects the pulp and, secondarily, affects the periodontium; by periodontal destruction that secondarily affects the root canal; or by concomitant presence of both pathologies. The review did not identify evidence for a distinct pathophysiology between an endo-periodontal and a periodontal lesion. Nonetheless, the communication between the pulp/root canal system and the periodontium complicates the management of the involved tooth.

What is the case definition of an endo-periodontal lesion?

Endo-periodontal lesion is a pathologic communication between the pulpal and periodontal tissues at a given tooth that may occur in an acute or a chronic form. The primary signs associated with this lesion are deep periodontal pockets extending to the root apex and/or negative/altered response to pulp vitality tests. Other signs/symptoms may include radiographic evidence of bone loss in the apical or furcation region, spontaneous pain or pain on palpation/percussion, purulent exudate/suppuration, tooth mobility, sinus tract/fistula, and crown and/or gingival color alterations. Signs observed in endo-periodontal lesions associated with traumatic and/or iatrogenic factors may include root perforation, fracture/cracking, or external root resorption. These conditions drastically impair the prognosis of the involved tooth.

Which are the current key gaps in knowledge that would inform a better classification of periodontitis and should be addressed in future research?

Future research should:

1. Develop improved methodologies to assess more accurately the longitudinal soft and hard tissue changes associated with periodontitis progression
2. Identify genetic, microbial, and host response-associated markers that differentiate between distinct periodontitis phenotypes, or which can reflect the initiation and progression of periodontitis.
3. Expand existing epidemiological databases to include world regions currently underrepresented, utilizing consistent, standardized methodologies, and capturing and reporting detailed data on

both patient-related, oral, and periodontal variables. Open access to the detailed data is crucial to facilitate comprehensive analyses.

4. Integrate multi-dimensional data platforms (clinical, radiographic, -omics) to facilitate systems biology approaches to the study of periodontal and peri-implant diseases and conditions
5. Use existing databases/ develop new databases that will facilitate the implementation, validation and continuous refinement of the newly introduced periodontitis classification system.

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FIGURE 1 Participants of Workgroup 2

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2017 WORLD WORKSHOP

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Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objectives: This review proposes case definitions and diagnostic considerations of systemic disorders and conditions that affect the periodontal attachment apparatus.

Importance: Periodontal diseases and certain systemic disorders share similar genetic and/or environmental etiological factors, and affected patients may show manifestations of both diseases. Characterizing these diseases and the nature of the association between them could have important diagnostic value and therapeutic implications for patients.

Findings: Numerous systemic disorders and certain medications can affect the periodontal attachment apparatus and cause loss of periodontal attachment and alveolar bone. Although many of these disorders are rare or uncommon, they often cause significant loss of periodontal tissue by influencing periodontal inflammation or through mechanisms distinct from periodontitis. Most of these disorders are due to innate mechanisms and some are acquired via environmental factors or lifestyle. Several disorders affect periodontal inflammation through alterations in the host immune response to periodontal infection; others cause defects in the gingiva or periodontal connective tissue, instigate metabolic changes in the host that affect various tissues of the periodontal apparatus, or operate by other mechanisms. For some systemic disorders that are more common, their contribution to the loss of periodontal tissue is modest, while for others, contribution is not supported by clear evidence. Few systemic medications are associated with increased loss of periodontal tissue, and these are typically medications used in the treatment of malignancies.

Conclusions: This review identifies systemic diseases and conditions that can affect the periodontal attachment apparatus and cause loss of periodontal supporting tissues and, where possible, presents case definitions for these. Many of these diseases are associated with a profound loss of periodontal attachment and alveolar bone, and for some of these disorders the periodontal manifestations may be among the first signs of the disease. These case definitions may be useful in the early diagnosis of these diseases and may contribute to an improvement in the management of periodontal manifestations and improve the quality of life for these patients.

KEYWORDS
attachment loss, diagnosis, genetic disease, immune response, inflammation, periodontal disease, systemic disease

INTRODUCTION

The pathogenesis of periodontal diseases is influenced by various host factors, including immune response, anatomical factors, and tissue structural factors. Most of these factors are determined by the genetic profile of the host and may be modified by environmental and host behavioral factors. Periodontal diseases and certain systemic disorders share similar genetic and/or environmental etiological factors and, therefore, affected individuals may show manifestations of both diseases. Hence, loss of periodontal tissue is a common manifestation of certain systemic disorders, which could have important diagnostic value and therapeutic implications.

This paper reviews systemic disorders and medications that may affect the periodontal attachment apparatus and proposes case definitions and diagnostic considerations for these diseases. The disorders are classified according to the magnitude and mechanisms of their effects on the periodontium. First, we describe conditions that have a major impact on the presentation and severity of periodontitis, typically resulting in severe, early-onset periodontitis. Second, we describe conditions that have a moderate impact on the severity of periodontitis and have been shown to result in increased prevalence and severity of periodontitis but do not otherwise have a specific clinical presentation that differs from chronic periodontitis. Finally, we describe conditions that can cause destruction of the periodontal attachment independent of plaque-induced periodontitis.

The issue of providing accurate case definitions for all these conditions is difficult given that a case would generally be defined as periodontal breakdown in the presence of the specific systemic condition. However, where possible we have tried to provide case definitions along these lines. In addition, we have not included conditions that may affect the gingival tissues but have not been shown to contribute to periodontal breakdown (such as the leukemias). These conditions are the subject of another review in this series.

METHODS

Focused questions

This report used a review approach aimed at answering the following questions:

1. Which systemic disorders and medications can cause or be associated with loss of periodontal support?
2. What is the strength of the evidence of the reported association between the identified disorders/medications and loss of periodontal support?

Literature search strategies

The PubMed electronic database was used in all online searches, and no limitation on the time of publication was used. Because of the large number of disorders involved, the search strategy had to be modified accordingly. Therefore, instead of a single search, we performed multiple unique search sessions as described below.

1. The initial search involved the disorders listed in the 1999 Classification System for Periodontal Diseases and Conditions.[1] The keywords used in the online searches were (the name of disorder) AND (periodontal disease OR periodontitis OR attachment loss). We used relevant Medical Subject Headings (MESH) when available for the disorder and used synonyms and spelling variants. In addition to the diseases and conditions listed in the 1999 classification, the above keyword convention was used to perform unique literature searches for each of the following disorders: hyperglycemia, hypertension, emotional stress/depression, osteoporosis, and obesity.
2. The initial search was followed by an expanded search using the following keywords: (systemic disease OR genetic disease OR hereditary disease OR immune response) AND (periodontal disease OR periodontitis OR attachment loss).
3. A specific search was conducted for medications. We used the keywords (drug induced) AND (periodontitis OR attachment loss).

Screening and selection criteria of studies

Systemic disease is defined as a disease that affects multiple organs or tissues or that affects the body as a whole. The identified study titles were first screened to exclude studies not relevant to the focused questions. If the title was relevant, the abstract of the study was reviewed by one reviewer; if the text suggested the study may be eligible, the full text of the study was reviewed. The reference list of relevant studies was reviewed to identify additional studies. The reviewer evaluated the quality of the study and the strength of the evidence based on the methods used and the study findings. For rare diseases, different types of studies were included and evaluated, including case studies. For more common disorders, case studies were not included. Studies in non-English languages were evaluated only if the abstract in English provided sufficient information to evaluate the quality of the evidence. Systematic reviews and randomized controlled clinical trials were regarded the strongest evidence. If there were no relevant systematic reviews, consistency of findings from multiple studies indicated stronger evidence of association. In each of the unique searches, data extraction was performed by one reviewer. This review covered papers published from 1950 to March 2017.

Strength of associations and quality of evidence

Most disorders discussed in this paper are rare diseases and conditions that are typically described in case reports. Few systematic reviews are available for the small number of disorders that are somewhat more common. Hence, in the tables the strength of association between these disorders and loss of the periodontal attachment apparatus is evaluated based on the following criteria: a) severity of the reported periodontal findings; b) the number of published reports describing the association; and c) the consistency of periodontal effects reported in these studies. The quality of evidence is sometimes difficult to assess because of the relatively small number of published studies; therefore the types of study are presented in the tables in lieu of the quality of evidence. The strength of the associations is rated as follows:

- Not reported: published studies in persons affected with the systemic disorder did not describe the dental or periodontal status of these individuals.
- No association: published studies in persons affected with the systemic disorder did not report loss of alveolar bone or periodontal attachment.
- Inconclusive: few studies, with conflicting findings.
- Weak association: a single case report or case-control study showing an association or a few studies with consistent findings showing [a] modest increased risk for loss of alveolar bone or periodontal attachment.
- Moderate association: case reports, case-control studies, and narrative reviews showing consistent increased risk for loss of periodontal tissue, but systematic reviews were not available.
- Significant association: multiple case reports with consistent findings showing profound loss of periodontal tissue or one or more systematic reviews showing significantly increased risk for loss of alveolar bone or periodontal attachment.

OBSERVATIONS AND DISCUSSION

Table 1 shows the classification of systemic diseases and conditions that affect the periodontal attachment apparatus. Several systemic disorders are associated with significant loss of periodontal tissue, most of which are genetic diseases, although some are acquired or inflammatory in nature.

1 | SYSTEMIC DISORDERS THAT HAVE A MAJOR IMPACT ON THE LOSS OF PERIODONTAL TISSUE BY INFLUENCING PERIODONTAL INFLAMMATION

Several systemic disorders are associated with profound loss of periodontal tissue and comprise genetic and nongenetic disorders.

1.1 | Genetic disorders

Genetic disorders are caused by gene mutations or chromosome disorders that cause a change in the number or structure of chromosomes. These disorders are classified here according to their purported mechanisms of effect.

1.1.1 | Diseases associated with immunologic disorders (Table 2)

Individuals with Down syndrome (DS) have higher prevalence and severity of periodontal disease than individuals without DS[2] and the periodontal attachment loss starts in adolescence. Intrinsic abnormalities of the immune system may predispose these individuals to infections[3]; recent findings show a significant relationship between certain subpopulations of peripheral T lymphocytes and matrix metalloproteinase-3 (MMP-3), MMP-8, and MMP-9, which may indicate increased migration of T lymphocytes to the periodontium and, hence, a higher risk for periodontal supporting tissue loss.[4]

In leukocyte adhesion deficiency (LAD) syndromes, neutrophils are confined to blood vessels and are absent from the periodontium.[5] Periodontal tissue loss may be caused by the lack of neutrophil immune surveillance and by the disruption of neutrophil-associated homeostatic mechanisms.[5]

Individuals with Papillon-Lefèvre syndrome (PLS) develop severe gingival inflammation and pocket formation soon after eruption of teeth. The loss of periodontal attachment and alveolar bone progresses rapidly and leads to loss of the primary and permanent teeth at a young age.[2,6] The number of neutrophils and their recruitment to the site of infection in PLS are not compromised, but neutrophil functions may be deficient. The formation of neutrophil extracellular traps, which is a distinct antimicrobial mechanism, is negligible and neutrophil elastase and serine proteases are deficient.[7] Deficiency of cathepsin C results in a lack of protease 3 activation and deficiency of cathelicidin LL-37 peptide, thus compromising the host's ability to kill periodontal bacteria.[8] It has also been suggested that relentless recruitment and accumulation of hyperactive/reactive neutrophils in PLS causes the release of higher levels of proinflammatory cytokines, which together with reduced antimicrobial capacity of neutrophils, may lead to a locally destructive chronic inflammatory cycle that causes severe loss of periodontal tissues.[9]

The periodontal manifestations in Haim-Munk syndrome (HMS) include severe gingival inflammation soon after eruption of teeth, periodontitis, high rate of attachment loss, and early loss of teeth. Individuals with Chediak-Higashi syndrome (CHS) show early-onset severe gingival inflammation and generalized, deep probing depth affecting most of the dentition.[2] There is also severe alveolar bone loss that progresses rapidly and leads to premature loss of teeth.[10]

Oral ulcerations, periodontal inflammation, and periodontitis are common clinical manifestations in individuals with congenital neutropenia. The genetic diversity of congenital neutropenia may influence the prevalence and severity of periodontal manifestations.

TABLE 1 Systemic diseases and conditions that affect the periodontal attachment apparatus

Classification	Disorders	ICD-10 code
1.	**Systemic disorders that have a major impact on the loss of periodontal tissue by influencing periodontal inflammation**	
1.1.	**Genetic disorders**	
1.1.1.	**Diseases associated with immunologic disorders**	
	Down syndrome	Q90.9
	Leukocyte adhesion deficiency syndromes	D72.0
	Papillon-Lefèvre syndrome	Q82.8
	Haim-Munk syndrome	Q82.8
	Chediak-Higashi syndrome	E70.3
	Severe neutropenia	
	– Congenital neutropenia (Kostmann syndrome)	D70.0
	– Cyclic neutropenia	D70.4
	Primary immunodeficiency diseases	
	– Chronic granulomatous disease	D71.0
	– Hyperimmunoglobulin E syndromes	D82.9
	Cohen syndrome	Q87.8
1.1.2.	**Diseases affecting the oral mucosa and gingival tissue**	
	Epidermolysis bullosa	
	– Dystrophic epidermolysis bullosa	Q81.2
	– Kindler syndrome	Q81.8
	Plasminogen deficiency	D68.2
1.1.3.	**Diseases affecting connective tissues**	
	Ehlers-Danlos syndrome (types IV, VIII)	Q79.6
	Angioedema (C1-inhibitor deficiency)	D84.1
	Systemic lupus erythematosus	M32.9
1.1.4.	**Metabolic and endocrine disorders**	
	Glycogen storage disease	E74.0
	Gaucher disease	E75.2
	Hypophosphatasia	E83.30
	Hypophosphatemic rickets	E83.31
	Hajdu-Cheney syndrome	Q78.8
	Diabetes mellitus	E10 (type 1), E11 (type 2)
	Obesity	E66.9
	Osteoporosis	M81.9
1.2.	**Acquired immunodeficiency diseases**	
	Acquired neutropenia	D70.9
	HIV infection	B24
1.3.	**Inflammatory diseases**	
	Epidermolysis bullosa acquisita	L12.3
	Inflammatory bowel disease	K50, K51.9, K52.9
	Arthritis (rheumatoid arthritis, osteoarthritis)	M05, M06, M15-M19
2.	**Other systemic disorders that influence the pathogenesis of periodontal diseases**	
	Emotional stress and depression	F32.9
	Smoking (nicotine dependence)	F17

(Continues)

TABLE 1 (Continued)

Classification	Disorders	ICD-10 code
	Medications	
3.	**Systemic disorders that can result in loss of periodontal tissue independent of periodontitis**	
3.1.	**Neoplasms**	
	Primary neoplastic diseases of periodontal tissue	
	–Oral squamous cell carcinoma	C03.0 – 1
	–Odontogenic tumors	D48.0
	–Other primary neoplasms of periodontal tissue	C41.0
	Secondary metastatic neoplasms of periodontal tissue	C06.8
3.2.	**Other disorders that may affect periodontal tissue**	
	Granulomatosis with polyangiitis	M31.3
	Langerhans cell histiocytosis	C96.6
	Giant cell granulomas	K10.1
	Hyperparathyroidism	E21.0
	Systemic sclerosis (scleroderma)	M34.9
	Vanishing bone disease (Gorham - Stout syndrome)	M89.5

There is evidence that mutations in the *ELANE* gene that codes for neutrophil elastase are more important in the pathogenesis of periodontitis in individuals with neutropenia than are mutations in other genes.[11]

Among the primary immunodeficiency diseases, some studies reported severe periodontitis in individuals with chronic granulomatous disease (CGD) and hyperimmunoglobulin E syndromes (H-IgE). Individuals with CGD have gene mutations causing defects in the intracellular killing of phagocytosed microorganisms in leukocytes.[12] H-IgE is due to mutations in signal transducer and activator of transcription 3 (*STAT3*) or dedicator of cytokinesis 8 (*DOCK8*) genes, which code for a transcription factor and intracellular signaling proteins, respectively.

In individuals with Cohen syndrome, there is a higher prevalence and severity of bone loss than in age- and sex-matched controls.[13,14]

1.1.2 | Diseases affecting the oral mucosa and gingival tissue (Table 3)

Of the 4 types of epidermolysis bullosa (EB) periodontal diseases have been mainly associated with Kindler syndrome.[15,16] It has been hypothesized that molecular defects in the basement membrane zone in certain EB types, particularly Kindler syndrome, may result in reduced resistance at the junctional epithelium, which predisposes these individuals to develop periodontitis even in the absence of periodontal pathogens.[17] This was supported by the finding of atypical pocket junctional epithelium seen in a histologic examination of periodontal tissue in these patients.[15] Kindler syndrome is caused by mutations in the fermitin family homologue 1 gene (kindlin-1; also called *FERMT1*) that encodes the kindlin-1 protein, which is important for cell adhesion, spreading, and migration.[18] It has been shown more recently that kindlin-1 plays a crucial role in actin-dependent keratinocyte cell adhesion, which is essential for epidermal and periodontal health, and that a deficiency of this protein in keratinocytes will lead to reduced cell spreading, proliferation, and migration rate.[19] Animal models also show that kindlin-1 mutations can cause lack of integrin activation in the junctional epithelium, which may result in severe periodontal disease.[20]

Individuals with plasminogen deficiency may show alveolar bone loss, severe periodontitis, and early loss of teeth.[21,22] Plasminogen plays important roles in intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue remodeling, and angiogenesis, and deficiency in these functions seems to play a significant role in the pathogenesis of a number of diseases.[23] It is likely that the disruption of one or more of these processes due to plasminogen deficiency may result in the loss of the periodontal attachment apparatus in affected individuals, but the specific mechanism involved is not well understood.

1.1.3 | Diseases affecting the connective tissues (Table 3)

Individuals with Ehlers-Danlos syndrome (EDS) type VIII have gingival recession and generalized severe periodontitis that often leads to loss of all teeth.[24] Periodontitis also may occur in EDS type IV[25] and, to a lesser extent, in EDS type I.[26] EDS disorders are often caused by mutations in genes encoding fibrillary collagens or enzymes involved in the biosynthesis of these proteins.[27]

Angioedema (C1-inhibitor deficiency) is caused by inadequate control of bradykinin generation due to insufficient levels of protease inhibitors, increased activity of contact phase proteins, and/or inadequate degradation of bradykinin into inactive peptides. Angioedema may be hereditary or acquired and the 2 types are

TABLE 2 Genetic disorders that affect the host immune response and are associated with loss of periodontal tissue

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Down syndrome	Moderate	Case-control, narrative reviews	Intrinsic immune system defects	• Characteristic physical appearance, variable degree of cognitive impairment, and a range of physical disorders • Moderate to severe loss of periodontal attachment and alveolar bone	• Karyotype test is positive for trisomy of chromosome 21
Leukocyte adhesion deficiency syndromes	Significant	Case reports, narrative reviews, animal studies	Neutrophils are confined to blood vessels and do not migrate to periodontal sites, which causes a disruption of neutrophil-associated homeostasis	• History of severe recurrent infections with no pus formation • Leukocytosis is common • Severe gingival inflammation, acute gingival lesions, early-onset and rapidly progressive alveolar bone loss • Early loss of the primary and permanent teeth	• Flow cytometry shows low CD18 or CD15 expression on neutrophils (< 5% of normal) • Genetic testing for mutations in the beta-2 integrin (*ITGB2*) gene. Testing also shows absence of beta-2 integrin mRNA in leukocytes.
Papillon-Lefèvre syndrome	Significant	Case reports, narrative reviews	Not well understood, but compromised neutrophil function may play a role, such as negligible formation of extracellular traps, deficiency of elastase and serine proteases, deficiency of cathelicidin LL-37 peptide	• Hyperkeratotic lesions affecting multiple organs, particularly the palms, soles of the feet, elbows, and knees • Severe gingival inflammation, early-onset and rapidly progressive alveolar bone loss • Early loss of the primary and permanent teeth	• Genetic testing for mutations of the cathepsin C (*CTSC*) gene on chromosome 11q14. Also, a laboratory test has recently been developed for early screening for the absence of cathepsin C activity in urine.
Haim-Munk syndrome	Significant	Case reports, narrative reviews	Not well understood, but compromised neutrophil functions may play a role	• Palmoplantar hyperkeratotic lesions, arachnodactyly, acro-osteolysis, atrophic changes of the nails, and radiographic deformity of the fingers • Severe gingival inflammation soon after eruption of teeth, high rate of attachment loss • Early loss of the primary and permanent teeth	• Genetic testing for mutations of *CTSC* (exon 6, 2127A → G) • A clinical exam could differentiate this disorder from Papillon-Lefèvre syndrome
Chediak-Higashi syndrome	Significant	Case reports, narrative reviews	Gene mutations result in impaired function of multiple body cells and systems, particularly the immune system	• Partial oculocutaneous albinism, varying neurologic problems such as intellectual deficit and dementia, and recurrent pyogenic infections • Severe gingival inflammation, early-onset and rapidly progressive alveolar bone loss • Early loss of the primary and permanent teeth	• Genetic testing for mutations of the Chediak-Higashi syndrome (*CHS1*)/lysosomal trafficking regulator (*LYST*) gene • Peripheral blood smear demonstrates the classic giant azurophilic granules in neutrophils, eosinophils, and other granulocytes
Severe neutropenia					
- Congenital neutropenia (Kostmann syndrome)	Significant	Case reports, narrative reviews	Deficiency in the immune response due to low neutrophil count; neutrophils are deficient in the antibacterial peptide cathelicidin LL-37 and have reduced concentrations of the human neutrophil peptides 1–3 (HNP1-3; α-defensins)	• ANC < 500 cells/μL and static • Severe and recurrent infections: otitis media, bronchitis, pneumonia, osteomyelitis, cellulitis; fungal infections • Severe periodontitis is common • Higher risk for tooth loss • Oral ulcers	• ANC should be determined • Reduced plasma levels of hCAP-18 (proprotein of LL-37) determined by ELISA • Genetic testing for mutations in the elastase, neutrophil expressed (*ELANE*) gene • A bone marrow test also can assist in diagnosis

(*Continues*)

TABLE 2 (Continued)

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
- Cyclic neutropenia	Weak	Case reports, narrative reviews	Deficiency in the immune response due to intermittent low neutrophil count	• ANC < 500 cells/μL and occurs every 21 days, lasting 3 to 6 days at a time • Recurrent infections, less severe than in congenital neutropenia • Increased risk for periodontal attachment loss and oral ulcers	• Monitoring of neutrophil count 2 to 3 times per week for 6 weeks • Genetic testing for mutations in *ELANE*
Primary immunodeficiency diseases					
- Chronic granulomatous disease	Weak	Case reports, case series, narrative reviews	Phagocytes show defective respiratory burst activity, which leads to defect in the intracellular killing of phagocytosed microorganisms	• Recurrent, life-threatening bacterial and fungal infections of the skin, airways, lymph nodes, liver, brain, and bones • Severity of periodontal involvement is correlated with extent of the immune defect and ranges from gingival inflammation to generalized severe periodontitis	• Neutrophil-function testing followed by immunoblot confirmation • Genetic testing for mutations in genes encoding for: gp91phox, p47phox, p22phox, p67phox, and p40phox
- Hyperimmunoglobulin E syndromes	Significant for the autosomal recessive form associated with *DOCK8* mutations; weak for other forms	Case reports, case series, narrative reviews	Mutations in signal transducer and activator of transcription 3 (*STAT3*) gene affect a transcription factor, and mutations in dedicator of cytokinesis 8 (*DOCK8*) gene affect a protein involved in intracellular signaling	• Recurrent skin abscesses, eczema, pulmonary infections, and other clinical manifestations • Some, but not all, cases show severe gingival bleeding and generalized severe periodontitis • There is delayed eruption of the permanent teeth	• IgE > 1000 IU/mL, a weighted score > 30 of selected clinical/laboratory tests designed by the NIH • Genetic testing to confirm mutations of *STAT3* or *DOCK8*
- Agammaglobulinemia	No association	Case reports, narrative reviews			
- Hyperimmunoglobulin G syndromes	Not reported	Case reports, narrative reviews			
- Wiskott-Aldrich syndrome	Not reported	Case reports, narrative reviews			
- Severe combined immunodeficiency disorders	Not reported	Case reports, narrative reviews			
Cohen syndrome	Moderate	Case report (1), case-control study (1)	The disease causes granulocytopenia and neutropenia, which cause a deficiency in the immune response to infections	• Characteristic facial appearance, microcephaly, downward slanting eyes, hypotonia, joint laxity, mental retardation, neutropenia, myopia, and pigmentary retinopathy • Increased prevalence and severity of alveolar bone loss	• Reduced plasma levels of hCAP-18 (proprotein of the antibacterial peptide LL-37) determined by ELISA

ANC, absolute neutrophil count; CD, cluster of differentiation; ELISA, enzyme-linked immunosorbent assay; hCAP, human cationic antimicrobial protein; HNP, human neutrophil peptide; IgE, immunoglobulin E; NIH, National Institutes of Health.

TABLE 3 Genetic disorders that affect the gingiva or connective tissues and are associated with loss of periodontal tissue

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Diseases affecting gingival tissue					
Epidermolysis bullosa (EB)					
- Dystrophic EB	No association	Case reports, narrative reviews	Mutations in the collagen type VII alpha 1 chain (*COL7A1*) gene may affect type VII collagen formation	• Recurrent blister formation of skin and oral cavity that may be localized or generalized • Generalized gingival inflammation and severe loss of keratinized gingiva	• Skin biopsy of an induced blister via immunofluorescence microscopy mapping for basement membrane antigens • Genetic testing for mutations in *COL7A1*
- Kindler syndrome	Significant	Case reports, narrative reviews	Mutations in the fermitin family homologue 1 (kindlin-1; *FERMT1*) gene can cause lack of integrin activation, affect keratinocyte cell adhesion, and lead to molecular defects in the basement membrane zone	• Recurrent blister formation of skin and oral cavity • Photosensitivity • Severe periodontitis and alveolar bone loss that progress rapidly	• Skin biopsy of an induced blister via immunofluorescence microscopy • Genetic testing for mutations in *FERMT1*
Plasminogen deficiency	Significant	Case reports, narrative review	Not well understood; possible mechanisms involve defective fibrinolysis, fibrin deposition, and abnormal wound healing	• Chronic inflammatory disease of the mucous membranes of various organs • Ligneous conjunctivitis is common • Gingiva enlarged and ulcerated, may be covered with white-yellowish membrane, progressive alveolar bone loss and early loss of teeth	• Laboratory tests show decreased plasminogen activity and antigen level • Gingival biopsy shows positive staining for fibrin and negative for amyloid
Diseases affecting the connective tissues					
Ehlers-Danlos syndrome (type IV, VIII)	Significant	Case reports, narrative reviews	Mutations in genes encoding fibrillar collagens or enzymes involved in the biosynthesis of these proteins	• Joint hypermobility, skin extensibility, easy bruising and abnormal scarring, and pigmentary scarring of the lower legs (type VIII). May also have severe physical disability and life-threatening vascular complications. • Generalized, early-onset severe periodontitis and gingival recession • Early loss of the primary and permanent teeth	• Clinical findings of skin hyperextensibility, atrophic scars, and joint hypermobility • Genetic testing for mutations in collagen type V alpha 1 chain (*COL5A1*) and collagen type V alpha 2 chain (*COL5A2*) genes
Angioedema	Weak	Case reports (2)	Inadequate control of bradykinin generation due to a deficiency of protease inhibitors (C1-inhibitor) and/or inadequate degradation of bradykinin into inactive peptides	• Serious and potentially life-threatening attacks of subcutaneous and submucosal edemas of upper airways, face, abdomen, and extremities • Localized or generalized severe periodontitis	• Suggestive history and clinical findings • Consideration can be given for checking serum C1 inhibitor or ACE levels based on clinical suspicion
Systemic lupus erythematosus	Inconclusive	Case reports, narrative reviews, case- control studies	Tissue destruction may be due to hyperactivation of B and T lymphocytes, increased production of IgG, and production and accumulation of autoantibodies	• Joint pain and swelling affecting the fingers, hands, wrists, and knees • Skin rash and fatigue • Oral ulcers and increased prevalence of gingival inflammation and periodontitis	• Concomitant appearance of at least 4 of the following symptoms: malar erythema; discoid lesions; photosensitivity; nasal ulcers; arthritis; serositis; impaired renal function; neurological, hematological, immunological changes; and antinuclear antibodies

ACE, angiotensin-converting enzyme; IgG, immunoglobulin G.

clinically indistinguishable. A few case reports described patients with angioedema who also had periodontal attachment loss or localized aggressive periodontitis.[28,29]

In systemic lupus erythematosus (SLE) the affected tissues show increased accumulation of immune cells, antineutrophil cytoplasm antibodies and metalloproteinases, and altered production of cytokines and tumor necrosis factor in blood. These changes may cause hyperactivation of B and T lymphocytes, increased production of IgG, and production and accumulation of autoantibodies that cause tissue destruction.[30] An increase in the prevalence of gingivitis and periodontitis has been reported.[30] However, a recent study compared a group of patients with SLE with matched controls and found similar levels of periodontal attachment in the two groups.[31]

1.1.4 | Metabolic and endocrine disorders (Table 4)

Individuals with glycogen storage disease (GSD) type 1b suffer from myeloid dysfunctions, neutropenia, and neutrophil dysfunction attributed to endoplasmic reticulum stress generated by disruption of endogenous glucose production. Severe periodontal breakdown in patients with GSD type 1b have been reported.[2]

The oral manifestations of Gaucher disease (GD) are often detected during routine dental radiographic examinations.[32] These include loss of alveolar bone trabecular architecture, widening of bone marrow spaces, and presence of honeycomb-shaped radiolucent lesions, mainly in the premolar and molar regions. A few studies have reported periodontitis affecting individuals with GD.[33]

In individuals with hypophosphatasia (HPP) the dentin is not affected, although both the acellular and cellular cementum may be absent, hypocalcified, or dysplastic.[34] These defects in root cementum result in compromised periodontal attachment and reduction in alveolar bone height.[35] A knock-in mouse model based on a c.346G > A mutation in the alkaline phosphatase (*ALPL*) gene with a primarily dental phenotype of odontohypophosphatasia showed alterations in the alveolar bone, including radiolucencies and resorptive lesions, osteoid accumulation on the alveolar bone crest, and significant changes in several bone properties.[36,37] As a result, teeth roots are not adequately anchored to the alveolar bone via the periodontal ligament, which leads to premature loss of teeth in individuals with HPP.

In hypophosphatemic rickets (HR) there is alteration of bone and tooth mineralization that may lead to malformed and feeble bone and teeth and premature tooth loss.[38] HR is caused by mutations in the fibroblast growth factor 23 (*FGF23*) gene, which regulates phosphate and vitamin D homeostasis. Experimental ablation of *FGF23* in mice leads to ectopic matrix formation in pulp chambers, odontoblast layer disruption, narrowing of periodontal ligament space, and alteration of cementum structure.[39]

A recent systematic review concluded that postmenopausal women with osteoporosis or osteopenia exhibit greater loss of periodontal attachment compared with women with normal bone mineral density.[40] Individuals with Hajdu-Cheney syndrome develop osteoporosis and commonly present with severe periodontitis and premature loss of teeth.[41]

Diabetes mellitus (DM) and chronic hyperglycemia

Diabetes mellitus has, for many years, been recognized as an important risk factor for periodontal diseases and associated with significantly higher prevalence and severity of periodontitis.[42] More recent data have confirmed a significant association between chronic hyperglycemia and a high prevalence of severe periodontitis.[43,44] Although this evidence focuses particularly on the effects of type 2 DM, the effect appears to be similar, though less investigated, in type 1 DM.[45–47] The current global epidemic of type 2 DM has been well documented; World Health Organization data show a 4-fold increase in disease prevalence from 1980 to 2014, with a 2014 prevalence of 422 million people affected, representing an overall prevalence of 8% of the world population.[48] Furthermore, in many diabetic patients DM is undiagnosed, and the prevalence of these individuals is increasing.[49] Hence, DM represents an enormous public health challenge and is by far the principal systemic disease affecting periodontitis in terms of extent of population affected. In addition, there is accumulating evidence that periodontal inflammation may itself contribute to the onset and persistence of hyperglycemia, in that inflammation is associated with poorer glycemic control in individuals with DM and may be associated with an increase in incident DM in longitudinal prospective studies.[50]

Chronic hyperglycemia has direct and indirect detrimental effects on multiple organs and is implicated in the development and progression of diabetic micro- and macroangiopathy.[51,52] It may exert long-lasting detrimental effects on the cardiovascular system and other organs.[53] Hyperglycemia also leads to the development and accumulation of advanced glycation end products (AGEs), and the interaction between AGEs and their key receptor, RAGE, is thought to play a major role in the development of complications associated with hyperglycemia.[54]

The pathogenic mechanisms responsible for the effects of hyperglycemia on periodontitis have been extensively reviewed in the literature.[55–58] It should be noted, however, that interpretation of these findings may be confounded by the effects of comorbidities often seen in individuals with metabolic syndrome, including obesity and hypertension. Studies suggest that in the presence of hyperglycemia, there is a hyperinflammatory response to bacterial challenge, which may give rise to a range of changes in the host, including neutrophil defects, hyperinflammatory responsive monocytes, increased release of proinflammatory cytokines, oxidative stress reactions, and impaired healing responses.[55] A major factor that may drive many or all of these responses is the accumulation of AGEs and their interaction with their cognate receptors, RAGEs. Both circulating AGEs and local expression of RAGEs are elevated in individuals with DM who have periodontitis.[56] Using a rodent model of hyperglycemia, it has been shown that accelerated alveolar bone loss develops in diabetic mice infected with *Porphyromonas gingivalis* and that activation of RAGE contributes to the pathogenesis of periodontitis in persons with hyperglycemia.[59] Blocking of RAGE using soluble receptors for AGE subsequently was shown to reverse these effects independently of the level of hyperglycemia.[60]

TABLE 4 Metabolic and endocrine disorders that are associated with loss of periodontal tissues

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Glycogen storage disease (type 1b)	Significant	Case reports, narrative reviews	Deficiency in G6PT, defective glucose homeostasis, neutropenia, and neutrophil dysfunction	• Hypoglycemia, hepatosplenomegaly, seizures, myeloid dysfunctions, neutropenia, and recurrent bacterial infections • Severe periodontitis	• Genetic testing for mutations in the glucose 6-phosphatase, catalytic subunit (*G6PC*) gene and solute carrier family 37 member 4 (*SLC37A4*) gene encoding G6PT
Gaucher disease	Moderate	Case reports	Deficiency of the enzyme glucocerebrosidase causes formation of Gaucher cells, which infiltrate into organs of the reticuloendothelial system	• Anemia, neutropenia, spontaneous bleeding, hepatosplenomegaly, and defective bone remodeling and osteopenia • Loss of alveolar bone trabecular architecture, widening of PDL and bone marrow spaces, and presence of honeycomb-shaped radiolucent lesions mainly in the mandibular premolar and molar regions • Generalized severe alveolar bone loss may be present	• Glucocerebrosidase enzyme assay to assess enzyme activity in peripheral leukocytes • Genetic testing for mutations in the gene encoding glucocerebrosidase (*GCD*)
Hypophosphatasia	Significant	Case reports, animal models, narrative reviews	Mutations in the alkaline phosphatase (*ALPL*) gene are associated with impaired bone and tooth mineralization and defects in root cementum, which result in compromised periodontal attachment and reduction in alveolar bone height. The teeth are not adequately anchored to the alveolar bone via the PDL.	• Mild form: foot pain, stress fracture of the metatarsals • Severe form: skeletal deformities, short stature, waddling gait, bone pain, high risk for bone fractures • Defective cementum, alveolar bone loss, and premature loss of teeth	• Evaluation of comprehensive metabolic panel to assess for low alkaline phosphatase in the serum • Genetic testing for mutations in *ALPL*
Hypophosphatemic rickets	Weak	Case series	Mutations in fibroblast growth factor 23 (*FGF23*) gene influence mineral ion homeostasis and lead to alteration of bone and tooth mineralization and cementum structure	• Short stature and leg deformities • Endodontic involvement and spontaneous periapical infections not due to tooth decay or trauma • Alveolar bone loss, which may be severe • Increased prevalence of periodontitis • Premature loss of teeth	• The following 4 conditions must be present: increased serum alkaline phosphatase, normal serum parathyroid hormone, normal serum calcium, and decreased serum phosphate levels
Hajdu-Cheney syndrome	Moderate	Case reports	Mutations in the neurogenic locus notch homolog 2 (*NOTCH2*) gene for the Notch2 receptor protein involved in early development and remodeling of bone	• Short stature, small face, acro-osteolysis (resorption of the distal phalanx on X-ray), hearing loss, and osteoporosis • Severe periodontitis and premature loss of teeth	• Clinical diagnosis • Genetic testing can detect the truncating mutation in the terminal exon of *NOTCH2*
Osteoporosis	Significant	Animal models, surveys, longitudinal follow-up, case- control study, systematic reviews	Increased bone turnover leading to net bone loss, which can also be associated with other factors (such as estrogen level, vitamin D and calcium deficiency, lifestyle and behavioral factors)	• Decrease in bone mineral density and weakening of bone microarchitecture, leading to a high risk for bone fracture • Higher prevalence and severity of radiographic alveolar bone loss • No clear association with periodontitis (probing depth or clinical attachment loss)	• Clinical diagnosis

(*Continues*)

TABLE 4 (Continued)

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Diabetes mellitus	Significant	Surveys, case- control study, narrative reviews, systematic review	Accumulation of AGEs, which interact with receptor for AGEs (RAGE) and cause changes in multiple organs	• Chronic status of elevated blood glucose level • Increased prevalence and severity of attachment loss	• Fasting plasma glucose level • HBA1c test
Obesity	Significant	Animal models, surveys, case-control study, systematic reviews	Possible mechanisms include an impaired immune response and increased production of proinflammatory cytokines	• BMI ≥30 • Increased risk for periodontitis, periodontal progression, and loss of periodontal attachment	• Clinical diagnosis

AGE, advanced glycation end product; BMI, body mass index; G6PT, glucose-6-phosphate dehydrogenase; HbA_{1c}, glycated hemoglobin; PDL, periodontal ligament space.

Phenotypic features of periodontitis associated with hyperglycemia – The overwhelming evidence for the effects of diabetes on periodontitis comes from epidemiologic data. So far, there is little evidence that the clinical features of periodontitis in patients with DM are distinct from periodontitis in individuals who do not have DM. It has been suggested that dental and periodontal abscesses may be a common complication in DM.[61] A recent study in Saudi Arabia, (where the reported prevalence of DM is 23.9%), found that 58.6% of patients who were diagnosed with periodontal abscesses had HbA_{1c} ≥6.5%.[62] In general, however, an increased prevalence of periodontal abscesses in DM-associated periodontitis compared to periodontitis in individuals who do not have DM is not well documented. This may be partly due to the difficulty of diagnosing a periodontal abscess, particularly when in a chronic stage.[63]

Obesity

Obesity is a health risk frequently associated with complications such as type 2 DM, dyslipidemia, high blood pressure, abnormal fibrinolysis, cardiovascular disease, and other diseases. Adipose tissue is a complex organ with marked effects on whole-body physiology; it serves important roles, including lipid handling and secretion of numerous endocrine mediators, such as adipokines. However, not all individuals who are obese develop obesity-related metabolic and other disorders, possibly because of preserved normal adipose tissue architecture and function. Hence, adipose tissue dysfunction, rather than the amount of fat mass, may be a key factor in the pathophysiology of obesity-related health risk.[64]

Dysfunction of processes in adipose tissue compartments may trigger various metabolic disorders, including obesity, metabolic syndrome, lipodystrophy, and cachexia.[65] Studies show that crosstalk between T cells and adipose tissue shapes the inflammatory environment in obesity-associated metabolic diseases.[66] Likewise, obesity-induced changes to macrophages and adipocytes may lead to chronic inflammation and insulin resistance.[67] Adipose tissue dysfunction has been associated with an increased number of M1 macrophages, B cells, regulatory B cells, T helper (Th) 1 cells, Th17 cells, eosinophils, neutrophils, and mast cells.[68] These cells release myriad proinflammatory cytokines and chemokines, and have been shown to recirculate between adipose tissue, liver, spleen, and blood, contributing to systemic inflammation.[69] Other effects on the immune response include decreased phagocytic activity and impaired antigen presentation.[67]

Study findings also show that obesity increases susceptibility to bacterial and viral infections, and recent meta-analyses consistently support an epidemiological association between obesity and periodontitis, suggesting a 50% to 80% higher likelihood of periodontitis in individuals who are obese compared with individuals who are not.[70,71] It has been estimated in longitudinal follow-up studies that individuals who are obese have a 35% increased risk of developing periodontitis compared with normal-weight individuals,[72] and the risk may be higher among women who are obese compared with men who are obese.[73] On the other hand, there is no indication yet

that the response to periodontal treatment should differ for individuals who are obese versus individuals who are not.[74]

The biological mechanisms underlying the association between obesity and periodontitis are not well understood. However, impairment of systemic immune response and the increased risk for infection are potential mechanisms.[75,76] The increased production by adipose tissue of various humoral factors (adipokines) and proinflammatory cytokines may contribute to the pathogenesis of periodontitis.[77] Obesity also may abate the innate immune response in the periodontium, for example via attenuation of macrophage infiltration and activation.[78] This may explain the higher occurrence of spontaneous[79] and ligature-induced[80] periodontal breakdown in obese experimental animals.

1.2 | Acquired immunodeficiency diseases (Table 5)

Acquired neutropenia is a relatively rare disorder and very few studies have addressed it. One study reported severe periodontitis in a 15 year-old patient with autoimmune neutropenia in whom periodontal lesions improved significantly following administration of intravenous immunoglobulins.[81] There is a clear association between HIV infection and the occurrence of necrotizing ulcerative periodontitis and the increased attachment loss and gingival recession that correlate with declining CD4 counts.[82] This association is discussed in more detail in [paper 6, "Acute Forms of Periodontitis"].

1.3 | Inflammatory diseases (Table 6)

Epidermolysis bullosa acquisita is characterized by the presence of autoantibodies against type VII collagen. Clinically, patients may show generalized gingival inflammation and enlargement, gingival recession, alveolar bone loss, and mobile teeth.[83] Inflammatory bowel disease (IBD) and periodontitis have similar immunopathogenic responses, characterized by a hypersensitivity immune response to commensal gut bacteria and dental plaque bacteria, respectively, which may disrupt local homeostasis in susceptible individuals.[84] Studies show greater attachment loss and higher prevalence and severity of periodontitis in adults with IBD than in controls.[85] About half of individuals with IBD are also diagnosed with arthritis. A large study found a 13% increased risk for periodontitis, increased probing depths, and attachment loss in individuals with rheumatoid arthritis.[86]

2. | OTHER SYSTEMIC DISORDERS THAT MAY CONTRIBUTE TO PERIODONTAL TISSUE LOSS BY INFLUENCING THE PATHOGENESIS OF PERIODONTAL DISEASES (TABLE 7)

Clinical studies show a positive correlation between periodontal disease and stress and certain other psychological factors. Furthermore,

TABLE 5 Acquired immunodeficiency diseases that may be associated with loss of periodontal tissue

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Acquired neutropenia	Weak	Case report (1)	Occur due to decreased production or increased destruction of granulocytes, caused by autoimmune disease, cytotoxic chemotherapy or other drug, or idiopathic etiology	• ANC < 1500 cells/μL (mild), < 1000 cells/μL (moderate), or < 500 cells/μL (severe) • Increased risk for infections correlated with severity of neutropenia • Increased risk for periodontitis correlated with the severity of neutropenia	• Determine ANC
HIV infection	Weak	Surveys, case-control study, narrative reviews	Deficiency of the immune system due to infection with the HIV virus	• The CDC and Council of State and Territorial Epidemiologists recommend a revised case definition of HIV infection • Increased risk for infections, Kaposi sarcoma • Oral candidiasis, oral hairy leukoplakia, severe aphthous ulcers • Increased risk for necrotizing periodontal diseases	• Depends on the stage of infection. Generally, it is recommended to test for HIV antibody/p24 antigen via combination immunoassay and PCR-based HIV viral load.

ANC, absolute neutrophil count; CDC, Centers for Disease Control and Prevention; PCR, polymerase chain reaction.

TABLE 6 Inflammatory diseases that may be associated with loss of periodontal tissue

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Epidermolysis bullosa acquisita	Moderate	Case reports (2)	Autoimmune disease due to binding of pathogenic autoantibodies to target antigens	• Mechanobullous type: characterized by blisters, mild mucosal involvement, and healing with dense scars primarily at trauma-prone areas • Inflammatory form: present as a generalized vesiculobullous eruption primarily on the trunk and flexural areas • Recurrent blister formation of oral cavity that may be localized or generalized • Generalized gingival inflammation and severe alveolar bone loss that may be localized or generalized	• Detailed history and clinical evaluation for skin lesions, followed by direct immunofluorescence microscopy of perilesional skin and immunofluorescence on basement membrane zone-split skin
Inflammatory bowel disease	Significant	Animal models, case-control study, systematic review	Autoimmune disease in which a hypersensitivity immune response to commensal gut bacteria and dental plaque bacteria cause inflammation and alveolar bone loss in the genetically susceptible host	• Abdominal pain, fever, diarrhea, and weight loss • Colonoscopy showing polypoid mucosal changes, ulcerations, and inflammatory changes • Increased prevalence and severity of periodontitis and loss of periodontal attachment and alveolar bone	• History, colonoscopy, and intestinal biopsy
Arthritis	Significant	Animal models, systematic review	Rheumatoid arthritis is an autoimmune disease; osteoarthritis is due to gradual deterioration of cartilage	• Joint pain, swelling, stiffness, redness, and limited motion • Increased risk for loss of periodontal attachment and alveolar bone	• Clinical history and physical examination for arthritis

TABLE 7 Other systemic disorders that may contribute to the loss of periodontal tissue by influencing periodontal inflammation

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Emotional stress and depression	Weak	Animal models, narrative reviews, systematic review	Activation of the limbic-hypothalamic-pituitary-adrenal axis leads to the release of neuroendocrine peptides and hormones that modulate the immune response	• Changes in behavior, mood, and physiological markers • Risk factor for ulcerative periodontal disease; association with alveolar bone loss in animal models	• There is no specific test to diagnose stress • Diagnosis of depression may include a physical exam and psychological evaluation
Hypertension	Inconclusive	Surveys	Undetermined	• Chronic status of high blood pressure • Most studies reported no significant association with periodontitis or attachment loss	• Physical exam

experimentally induced stress significantly increases periodontal destruction in rats, whereas interventions to modulate the hypothalamic-pituitary-adrenal axis reverse this effect.[87] This suggests that stress and depression may potentiate periodontal breakdown.

There is inconclusive evidence that hypertension is associated with increased prevalence of periodontal disease or severity of attachment loss. Similarly, no significant association has been reported between sickle cell disease and attachment loss.

The classes of medication that may affect periodontal attachment are summarized in Table 8. Certain medications, particularly cytotoxic chemotherapeutics, could lead to neutropenia, transient or prolonged, and hence may be associated with increased risk for periodontitis, but few studies are available.

3 | SYSTEMIC DISORDERS THAT CAN RESULT IN LOSS OF PERIODONTAL TISSUE INDEPENDENT OF PERIODONTITIS

A number of disorders may affect periodontal tissue and cause loss of alveolar bone independently of plaque-induced periodontitis. With the exception of apical periodontitis, these are uncommon or very rare conditions, and many are neoplastic lesions. This review places particular emphasis on conditions that may extend to the marginal periodontal tissue and, thus, at times mimic clinical features of periodontitis, but the majority of the lesions described arise from the deeper periodontal tissue. Differential diagnosis of these lesions, and distinguishing clinically between periodontitis and other conditions affecting periodontal tissue, presents a considerable challenge to clinicians and can often only

TABLE 8 Summary of systemic medications with reported effects on periodontitis

Type of medication	Effect on periodontitis	Quality of evidence of association	Reference no.
For malignancies			
Anticancer chemotherapy	Increase	Case-control	[93]
VEGF inhibitors (bevacizumab)	Increase	Case report	[94,95]
TKIs (sunitinib, pazopanib)	Increase	Case report	[96]
Anti-inflammatory agents			
NSAIDs	Decrease	Case-control study; case series	Reviewed in [97]
Anti-TNF therapies	Decrease	Case-control	[98]
Miscellaneous			
Bisphosphonates	Decrease	Small RCT	[99]

NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

TABLE 9 Neoplasms associated with loss of periodontal tissue

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Neoplastic diseases of periodontal tissue					
- Oral squamous cell carcinoma	Moderate	Several case reports	Malignant epithelial neoplasm	• Localized swelling or ulceration of the gingiva, typically in the mandibular molar region • Other features similar to localized periodontitis • Regional lymphadenopathy • Risk for late-stage metastases	• Biopsy
- Odontogenic tumors	Moderate	Case reports	Neoplasm of odontogenic epithelium	• Early lesion: mandibular or maxillary localized swelling and tooth displacement • Late features: similar to localized periodontitis	• Biopsy
- Other primary neoplasms of periodontal tissue	Moderate	Case reports	Malignant neoplasm	• Osteolytic expanding lesion in the jaw	• Biopsy
Secondary metastatic neoplasms of periodontal tissue	Moderate	Case reports	Malignant neoplasm	• Osteolytic expanding lesion(s) in jaws • Presence of primary lesion elsewhere in the body; location of primary neoplasm varies according to the type of neoplasm	• Biopsy • Systemic examination to rule out primary lesion

be resolved by biopsy and histopathologic examination (see Appendix 1 in online *Journal of Clinical Periodontology*). Clinical features of many of these conditions that might arouse suspicion and suggest the need for biopsy are listed in Tables 9 and 10. Given the destructive nature of the majority of these conditions, it is not usually possible to speculate on the potential for periodontal healing after treatment, as tooth loss is typically carried out as part of treatment.

3.1 | Neoplasms

Neoplastic diseases may occur as primary lesions of periodontal tissue or as secondary metastatic neoplasms (Table 9). Oral squamous cell carcinoma (OSCC) arising in the gingivae is generally reported to be approximately 10% of all OSCC cases. The clinical features of OSCC may often resemble localized periodontitis or acute periodontal infection, with gingival redness, swelling, increased probing depths, and radiographic bone loss.

3.2 | Other disorders that may affect periodontal tissue (Table 10)

This group includes several rare disorders that affect multiple organs and have idiopathic, unknown etiology, or other causes such as hormonal change or autoimmune disease. There is evidence that these disorders may cause progressive loss of the alveolar bone and increase the mobility of affected teeth. In granulomatosis with polyangiitis and Langerhans cell histiocytosis, the lesions may affect the periodontal tissue and resemble periodontitis. Giant cell granulomas manifest as expanding epulis-like gingival swellings and cause expanding osteolytic lesions in the deep periodontal tissue, which can, on occasion, expand toward the marginal periodontal tissue. In hyperparathyroidism, single or multiple osteolytic lesions (brown tumors) in the jaw have been reported and can mimic bone loss due to periodontitis.[88] In addition, loss of the lamina dura and widening of the periodontal ligament may be common findings.[89] Other diseases that may cause alveolar bone loss include systemic sclerosis (scleroderma)[90] and vanishing bone disease.[91,92]

CONCLUSIONS

This review describes the systemic disorders and conditions that can affect the periodontal apparatus and cause loss of periodontal attachment and alveolar bone, and presents case definitions and diagnostic considerations of these disorders. Some of these disorders may have direct effect on periodontal inflammation through alterations in the host immune response to periodontal infection, which leads to significant loss of periodontal attachment and alveolar bone. Other disorders cause defects in the gingiva or periodontal connective tissues or instigate metabolic changes in the host that affect various tissues of the periodontal apparatus. Affected individuals may show manifestations of both diseases because periodontitis and certain systemic disorders share similar genetic and/

TABLE 10 Other diseases and conditions that may be associated with loss of periodontal tissue

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Granulomatosis with polyangiitis	Weak	Case report (1)	Peripheral small vessel necrotizing vasculitis	• Respiratory and renal impairment • Characteristic fiery red hyperplastic gingivitis • Alveolar bone loss	• Clinical appearance • Biopsy
Langerhans cell histiocytosis	Moderate	Case series and case reports	Due to proliferation of cells with characteristics similar to bone marrow–derived Langerhans cells	• Wide spectrum of clinical presentations, including solitary chronic bone lesions, diabetes insipidus, and proptosis • Premature eruption of primary teeth, osteolytic lesions in the periodontal tissues, generalized periodontal inflammation and increased pocket depths, severe alveolar bone loss, and premature loss of teeth	• Tissue biopsy of an osteolytic bone lesion or skin lesion with positive immunohistochemical staining for CD1a and CD207 to demonstrate the presence of Langerhans cells
Giant cell granuloma	Moderate	Case series	Reactive proliferation	• Peripheral GCG: expanding epulis-like gingival swelling, occasional loss of periodontal supporting tissue • Central GCG: loss of deep periodontal supporting tissue, which may expand toward marginal periodontal tissue • No systemic features	• Biopsy
Hyperparathyroidism	Moderate	Case series	Primary: benign adenoma of parathyroid glands; secondary: result of hypercalcemia; tertiary: parathyroid hypertrophy following secondary type	• Weakness, kidney stones, excessive urination, abdominal pain, bone and joint pain • Widening of the PDL and single or multiple osteolytic lesions (brown tumors) in the jaw that may mimic bone loss due to periodontal disease	• Test shows elevated serum PTH • Biopsy
Systemic sclerosis (scleroderma)	Moderate	Case reports	Autoimmune disease of the connective tissues	• Many different systemic presentations • Widening of the PDL and higher prevalence of periodontitis	• Physical exam • Raynaud phenomenon • Autoantibody screening
Vanishing bone disease	Moderate	Case reports	Unknown	• Progressive destruction of one or multiple bones • Progressive loss of the mandibular alveolar bone and increased mobility of teeth	• Clinical and radiographic exams • Biopsy

CD, cluster of differentiation; GCG, giant cell granuloma; PDL, periodontal ligament space; PTH, parathyroid hormone.

or environmental risk factors. Few medications are associated with increased loss of periodontal tissue and are typically medications used in the treatment of malignancies.

Characterizing these diseases and the mechanisms of their effects on the periodontal attachment apparatus could have important diagnostic value and therapeutic implications for patients.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

Mucogingival conditions in the natural dentition: Narrative review, case definitions, and diagnostic considerations

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Background: Mucogingival deformities, and gingival recession in particular, are a group of conditions that affect a large number of patients. Since life expectancy is rising and people are retaining more teeth both gingival recession and the related damages to the root surface are likely to become more frequent. It is therefore important to define anatomic/morphologic characteristics of mucogingival lesions and other predisposing conditions or treatments that are likely to be associated with occurrence of gingival recession.

Objectives: Mucogingival defects including gingival recession occur frequently in adults, have a tendency to increase with age, and occur in populations with both high and low standards of oral hygiene. The root surface exposure is frequently associated with impaired esthetics, dentinal hypersensitivity and carious and non-carious cervical lesions. The objectives of this review are as follows (1) to propose a clinically oriented classification of the main mucogingival conditions, recession in particular; (2) to define the impact of these conditions in the areas of esthetics, dentin hypersensitivity and root surface alterations at the cervical area; and (3) to discuss the impact of the clinical signs and symptoms associated with the development of gingival recessions on future periodontal health status.

Results: An extensive literature search revealed the following findings: 1) periodontal health can be maintained in most patients with optimal home care; 2) thin periodontal biotypes are at greater risk for developing gingival recession; 3) inadequate oral hygiene, orthodontic treatment, and cervical restorations might increase the risk for the development of gingival recession; 4) in the absence of pathosis, monitoring specific sites seems to be the proper approach; 5) surgical intervention, either to change the biotype and/or to cover roots, might be indicated when the risk for the development or progression of pathosis and associated root damages is increased and to satisfy the esthetic requirements of the patients.

Conclusions: The clinical impact and the prevalence of conditions like root surface lesions, hypersensitivity, and patient esthetic concern associated with gingival recessions indicate the need to modify the 1999 classification. The new classification includes additional information, such as recession severity, dimension of the gingiva (gingival biotype), presence/absence of caries and non-carious cervical lesions, esthetic concern of the patient, and presence/absence of dentin hypersensitivity.

KEYWORDS

attachment loss, classification, diagnosis, disease progression, esthetics, gingival recession, periodontal biotype

INTRODUCTION AND AIMS

Mucogingival deformities are a group of conditions that affect a large number of patients. Classification and definitions are available in a previous review[1] and in the consensus report on mucogingival deformities and conditions around teeth (Table 1).

Among the mucogingival deformities, lack of keratinized tissue and gingival recession are the most common and are the main focus of this review. A recent consensus concluded that a minimum amount of keratinized tissue is not needed to prevent attachment loss when good conditions are present. However, attached gingiva is important to maintain gingival health in patients with suboptimal plaque control.[2] Lack of keratinized tissue is considered a predisposing factor for the development of gingival recessions and inflammation.[2] Gingival recession occurs frequently in adults, has a tendency to increase with age,[3] and occurs in populations with both high and low standards of oral hygiene.[4–6] Recent surveys revealed that 88% of people aged ≥65 years and 50% of people aged 18 to 64 years have ≥1 site with gingival recession.[3] Several aspects of gingival recession make it clinically significant.[3,7,8] The presence of recession is esthetically unacceptable for many patients; dentin hypersensitivity may occur; the denuded root surfaces are exposed to the oral environment and may be associated with carious and non-carious cervical lesions (NCCL), such as abrasions or erosions. Prevalence and severity of NCCL appear to increase with age.[9] Because life expectancy is rising and people are retaining more teeth, both gingival recession and the related damages to the root surface are likely to become more frequent.

The focus of this review is to propose a clinically oriented classification of the mucogingival conditions, especially gingival recession; and to define the patient and site impact of these conditions regarding esthetics, dentinal hypersensitivity and root surface alterations at the cervical area. Therefore, definition of the "normal" mucogingival condition is the baseline to describe "abnormalities". The definition of anatomic and morphologic characteristics of different periodontal biotypes and other predisposing conditions and treatments will be presented. The third focus of this review is to discuss the impact of the clinical signs and symptoms associated with the development of gingival recessions on future periodontal health status.

TABLE 1 Mucogingival deformities and conditions around teeth[a]

1. gingival/soft tissue recession
   a. facial or lingual surfaces
   b. interproximal (papillary)
2. lack of keratinized gingiva
3. decreased vestibular depth
4. aberrant frenum/muscle position
5. gingival excess
   a. pseudo-pocket
   b. inconsistent gingival margin
   c. excessive gingival display
   d. gingival enlargement
6. abnormal color

[a](AAP 1999, Consensus Report)

METHODS

This article is based mainly on the contribution of the most recent systematic reviews and meta-analyses. In addition, case report, case series, and randomized clinical trials published more recently are included. The authors critically evaluated the literature associated with mucogingival deformities in general and gingival recession in particular to answer the following most common and clinically relevant questions: 1) Is thin gingival biotype a condition associated with gingival recession? 2) Is it still valid that a certain amount of attached gingiva is necessary to maintain gingival health and prevent gingival recession? 3) Is the thickness of the gingiva and underlying alveolar bone critical in preventing gingival recession? 4) Does daily toothbrushing cause gingival recession? 5) What is the impact of intrasulcular restorative margin placement on the development of gingival recession? 6) What is the impact of orthodontic treatment on the development of gingival recession? 7) Is progressive gingival recession predictable? If so, could it be prevented by surgical treatment? 8) What is the impact of the exposure to the oral environment on the root surface in the cervical area?

Information Sources

An extensive literature search was performed using the following databases (searched from March to June 2016): 1) PubMed; 2) the Cochrane Oral Health Group Specialized Trials Registry (the Cochrane Library); and 3) hand searching of the *Journal of Periodontology*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, and *Journal of Periodontal Research*.

Search

The following search terms were used to identify relevant literature: 1) attached gingiva; 2) gingival augmentation; 3) periodontal/gingival biotype; 4) gingival recession; 5) keratinized tissue; 6) dentin hypersensitivity 7) mucogingival therapy; 8) orthodontic treatment; 9) patient reported outcome; 10) non-carious cervical lesions; 11) cervical caries; and 12) restorative margin.

TABLE 2 Classification system of four different classes of root surface concavities

CEJ	Step	Descriptors
Class A	-	CEJ detectable without step
Class A	+	CEJ detectable with step
Class B	-	CEJ undetectable without step
Class B	+	CEJ undetectable with step

NORMAL MUCOGINGIVAL CONDITION

Definition

Within the individual variability of anatomy and morphology "normal mucogingival condition" can be defined as the "absence of pathosis (i.e. gingival recession, gingivitis, periodontitis)". There will be extreme conditions without obvious pathosis in which the deviation from what is considered "normal" in the oral cavity lies outside of the range of individual variability. Accepting this definition, some of the "mucogingival conditions and deformities" listed previously (Table 1) such as lack of keratinized tissues, decreased vestibular depth, aberrant frenum/muscle position, are discussed since these are conditions not necessarily associated with the development of pathosis. Conversely, in individual cases they can be associated with periodontal health. In fact, it is well-documented and a common clinical observation that periodontal health can be maintained despite the lack of keratinized tissue, as well as in the presence of frena and shallow vestibule when the patient applies appropriate oral hygiene measures and professional maintenance in the absence of other factors associated with increased risk of development of gingival recession, gingivitis, and periodontitis.[2,10] Thereby, what could make the difference, for the need of professional intervention, is patient behavior in terms of oral care and the need for orthodontic, implant, and restorative treatments.

CASE DEFINITIONS

Periodontal biotype

One way to describe individual differences as they relate to the focus of this review is the "periodontal biotype". The "biotype" has been labeled by different authors as "gingival" or "periodontal" "biotype", "morphotype" or "phenotype". In this review, it will be referred to as *periodontal biotype*. The assessment of periodontal biotype is considered relevant for outcome assessment of therapy in several dental disciplines, including periodontal and implant therapy, prosthodontics, and orthodontics. Overall, the distinction among different biotypes is based upon anatomic characteristics of components of the masticatory complex, including 1) gingival biotype, which includes in its definition gingival thickness (GT) and keratinized tissue width (KTW); 2) bone morphotype (BM); and 3) tooth dimension.

A recent systematic review using the parameters reported previously, classified the "biotypes" in three categories:[11]

- *Thin scalloped* biotype in which there is a greater association with slender triangular crown, subtle cervical convexity, interproximal contacts close to the incisal edge and a narrow zone of KT, clear thin delicate gingiva, and a relatively thin alveolar bone.
- *Thick flat* biotype showing more square-shaped tooth crowns, pronounced cervical convexity, large interproximal contact located more apically, a broad zone of KT, thick, fibrotic gingiva, and a comparatively thick alveolar bone.
- *Thick scalloped biotype* showing a thick fibrotic gingiva, slender teeth, narrow zone of KT, and a pronounced gingival scalloping.

The strongest association within the different parameters used to identify the different biotypes is found among GT, KTW, and BM. These parameters have been reported to be frequently associated with the development or progression of mucogingival defects, recession in particular.

Keratinized tissue width ranges in a thin biotype from 2.75 (0.48) mm to 5.44 (0.88) mm and in a thick biotype from 5.09 (1.00) mm to 6.65 (1.00) mm. The calculated weighted mean for the thick biotype was 5.72 (0.95) mm (95% CI 5.20; 6.24) and 4.15 (0.74) mm (95% CI 3.75; 4.55) for the thin biotype.

Gingival thickness ranges from 0.63 (0.11) mm to 1.79 (0.31) mm. An overall thinner GT was assessed around the cuspid and ranged from 0.63 (0.11) mm to 1.24 (0.35) mm, with a weighted mean (thin) of 0.80 mm (0.19). When discriminating between either thin or thick periodontal biotype in general, a thinner GT can be found in a thin biotype population regardless of the selected study.

Bone morphotype resulted in a mean buccal bone thickness of 0.343 (0.135) mm for thin biotype and 0.754 (0.128) mm for thick/average biotype. *Bone morphotypes* have been radiographically measured with cone-beam computed tomography (CBCT).[12,13]

Tooth position

The influence of tooth position in the alveolar process is important. The bucco-lingual position of teeth shows increased variability in GT, i.e., buccal position of teeth is frequently associated with thin gingiva[14] and thin labial bone plate.[13]

Prevalence of different biotypes varies in studies that consider different parameters in this classification. In general, a thick biotype (51.9%) is more frequently observed than a thin biotype (42.3%) when assessed on the basis of gingival thickness, and distributed more equally when assessed on the basis of gingival *morphotype* (thick 38.4%, thin 30.3%, normal 45.7%).

It is generally stated that thin biotypes have a tendency to develop more gingival recessions than do thick ones.[2,10] This might influence the integrity of the periodontium through the patient's life and constitute a risk when applying orthodontic,[15] implant,[16] and restorative treatments.[17]

Gingival thickness, is assessed by:

- Transgingival probing (accuracy to the nearest 0.5 mm). This technique must be performed under local anesthesia, which could induce a local volume increase and possible patient discomfort.[18]
- Ultrasonic measurement.[19] This shows a high reproducibility (within 0.5 to 0.6 mm range) but a mean intra-individual measurement error is revealed in second and third molar areas. A repeatability coefficient of 1.20 mm was calculated.[20]
- Probe visibility[21] after its placement in the facial sulcus. Gingiva was defined as thin (≤1.0 mm) or thick (>1 mm) upon the observation of the periodontal probe visible through the gingiva. This method was found to have a high reproducibility by De Rouck et al,[22] showing 85% inter-examiner repeatability (*k* value = 0.7, *P*-value = 0.002). The authors scored GT as thin, medium, or thick. Recently, a color-coded probe was proposed to identify four gingival biotypes (thin, medium, thick and very thick).[23]

Keratinized tissue width is easily measured with a periodontal probe positioned between the gingival margin and the mucogingival junction.

Although *bone thickness* assessment through CBCT has high diagnostic accuracy[12,13,24] the exposure to radiation is a potentially harmful factor.

Gingival recession

Gingival recession is defined as the apical shift of the gingival margin with respect to the cemento-enamel junction (CEJ);[1] it is associated with attachment loss and with exposure of the root surface to the oral environment. Although the etiology of gingival recessions remains unclear, several predisposing factors have been suggested.

Periodontal biotype and attached gingiva

A thin periodontal biotype, absence of attached gingiva, and reduced thickness of the alveolar bone due to abnormal tooth position in the arch are considered risk factors for the development of gingival recession.[2,3,11] The presence of attached gingival tissue is considered important for maintenance of gingival health. The current consensus, based on case series and case reports (low level of evidence), is that about 2 mm of KT and about 1 mm of attached gingiva are desirable around teeth to maintain periodontal health, even though a minimum amount of keratinized tissue is not needed to prevent attachment loss when optimal plaque control is present.[2]

The impact of toothbrushing

"Improper" toothbrushing method has been proposed as the most important mechanical factor contributing to the development of gingival recessions.[3,25–28] A recent systematic review however, concluded that the "data to support or refute the association between toothbrushing and gingival recession are inconclusive".[28,29] Among the 18 examined studies, one concluded that the toothbrushes significantly reduced recessions on facial tooth surfaces over 18 months, two concluded that there appeared to be no relationship between toothbrushing frequency and gingival recession, while eight studies reported a positive association between toothbrushing frequency and recession. Several studies reported potential risk factors like duration of toothbrushing, brushing force, frequency of changing the toothbrush, brush (bristle) hardness and tooth-brushing technique.

The impact of cervical restorative margins

A recent systematic review[2] reported clinical observations suggesting that sites with minimal or no gingiva associated with intrasulcular restorative margins are more prone to gingival recession and inflammation. The authors concluded that gingival augmentation is indicated for sites with minimal or no gingiva that are receiving intra-crevicular restorative margins. However, these conclusions are based mainly on clinical observations (low level of evidence).

The impact of orthodontics

There is a possibility of gingival recession initiation or progression of recession during or after orthodontic treatment depending on the direction of the orthodontic movement.[30,31] Several authors have demonstrated that gingival recession may develop during or after orthodontic therapy.[32–36] The reported prevalence is spanning 5% to 12% at the end of treatment. Authors report an increase of the prevalence up to 47% in the long-term observation (5 years). However, it has been demonstrated that, when a facially positioned tooth is moved in a lingual direction within the alveolar process, the apico-coronal tissue dimension on its facial aspect will increase in width.[37,38] A recent systematic review[2] concluded that the direction of the tooth movement and the bucco-lingual thickness of the gingiva may play important roles in soft tissue alteration during orthodontic treatment. There is a higher probability of recession during tooth movement in areas with <2 mm of gingiva. Gingival augmentation can be indicated before the initiation of orthodontic treatment in areas with <2 mm. These conclusions are mainly based on historic clinical observations and recommendations (low level of evidence).

Other conditions

There is a group of conditions, frequently reported by clinicians that could contribute to the development of gingival recessions (low level of evidence).[39] These include persistent gingival inflammation (e.g. bleeding on probing, swelling, edema, redness and/or tenderness) despite appropriate therapeutic interventions and association of the inflammation with shallow vestibular depth that restricts access for effective oral hygiene, frenum position that compromises effective oral hygiene and/or tissue deformities (e.g. clefts or fissures). Future studies and documentation focusing on these conditions should be done.

Diagnostic considerations

Proposed clinical elements for a treatment-oriented recession classification are as follows.

Recession depth A recent meta-analysis concludes that the deeper the recession, the lower the possibility for complete root coverage.[40] Since recession depth is measured with a periodontal probe positioned between the CEJ and the gingival margin, it is clear that the detection of the CEJ is key for this measurement. In addition, the CEJ is the landmark for root coverage. In many instances, however, CEJ is not detectable because of root caries and / or non-carious cervical lesions (NCCL), or is obscured by a cervical restoration. Modern dentistry should consider the need for anatomical CEJ reconstruction before root coverage surgery to re-establish the proper landmark.[41,42]

Gingival thickness GT <1 mm is associated with reduced probability for complete root coverage when applying advanced flaps.[43,44] GT can be measured with different approaches, as reported previously. To date, a reproducible, and easy approach is observing a periodontal probe detectable through the soft tissues after being inserted into the sulcus.[21–23]

Interdental clinical attachment level (CAL) It is widely reported that recessions associated with integrity of the interdental attachment have the potential for complete root coverage, while loss of interdental attachment reduces the potential for complete root coverage and very severe interdental CAL loss impairs that possibility; some studies, however, report full root coverage in sites with limited interdental attachment loss.[45,46]

A modern recession classification based on the interdental CAL measurement has been proposed by Cairo et al.[47]

- **Recession Type 1 (RT1)**: Gingival recession with no loss of interproximal attachment. Interproximal CEJ is clinically not detectable at both mesial and distal aspects of the tooth.
- **Recession Type 2 (RT2)**: Gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss (measured from the interproximal CEJ to the depth of the interproximal sulcus/pocket) is less than or equal to the buccal attachment loss (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).
- **Recession Type 3 (RT3)**: Gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss (measured from the interproximal CEJ to the apical end of the sulcus/pocket) is greater than the buccal attachment loss (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).

This classification overcomes some limitations of the widely used Miller classification[48] such as the difficult identification between Class I and II, and the use of "bone or soft tissue loss" as interdental reference to diagnose a periodontal destruction in the interdental area.[49] In addition, Miller classification was proposed when root coverage techniques were at their dawn and the forecast of potential root coverage in the four Miller classes is no longer matching the treatment outcomes of the most advanced surgical techniques.[49]

The Cairo classification is a treatment-oriented classification to forecast the potential for root coverage through the assessment of interdental CAL. In the Cairo RT1 (Miller Class I and II) 100% root coverage can be predicted; in the Cairo RT2 (overlapping the Miller class III) some randomized clinical trials indicate the limit of interdental CAL loss within which 100% root coverage is predictable applying different root coverage procedures; in the Cairo RT3 (overlapping the Miller class IV) full root coverage is not achievable.[46,47]

Clinical conditions associated with gingival recessions

The occurrence of gingival recession is associated with several clinical problems that introduce a challenge as to whether or not to choose surgical intervention. A basic question to be answered is: *what occurs if an existing gingival recession is left untreated?* A recent meta-analysis assessed the long-term outcomes of untreated facial gingival recession defects.[50] The authors concluded that untreated facial gingival recession in subjects with good oral hygiene is highly likely to result in an increase in the recession depth during long-term follow-up. Limited evidence, however, suggests that the presence of KT and/or greater gingival thickness decrease the likelihood of a recession depth increase or of development of new gingival recession.

Agudio et al.[51] (2016) compared the periodontal conditions of gingival augmentation sites versus untreated homologous contralateral sites presenting with thin gingival biotype with or without recessions in a population of highly motivated patients. At the end of the follow-up period (mean of 23.6 ± 3.9 years, range 18 to 35 years), the extent of the recession was reduced in 83% of the 64 treated sites, whereas it was increased in 48% of the 64 untreated sites. However, the amount of recession increase in 20 years was very limited: 1 mm in 24 units, 2 mm in 6 and 3 mm in one. This study showed that thin gingival biotypes augmented by grafting procedures remain more stable over time than do thin gingival biotypes; however, highly motivated patients can prevent the development / progression of gingival recession and inflammation for more than 20 years. Limited evidence also suggests that existing or progressing gingival recession does not lead to tooth loss.[50,51] Even though progression of gingival recession seems not to impair the long-term survival of teeth it may be associated with problems like esthetic impairment, dentin hypersensitivity, and tooth conditions that concern the patient and the clinician.

Esthetics Smile esthetics is becoming a dominant concern for patients, in particular when dental treatment is required. However, most of the articles that have been published on this topic did not consider patient-reported outcomes.[2,52] A recent survey of the American Academy of Cosmetic Dentistry (2013) consisting of 659 interviews reported that 89% of the patients decided to start cosmetic dental treatment in order to improve physical attractiveness and self-esteem. Several factors are important in the esthetics of the smile, including the facial midline, the smile line, interdental papillary recession, the size, shape, position, and color of the teeth, the gingival scaffold, and the lip framework.[53–59] All of these factors contribute to the esthetics of a smile. In particular, factors associated with the

TABLE 3 Classification of gingival biotype and gingival recession

Gingival site				Tooth site	
	REC Depth	GT	KTW	CEJ (A / B)	Step (+/-)
No recession					
RT1					
RT2					
RT3					

RT = recession type, REC Depth = depth of the gingival recession, GT= gingival thickness, KTW= keratinized tissue width, CEJ = cement enamel junction (Class A = detectable CEJ. Class B = undetectable CEJ), Step = root surface concavity (Class + = presence of a cervical step >0.5 mm. Class – = absence of cervical step).

gingival scaffold are the position of the free gingival margins, the color/texture of the gingiva, the presence of scars, and the amount of gingiva displayed by the smile.[53,54,56–58] However, even if all of these factors are identified by the clinicians, little information is available about which variables are better perceived by the patients.[60] It is very clear that esthetic ratings are based on subjective assessment. In a recent study patients' perception of facial recessions and their requests for treatment were evaluated by means of a questionnaire.[61] Of 120 enrolled patients, 96 presented 783 gingival recessions, of which 565 had been unperceived. Of 218 perceived recessions, 160 were asymptomatic, 36 showed dental hypersensitivity, 13 esthetic issues, and nine esthetic + hypersensitivity issues. Only 11 patients requested treatment for their 57 recessions. The authors concluded that perception of gingival recessions and the patients' requests for treatment should be evaluated carefully before proceeding to treatment. Interestingly, a survey among dentists showed that esthetics account for 90.7% of the justification for root coverage procedures.[62] Recently, the Smile Esthetic Index (SEI) has been proposed and validated.[63] Ten variables were chosen as determinants for the esthetics of a smile: smile line and facial midline, tooth alignment, tooth deformity, tooth dyschromia, gingival dyschromia, gingival recession, gingival excess, gingival scars, and diastema/missing papillae. The presence/absence of the aforementioned variables correspond to a number (0 or 1), and the sum of the attributed numbers represent the SEI of that subject (from 0 – very bad, to 10 – very good). The SEI was found to be a reproducible method to assess the esthetic component of the smile, useful for the diagnostic phase and for setting appropriate treatment plans.

Dentin hypersensitivity Dentin hypersensitivity (DH) is a common, often transient oral pain condition. The pain, short and sharp, resulting immediately on stimulation of exposed dentin and resolving on stimulus removal, can affect quality of life.[64,65] Of a study population of 3,000 patients, 28% stated that DH affected them importantly or very importantly.[66] Prevalence figures range widely from 15% to 74% depending on how the data were collected. Risk factors include gingival recession. Furthermore, an erosive diet and lifestyle are linked to tooth wear and dentin hypersensitivity, especially in young adults.[66] Because life expectancy is rising and people are retaining more vital or minimally restored teeth,[67] dentin hypersensitivity occurs more frequently. Treatment modalities include the use of different agents applied to the root surfaces[68] or the application of root coverage procedures.[69] In a recent systematic review,[69] the authors analyzed nine studies on the influence of root coverage procedures on cervical DH. A reduction in Cervical DH was reported in all studies reviewed. The mean percentage of decreased DH was 77.83%. The authors concluded that these results must be viewed with caution because most of the studies had a high risk of bias and cervical DH was assessed as a secondary outcome. There is not enough evidence to conclude that surgical root coverage procedures predictably reduce cervical DH.

Tooth conditions Different conditions of the tooth, including *root caries*[67] *and non-carious cervical lesions (NCCL)*[70,71] may be associated with a gingival recession. Historically, NCCL have been classified according to their appearance: wedge-shaped, disc-shaped, flattened and irregular areas.[70,71] A link between the morphological characteristics of the lesions and the main etiological factors is suspected. Thus, a U-shaped or disk-shaped broad and shallow lesion, with poorly defined margins and adjacent smooth enamel suggests an extrinsic erosive cause by acidic foods, beverages, and medication. Lesions caused by abrasive forces, such as improper toothbrushing techniques, generally exhibit sharply defined margins and on examination reveal hard surface traces of scratching. There is no scientifically sound evidence that abnormal occlusal loading causes non-carious cervical lesions (abfraction).[9] However, the shape cannot be considered determinative of the etiology. Recent studies found a prevalence of NCCL ranging from 11.4% to 62.2%. A common finding is that prevalence and severity of NCCL appears to increase with age.[70–72]

The presence of these dental lesions causes modifications of the root/tooth surface with a potential disappearance of the original CEJ and/or the formation of concavities (steps) of different depth and extension on the root surface. Pini-Prato et al.[73] (2010) classified the presence/absence of CEJ as Class A (detectable CEJ) or Class B (undetectable CEJ), and the presence/absence of cervical concavities (step) on the root surface as Class + (presence of a cervical step >0.5 mm) or Class – (absence of cervical step). Therefore, a classification includes four different scenarios of tooth-related conditions associated with gingival recessions. (Table 2).

The prevalence of tooth deformities associated with gingival recessions is very high. In the cited study[73] more than half of the 1,010 screened gingival recessions were associated with tooth deformities: 469 showed an identifiable CEJ without a step on the root surface (Class A-, 46%); 144 an identifiable CEJ associated with a step (Class A+, 14%); 244 an unidentifiable CEJ with a step (Class B+, 24%); and 153 an unidentifiable CEJ without any associated step (Class B-, 15%). The presence of NCCL is associated with a reduced probability for complete root coverage.[74,75]

DIAGNOSTIC AND TREATMENT CONSIDERATIONS BASED ON CLASSIFICATION OF PERIODONTAL BIOTYPES, GINGIVAL RECESSION, AND ROOT SURFACE CONDITIONS

On the basis of the various aspects discussed in the present review a diagnostic approach of the dento-gingival unit is proposed to classify gingival recessions and the associated relevant mucogingival conditions and cervical lesions with a treatment-oriented vision (Table 3). The proposed diagnostic table is based on a 4 × 5 matrix and is explained through the following cases a to d.

1. Absence of gingival recessions

The classification is based on the assessment of the gingival biotype, measured through GT and KTW, either in the full oral cavity or in single sites (Table 3).

Case a. Thick gingival biotype without gingival recession: prevention through good oral hygiene instruction and monitoring of the case.

Case b. Thin gingival biotype without gingival recession: this entails a greater risk for future development of gingival recessions. Attention of the clinicians to prevention and careful monitoring should be enhanced. With respect to cases with severe thin gingival biotype application of mucogingival surgery in high-risk sites could be considered to prevent future mucogingival damage. This applies especially in cases in which additional treatment like orthodontics, restorative dentistry with intrasulcular margins, and implant therapy are planned.

2. Presence of gingival recessions

A treatment-oriented classification could be based on the interdental clinical attachment level (score Cairo *RT1-3*) and enriched with the qualifiers *recession depth*, *gingival thickness*, *keratinized tissue width*, and *root surface condition*. Other potential contributors are *tooth position*, *cervical tooth wear and number of adjacent recessions*.

Mucogingival deformities and conditions around teeth*

1. Periodontal biotype
   a. thin scalloped
   b. thick scalloped
   c. thick flat
2. gingival/soft tissue recession
   a. facial or lingual surfaces
   b. interproximal (papillary)
   c. severity of recession (Cairo RT1, 2, 3)
   d. gingival thickness
   e. gingival width
   f. presence of NCCL / cervical caries
   g. patient aesthetic concern (Smile Esthetic Index)
   h. presence of hypersensitivity
3. lack of keratinized gingiva
4. decreased vestibular depth
5. aberrant frenum/muscle position
6. gingival excess
   a. pseudo-pocket
   b. inconsistent gingival margin
   c. excessive gingival display
   d. gingival enlargement
7. abnormal color

***FIGURE 1** Modified from the AAP 1999 Consensus Report, shown in Table 1.

Case c. A conservative clinical attitude should employ charting the periodontal and root surface lesions and monitoring them overtime for deterioration. The distance from the CEJ to FGM should be recorded as well as the distance between MGJ and FGM to determine the amount of KT present. Development and increased severity of both periodontal and dental lesions would orient clinicians toward appropriate treatment (see **Case d**).

Case d. A treatment-oriented approach, especially in thin biotypes and when justified by patient concern or complaint in terms of esthetics and/or dentin hypersensitivity and by the presence of cervical caries or NCCL, should consider mucogingival surgery for root coverage and CEJ reconstruction when needed. This applies especially to cases in which additional treatment like orthodontics, restorative dentistry with intrasulcular margins, and implant therapy are planned.

Recent information on the best approaches to prevent the occurrence of gingival recessions or to treat single or multiple recessions can be found in reviews and reports from the 2014 European Federation of Periodontology (EFP) and 2015 American Academy of Periodontology (AAP) workshops.[2,8,45,46,76,77]

The clinical impact and the prevalence of the root surface lesion, hypersensitivity and patient aesthetic concern associated to gingival recessions indicates the need to modify the 1999 classification on mucogingival deformities and conditions.

The new classification includes additional information, such as periodontal biotype, recession severity, dimension of the residual gingiva, presence/absence of caries and non-carious cervical lesions, aesthetic concern of the patient, and presence of dentin hypersensitivity (Figure 1).

SUMMARY AND CONCLUSIONS

Periodontal health can be maintained in most patients under optimal oral conditions even with minimal amounts of keratinized tissue. However, there is an increased risk of development or progression of gingival recession in cases presenting with thin periodontal biotypes, suboptimal oral hygiene, and requiring restorative/ orthodontic treatment.

- Development and progression of gingival recession is not associated with increased tooth mortality. It is, however, causing esthetic concern in many patients and is frequently associated with the occurrence of dentin hypersensitivity and carious/non-carious cervical lesions on the exposed root surface.
- Esthetic concern, dentin hypersensitivity, cervical lesions, thin gingival biotypes and mucogingival deformities are best

addressed by mucogingival surgical intervention when deemed necessary.

- A novel treatment-oriented classification based on the assessment of gingival biotype, gingival recession severity and associated cervical lesions is proposed to help the clinical decision process.

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2017 WORLD WORKSHOP

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Occlusal trauma and excessive occlusal forces: Narrative review, case definitions, and diagnostic considerations

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objectives: This narrative review determines the effects of occlusal trauma and excessive occlusal forces on the periodontium, including the initiation and progression of periodontitis, abfraction, and gingival recession. Case definitions, diagnostic considerations, and the effects of occlusal therapy are also reviewed and discussed.

Importance: The role of occlusal trauma in the initiation and progression of periodontitis remains a controversial subject in periodontology. Because occlusal trauma can only be confirmed histologically, its clinical diagnosis depends on clinical and radiographic surrogate indicators which make clinical trials difficult.

Findings: Investigations have generally agreed that occlusal trauma and excessive occlusal forces do not initiate periodontitis or loss of connective tissue attachment. When plaque-induced periodontitis and occlusal trauma are present at the same time, there is weak evidence that the occlusal trauma may increase the rate of connective tissue loss. Occlusal therapy is indicated as part of periodontal therapy to reduce mobility and increase patient comfort and masticatory function. Existing data do not support the existence of abfraction as a cause for gingival recession.

Conclusions: Occlusal trauma does not initiate periodontitis, and there is weak evidence that it alters the progression of the disease. There is no credible evidence to support the existence of abfraction or implicate it as a cause of gingival recession. Reduction of tooth mobility may enhance the effect of periodontal therapy.

KEYWORDS

attachment loss, classification, diagnosis, disease progression, esthetics, gingival recession, periodontal biotype

The literature concerning the relationship between periodontal diseases and occlusal forces is reviewed. In addition, studies that have examined effects of excessive occlusal forces, abfraction, and gingival recession are reviewed. Finally, this information is used to consider the revision of the classification of periodontal diseases and conditions.

MATERIALS AND METHODS

For this narrative review, a literature search was conducted using PubMed and Web of Science. A search strategy for the database was performed to find studies that matched the following terms: (periodontal disease OR periodontitis OR periodontium) AND

(traumatic dental occlusion OR traumatic dental occlusions OR occlusal force OR occlusal forces OR occlusal discrepancies OR occlusal discrepancy OR occlusal interference OR occlusal interferences OR occlusal trauma OR occlusal traumatism); (occlusal) AND (non carious cervical lesion OR non carious cervical lesions); (occlusal) AND (abfraction OR abfractions); and gingival recession AND occlusal. Databases were searched without language restrictions using MeSH terms, key words, and other free terms, and Boolean operators (OR, AND) were used to combine searches. Randomized controlled clinical trials, cohort studies, case control studies, case series, review articles, guidelines, animal research, and in vitro research were eligible for inclusion in this review. Databases were searched up to February 2017, with no limits on the year of publication.

Manual searches of *Journal of Periodontology*, *Journal of Clinical Periodontology*, *Periodontology 2000*, *Journal of Periodontal Research*, and *International Journal of Periodontics and Restorative Dentistry* were also conducted. Initially, one reviewer screened the titles and abstracts of articles. Articles that indicated a possible match were obtained for full review for potential inclusion. Important historic articles were included. To complement the search, reference lists of main articles related to this narrative review were also assessed. Due to the heterogeneity of the studies, a meta-analysis was not conducted. A total of 93 articles were included in the review and included both human and animal studies.

CASE DEFINITIONS AND DIAGNOSTIC CONSIDERATIONS

Excessive occlusal force is defined as occlusal force that exceeds the reparative capacity of the periodontal attachment apparatus, which results in occlusal trauma and/or causes excessive tooth wear (loss).[1–3]

Occlusal trauma is a term used to describe injury resulting in tissue changes within the attachment apparatus, including periodontal ligament, supporting alveolar bone and cementum, as a result of occlusal force(s).[4] Occlusal trauma may occur in an intact periodontium or in a reduced periodontium caused by periodontal disease.

Primary occlusal trauma is injury resulting in tissue changes from excessive occlusal forces applied to a tooth or teeth with normal periodontal support.[4] It occurs in the presence of normal clinical attachment levels, normal bone levels, and excessive occlusal force(s).

Secondary occlusal trauma is injury resulting in tissue changes from normal or excessive occlusal forces applied to a tooth or teeth with reduced periodontal support.[4] It occurs in the presence of attachment loss, bone loss, and normal/excessive occlusal force(s).

Fremitus is a palpable or visible movement of a tooth when subjected to occlusal forces.[4]

Bruxism or tooth grinding is a habit of grinding, clenching, or clamping the teeth.[4] The force generated may damage both tooth and attachment apparatus.

Despite the consensus on the definition of primary and secondary occlusal trauma, specific criteria to distinguish between "normal" and "reduced" periodontal support have not been identified from controlled studies. In an in vitro study, periodontal ligament stress increased significantly after reducing 60% of bone support.[5]

Because trauma from occlusion is defined and diagnosed on the basis of histologic changes in the periodontium, a definitive diagnosis of occlusal trauma is not possible without block section biopsy. Consequently, multiple clinical and radiographic indicators are used as surrogates to assist the presumptive diagnosis of occlusal trauma. Clinical diagnosis that occlusal trauma has occurred or is occurring may include progressive tooth mobility, fremitus, occlusal discrepancies/disharmonies, wear facets (caused by tooth grinding), tooth migration, tooth fracture, thermal sensitivity, root resorption, cemental tear, and widening of the periodontal ligament space upon radiographic examination (Table 1).[6,7] These clinical signs and symptoms may indicate other pathoses. For instance, loss of clinical attachment can affect the severity of mobility. Also, it is often very difficult to determine whether the wear facets are caused by functional contacts or parafunctional habits, such as bruxism. Therefore, differential diagnoses should be established. Supplementary diagnostic procedures, such as pulp vitality tests and evaluation of parafunctional habits, may be considered.

Non-carious cervical lesions (NCCLs) involve loss of hard tissue at the cervical third of the crown and subjacent root surface, through processes unrelated to caries.[8] Gingival recession is defined as location of the gingival margin apical to the cemento-enamel junction.[4] NCCLs are usually accompanied by gingival recession.[9] NCCLs are a group of lesions and the etiology is multifactorial.[10] Abfraction, a hypothetical tooth–surface lesion caused by occlusal forces, is one of the proposed etiologies for NCCLs, and other etiologies include abrasion, erosion, corrosion, or a combination.[4,8,11] The lesion of abfraction has been described as wedge-shaped defects that occur at the cemento-enamel junction of affected teeth as a result of flexure and eventual fatigue of enamel and dentin.[8,12–14] Excessive occlusal forces have long been proposed to be a causative factor in the development of abfraction and gingival

TABLE 1 Proposed clinical and radiographic indicators of occlusal trauma

1. Fremitus	7. Thermal sensitivity
2. Mobility	8. Discomfort/pain on chewing
3. Occlusal discrepancies	9. Widened PDL space
4. Wear facets	10. Root resorption
5. Tooth migration	11. Cemental tear
6. Fractured tooth	

PDL, periodontal ligament.

recession.[2,3,11–16] Because abfraction is not currently supported by appropriate evidence, a definitive diagnosis is not possible. NCCLs may result from abrasion, erosion, or corrosion. Therefore, in cases of NCCLs, toothbrushing habits, diet, eating disorders as well as occlusal relationships and parafunctional habits should be thoroughly evaluated.

NARRATIVE REVIEW

Effects of occlusal trauma on the initiation and progression of periodontitis

Histologically, a tooth affected by occlusal trauma demonstrates distinct zones of tension and pressure within the adjacent periodontium. The location and severity of the lesions vary based on the magnitude and direction of applied forces.[2] On the pressure side, these changes may include increased vascularization and permeability, hyalinization/necrosis of the periodontal ligament, hemorrhage, thrombosis, bone resorption, and in some instances, root resorption and cemental tears. On the side of tension, these changes may include elongation of the periodontal ligament fibers and apposition of alveolar bone and cementum.[3,17–19]

Collectively, the histologic changes reflect an adaptive response within the periodontium to occlusal trauma.[2,20] As a result of sustained occlusal trauma, the density of the alveolar bone decreases while the width of the periodontal ligament space increases, which leads to increased tooth mobility and often a radiographic widening of the periodontal ligament space, either limited to the alveolar crest or through the entire width of the alveolar bone.[17,18,21] In addition, fremitus, or palpable functional mobility of a tooth, is another significant clinical sign of occlusal trauma.[22]

Historic studies

In the early 20th century, a report indicated an association between excessive occlusal forces and pyorrhea alveolaris (i.e., periodontitis).[1] It was further suggested by other early investigators that excessive occlusal force was the cause of periodontitis.[2,3,23,24] They felt that occlusal forces had to be controlled to successfully treat periodontitis.[3,17]

In the1930s to the 1940s, the role of excessive occlusal forces in the progression of periodontitis was disputed.[25,26] Using human autopsy material, it was concluded that gingival inflammation extending into the supporting bone was the cause of periodontal destruction. In a subsequent animal experiment, it was found that the excessive occlusal forces caused changes in the direction of the periodontal membrane fibers so that gingival inflammation passed directly into such areas.[18] Later, another study based on human autopsy material agreed that inflammation appeared to begin in the gingiva and subsequently progressed into the adjacent periodontal supporting tissue[19,20] It was further proposed that inflammation progressed in an altered pathway in teeth subjected to occlusal trauma. The combined effect of occlusal trauma and bacterial plaque–induced inflammation was termed "co-destruction." This theory was then challenged by other investigators.[27–29] Using human autopsy material again, the altered pathway of destruction was questioned because bacterial plaque was always present in close proximity to the site of periodontal destruction, and this suggested that inflammation and bone loss were associated with the presence of bacterial plaque rather than excessive occlusal forces. The historic studies used autopsy material that provided little or no information on the periodontal conditions and occlusal conditions of these study subjects. It was after the co-destruction theory was presented that researchers started to examine the concept of multiple risk factors that resulted in the initiation and progression of periodontal diseases.

Animal studies

By their nature, historic observations failed to prove any causal relationship between occlusal trauma and the initiation or progression of periodontal disease. In an attempt to prove a relationship between occlusion and periodontal disease, multiple animal studies with strict controls and designs were performed in the 1970s. There were two significant groups, one from Eastman Dental Center in Rochester, NY,[30–34] and the other one from the University of Gothenburg in Sweden.[35–38] The effects of occlusal trauma and gingival inflammation in animals were investigated. The Eastman group used repeated applications of orthodontic-like forces on the teeth of squirrel monkeys, and the Gothenburg group used occlusal forces similar to those of a "high" restoration in beagle dogs. Both groups examined the effects of excessive occlusal forces on the periodontium with a duration from a few weeks up to 6 months in the presence and absence of bacterial plaque-induced periodontitis.

Despite the different animal models and the different types of occlusal forces applied, the results of these two studies were similar in many respects. When oral hygiene was maintained and inflammation was controlled, occlusal trauma resulted in increased mobility and loss of bone density without loss of connective tissue attachment, during the length of the study. If the occlusal forces were removed, the loss of bone density was reversible. In contrast, in the presence of plaque-induced periodontitis and occlusal trauma, there was greater loss of bone volume and increased mobility, but loss of connective tissue attachment was the same as on teeth subjected to periodontitis alone in the squirrel monkey.[31] In the beagle dog model, when occlusal trauma was superimposed on periodontitis, there was an accelerated loss of connective tissue attachment.[35] Based on the findings of these studies, it was concluded that without plaque-induced inflammation, occlusal trauma does not cause irreversible bone loss or loss of connective tissue attachment. Therefore, occlusal trauma is not a causative agent of periodontitis.

Using rat models, more recent studies re-examined the association of occlusal trauma and periodontal bone loss.[39–41] Occlusal trauma was induced by either placing inlay or metal wire bonding to raise the occlusal surfaces. The receptor activator of nuclear factor-kappa B ligand (RANKL) is an important factor in osteoclast

differentiation, activation, and survival.[42] RANKL interacts with RANK receptor on osteoclasts to initiate bone resorption. During excessive occlusal loading, the destruction of the periodontal ligament was observed, and the RANKL associated with osteoclasts and osteoblasts was demonstrated via immunohistochemistry.[39] In the presence of lipopolysaccharide-induced inflammation, the expression of RANKL on endothelial cells, inflammatory cells, and periodontal ligament cells was enhanced by occlusal trauma.[40] It was suggested that RANKL expression on these cells was closely involved in the increase of osteoclasts induced by occlusal trauma. Further, loss of connective tissue attachment at the onset of experimental periodontitis was increased when inflammation was combined with occlusal trauma.[41] In addition, estrogen deficiency, nicotine, and diabetes were all shown to enhance bone loss in rats with combined with occlusal trauma and ligature-induced periodontitis.[43–45]

None of the animal studies were able to reproduce all aspects of human periodontitis. In addition, the animal studies used excessive forces and were conducted for a relatively short duration (a few weeks to a few months). Nonetheless, the results from animal studies suggested that occlusal trauma does not cause periodontitis, but it may be a cofactor that can accelerate the periodontal breakdown in the presence of periodontitis.

Clinical studies

Tooth mobility has been described as one of the common clinical signs of occlusal trauma.[3,17,18,20,25,28] However, increased tooth mobility may result from inflammation and/or bone loss or attachment loss alone. Progressive mobility may be suggestive of ongoing occlusal trauma, but assessments at different time points are necessary to make this determination.[46] In an epidemiologic study, a group of subjects was re-examined for loss of periodontal clinical attachment after 28 years. It was found that baseline tooth mobility was a factor related to clinical attachment loss.[47] In addition, mobile teeth with a widened periodontal ligament space had greater probing depth, more attachment loss, and increased alveolar bone loss than non-mobile teeth.[7] Tooth mobility was also found to affect the results following periodontal therapy.[48,49] It was shown that teeth with mobility did not gain as much clinical attachment as those without mobility following periodontal treatment.[48] Further, teeth with increased mobility demonstrated significantly more clinical attachment loss during the maintenance period.[49] A recent study on regenerative surgery indicated that mobile teeth treated with regeneration did not respond as well as non-mobile teeth. However, no association was drawn between mobility and occlusal forces.[50]

The relationship between cusps is an important factor in the transmission of occlusal forces to the periodontium.[51] Due to the limitations of clinical diagnosis of occlusal trauma and ethical considerations, most clinical studies have focused on teeth with occlusal discrepancies/disharmonies, which are defined as "contacts of opposing surfaces of teeth that are not in harmony with each other or with the anatomic and physiologic control of the mandible."[4] In an early retrospective study, the relationship between periodontal parameters and molar non-working contacts was examined.[52] It was found that molar teeth with non-working contacts had greater probing depths and bone loss compared with those without non-working contacts. Conversely, other studies looked at occlusal disharmonies in patients with periodontitis and failed to find any correlation between abnormal occlusal contacts and periodontal parameters, including probing depth, clinical attachment level, and bone loss.[6,7,53] Nevertheless, teeth with frank signs of occlusal trauma, including fremitus and a widened periodontal ligament space, demonstrated greater probing depth, clinical attachment loss, and bone loss.[7]

A series of retrospective studies investigated the association between occlusal discrepancies and the progression of periodontitis in a private practice setting.[54,55] All patients included had moderate to severe chronic periodontitis. These studies found that teeth with occlusal discrepancies had significantly deeper initial probing depths, more mobility, and poorer prognoses than those teeth without occlusal discrepancies.[54] Teeth with occlusal discrepancies demonstrated a significant increase in probing depth and a worsening prognosis with time. Multiple types of occlusal contacts, including premature contacts in centric relation, posterior protrusive contact, non-working contacts, combined working and non-working contacts, and the length of slide between centric relation and centric occlusion were associated with significantly deeper probing depths and increased assignment to a less favorable prognosis.[55] In a more recent cross-sectional epidemiologic study, the non-working side contact was also associated with deeper probing depth and more clinical attachment loss.[56]

Based on those observations, if occlusal trauma has any relationship to the progression of periodontitis, then its elimination should improve clinical periodontal conditions. Occlusal adjustment is defined as "reshaping the occluding surfaces of teeth by grinding to create harmonious contact relationships between the maxillary and mandibular teeth."[4] The evidence linking occlusal adjustment to improvement in periodontal parameters is limited. In an earlier study, the flow rate and quality of gingival crevicular flow (GCF) after removal of occlusal interferences was examined in patients with advanced periodontitis.[57,58] It was found that occlusal adjustment reduced the protein content and collagenase activity without affecting the quantity of GCF. Later, a well-controlled clinical trial was conducted to evaluate the effect of the occlusal adjustment on healing outcomes after periodontal treatment.[59] In this study, half of the patients received occlusal adjustment by selective grinding before receiving surgical or non-surgical periodontal therapy. The other half did not receive occlusal adjustment. After healing, the group that received occlusal adjustment before periodontal treatment gained 0.4 mm improvement in mean clinical attachment levels compared with those without pre-treatment occlusal adjustment. However, it was noted that the post-treatment reduction of probing depth and mobility were comparable. During long-term periodontal maintenance, the parafunctional habits that are not treated with a bite guard and the presence of mobility were both associated with increased clinical attachment loss and tooth loss.[60,61] In another study conducted in a private practice, the response of patients with periodontitis and occlusal discrepancies to occlusal adjustment

was examined. Regardless of the periodontal treatment status, the probing depth of teeth with untreated occlusal discrepancies was increased by a mean of 0.066 mm/year while a decreased probing depth of 0.122 mm/year was noted on teeth with occlusal adjustment.[62]

Collectively, these clinical studies demonstrated the added benefit of occlusal therapy in the management of periodontal disease, but they do not provide strong evidence to support routine occlusal therapy. Clearly, occlusal therapy is not a substitute for conventional periodontal treatment for resolving plaque-induced inflammation. However, it may be beneficial to perform occlusal therapy in conjunction with periodontal treatment in the presence of clinical indicators of occlusal trauma, especially relating to the patient's comfort and masticatory function. The patient's occlusion should be carefully examined and recorded before and after treatment. The occlusion of periodontally compromised teeth should be designed to reduce the forces to be within the adaptive capabilities of the reduced periodontal attachment. Overall, in the presence of occlusal trauma, occlusal therapy may slow the progression of periodontitis and improve the prognosis.

Excessive occlusal forces and abfraction

In the late 1970s, excessive occlusal loading was first proposed to cause cervical stress that results in the formation of non-carious cervical lesions (NCCLs).[15] This purported occlusally generated lesion was termed abfraction.[11,13] Although there is theoretic evidence in support of abfraction, predominantly from finite element analysis (FEA) studies, caution is advised when interpreting results of these studies because FEA does not replicate a clinical situation.[63–69] In FEA models, different researchers have assumed significantly different physical properties of the dental tissues. Also, arbitrary magnitudes, directions, and durations of forces have been used, which makes comparison between studies difficult. Cross-sectional studies have indicated associations between NCCLs, bruxism, and occlusal factors, such as presence of occlusal wear facets, group function, and premature contacts, but these investigations do not confirm causal relationships.[9,70–74] Despite the positive association, the size of NCCLs and the extent of occlusal wear was not correlated.[9]

Only a few studies have sought evidence for a causal relationship between occlusion and NCCLs.[75–77] An increased incidence of NCCLs was associated with presence of occlusal wear facets after a 3-year follow-up in a group of dental students.[75] To the contrary, in a split-mouth design, it was shown that the elimination of excursive interferences by occlusal adjustment did not decrease the progression NCCLs.[76] More recently, a 5-year prospective clinical trial found that progression of NCCLs was associated with relative occlusal forces in maximum intercuspation position, but not diet, toothbrushing, presence of occlusal wear facets, group function, or parafunctional habits.[77] If excessive occlusal forces were contributing to the etiology of NCCLs, it would be expected that parafunctional habits, such as bruxism and clenching, would exacerbate the progression of NCCLs. Two studies have reported a correlation between self-reported bruxism and NCCLs.[78,79] Although some studies suggested an association, the causal relationship between excessive occlusal forces and the progression of NCCLs is still uncertain. Therefore, abfraction is still a biomechanically based theoretic concept, and it is not supported by appropriate clinical evidence.

Effects of excessive occlusal forces on gingival recession

Historically, it has been suggested that excessive occlusal force might be a factor in gingival recession and the loss of gingiva.[2,3] The term “Stillman's cleft” is defined as narrow, triangular-shaped gingival recession on the facial aspect of the tooth. It was postulated that excessive occlusal force caused the Stillman's cleft. However, these historic references are based on uncontrolled clinical observations.

By examining teeth with gingival recession, no correlation was identified between mobility and gingival recession.[80] Compared with contralateral teeth without recession, teeth with recession showed either no or similar mobility. In a clinical investigation on the etiology of gingival recession, a positive association between occlusal trauma and gingival recession was reported;[16] however, this association disappeared when tooth malposition was present. In evaluation of the relationship between incisor inclination and periodontal status, labial gingival recession of the mandibular incisors was related to linguoversion.[81] However, there was no further analysis of the functional occlusal relationship. A recent retrospective study also failed to establish a relationship between the presence of occlusal discrepancies and initial width of the gingival tissue or between occlusal treatment and changes in the width of the gingiva.[82] Hence, existing data do not provide any solid evidence to substantiate the effects of occlusal forces on NCCLs and gingival recession.

Effects of orthodontic forces on the periodontium

Clinical studies have demonstrated that with good plaque control, teeth with a reduced but healthy periodontium can undergo successful tooth movement without compromising the periodontal support.[83,84] However, a non-controlled orthodontic force can negatively affect the periodontium and result in root resorption, pulpal disorders, and alveolar bone resorption.[85,86]

The long-term effects of orthodontic forces on the periodontium have been controversial.[87–91] A recent systematic review demonstrated that orthodontic therapy was associated with 0.03 mm of gingival recession, 0.13 mm of alveolar bone loss, and 0.23 mm of increased pocket depth when compared with no treatment.[92] Overall, the existing evidence suggested that orthodontic treatment has minimal detrimental effects to the periodontium.

CONCLUSIONS

Animal and human studies have indicated some association between occlusal trauma/occlusal discrepancies and progression of

periodontal disease. Nevertheless, all investigators agreed that excessive occlusal forces do not initiate plaque-induced periodontal diseases or loss of periodontal attachment, and more recent studies support this conclusion. In addition, based on the existing data, there does not appear to be any scientific evidence to prove that excessive occlusal forces cause abfraction or gingival recession.

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2017 WORLD WORKSHOP

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Dental prostheses and tooth-related factors

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objectives: This narrative review summarizes the current evidence about the role that the fabrication and presence of dental prostheses and tooth-related factors have on the initiation and progression of gingivitis and periodontitis.

Findings: Placement of restoration margins within the junctional epithelium and supracrestal connective tissue attachment can be associated with gingival inflammation and, potentially, recession. The presence of fixed prostheses finish lines within the gingival sulcus or the wearing of partial, removable dental prostheses does not cause gingivitis if patients are compliant with self-performed plaque control and periodic maintenance. However, hypersensitivity reactions to the prosthesis dental material can be present. Procedures adopted for the fabrication of dental restorations and fixed prostheses have the potential to cause traumatic loss of periodontal supporting tissues. Tooth anatomic factors, root abnormalities, and fractures can act as plaque-retentive factors and increase the likelihood of gingivitis and periodontitis.

Conclusions: Tooth anatomic factors, such as root abnormalities and fractures, and tooth relationships in the dental arch and with the opposing dentition can enhance plaque retention. Restoration margins located within the gingival sulcus do not cause gingivitis if patients are compliant with self-performed plaque control and periodic maintenance. Tooth-supported and/or tooth-retained restorations and their design, fabrication, delivery, and materials have often been associated with plaque retention and loss of attachment. Hypersensitivity reactions can occur to dental materials. Restoration margins placed within the junctional epithelium and supracrestal connective tissue attachment can be associated with inflammation and, potentially, recession. However, the evidence in several of the reviewed areas, especially related to the biologic mechanisms by which these factors affect the periodontium, is not conclusive. This highlights the need for additional well-controlled animal studies to elucidate biologic mechanisms, as well as longitudinal prospective human trials. Adequate periodontal assessment and treatment, appropriate instructions, and motivation in self-performed plaque control and compliance to maintenance protocols appear to be the most important factors to limit or avoid potential negative effects on the periodontium caused by fixed and removable prostheses.

KEYWORDS

anatomy, classification, dental prostheses, dental restorations, gingivitis, periodontitis, tooth

The anatomy, position, and relationships of teeth within the dental arches are among the factors that have been associated[1] with plaque retention, gingivitis, and periodontitis. Factors related to the presence, design, fabrication, delivery, and materials of tooth-supported prostheses have been suggested to influence the periodontium, generally related to localized increases in plaque accumulation and, less often, to traumatic and allergic reactions to dental materials. This article reviews the role of tooth-related factors and dental prostheses on the initiation and progression of gingivitis and periodontitis.

MATERIALS AND METHODS

For this narrative review, PubMed database was searched for the time period from 1947 up to April 2017, with the strategy found on Table 1. The following filters were applied to the search results: clinical trial, review, guideline, randomized controlled trial, meta-analysis, systematic reviews, humans, and English. The articles obtained, including those referenced in a previous article,[1] were input into a reference manager software.[1] One reviewer (CE) screened titles and abstracts for potential inclusion and discarded duplicates. If title and/or abstract did not provide sufficient information regarding the article content, the article was obtained for review. The selected articles were then obtained in full text and saved as .pdf files in the reference manager database. One reviewer (CE) performed all text reading of the selected publications. When titles of referenced articles, not included in the electronic search, were identified as potentially related to the area of interest of this review, these articles' abstracts were obtained, reviewed for potential inclusion, included in the database, and their full text reviewed.

RESULTS

Biologic width (BW)

BW has been defined as the cumulative apical–coronal dimensions of the junctional epithelium (JE) and supracrestal connective tissue attachment (SCTA).[2] In a cadaver study, variable supracrestal tissue dimensions (i.e., histologic gingival sulcus [GS], JE, and SCTA) were recorded, with the SCTA exhibiting the most constant average dimension.[3] While JE and SCTA exhibited average dimensions within 0.5 to 1 mm when examined on different tooth surfaces,[4,5] this study[3] and others[6,7] showed that dimensions of JE and SCTA can vary considerably,[8] regardless of the association with other factors such as tooth type,[9] surface,[4,9] biotype,[5] loss of attachment,[3] presence of restorations,[4] and crown elongation,[10] so that it is impossible to clearly define a "fixed" biologic width dimension.[9] Biologic width dimensions (JE and SCTA) can only be assessed by histology.[3,4,11] Other methods, such as transgingival probing[10,12–14] and parallel profile radiography, can be used to clinically measure the dimensions of the dentogingival unit, but are not appropriate to measure the true biologic width.[6,15]

Buccal crown margins placed within the junctional epithelium and supracrestal connective tissue attachment have been associated with recession, and histologic evaluation of these sites demonstrated crestal bone loss and supracrestal connective tissue remodeling within 0 to 8 weeks.[16] However, this limited case series was not designed to correlate the observed histologic changes to plaque indices or other mechanisms that could document, in humans, the biologic rationale for the observed changes. Moreover, in a prospective clinical trial, comparing crowns with interproximal margins placed within varying distances from the alveolar bone crest (groups: I = < 1 mm between crown margin and alveolar crest, II = 1 to 2 mm, and III = > 2 mm) it was observed that, while the presence of supragingival plaque was not different among groups, papillary bleeding index (PBI) was greater in group 1, which was associated with increased probing depths (PD) and a clear encroachment of the crown margins within the supracrestal tissue attachment.[17] Given the limited available evidence in humans, it is not possible to determine if the negative effects on the periodontium associated with restoration margins located within the supracrestal tissue attachment is caused by bacterial plaque, trauma, or a combination of these factors.

Fixed dental restorations and prostheses

For class II restorations, gingival inflammation is significantly greater around subgingival margins compared with supragingival margins,[18] even when supragingival plaque levels are not significantly different from prerestoration levels.[19] Furthermore, PD around amalgam restorations with subgingival margins were found to be greater than around contralateral unrestored teeth.[20] Direct restorations with overhangs greater than 0.2 mm are associated with crestal bone loss.[21] Unfortunately, a large prevalence of overhanging amalgam restorations were found in several populations associated with increases in bleeding on probing (BOP) and PD which exceeded the values found at sites with well-fitting restorations and unrestored teeth.[22] The correlation between overhanging margins and PD, gingival inflammation,[23,24] and interproximal bone loss[25–27] was greater for larger overhangs.[28] The removal of the overhangs during scaling and root planing causes a resolution of the gingival inflammation[29] and a decrease in PD due to gingival recession (GR)[30] similar to the resolution of gingivitis.[31] From a microbiologic standpoint and similar to indirect restorations,[32] the elimination of amalgam overhangs during periodontal therapy caused a decrease of *Aggregatibacter actinomycetemcomitans* and increase of *Streptococcus mutans*.[33]

For indirect restorations, overhangs between 0.5 and 1 mm are associated with an increase in gingival inflammation[29] and a more apical crestal bone level, while overhangs of less than 0.2 mm are not.[32,34] Other studies showed that subgingival margins were associated with increased signs of gingival inflammation[35–42] and, at times, increases in PD.[43–47]

A clear association is found between periodontal health and patient compliance with self-performed plaque control and periodontal maintenance after prosthodontic therapy with fixed dental

TABLE 1 Electronic search strategy used for the study

Topic	Search strategy		Search strategy
Biologic width	("biology"[MeSH Terms] OR "biology"[All Fields] OR "biologic"[All Fields]) AND width[All Fields]	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Fixed dental restorations and prostheses	("Crowns"[Mesh:NoExp] OR "Dental Prosthesis Design"[Mesh:NoExp] OR "Dental Restoration Failure"[Mesh] OR "Dental Restoration, Permanent" [Mesh:NoExp] OR "Dental Veneers"[Mesh])	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Dental materials	("dental materials"[Pharmacological Action] OR "dental materials"[MeSH Terms] OR "dental materials"[All Fields]) NOT ("dental implants"[MeSH Terms] OR "dental implants"[All Fields] OR "dental implant"[All Fields] OR "dental prosthesis, implant-supported"[MeSH Terms] OR "implant-supported dental prosthesis"[All Fields] OR "dental prosthesis, implant supported"[All Fields])	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Removable dental prostheses	("Dentures"[MeSH] OR "Dental Clasps"[MeSH])	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Enamel pearls	Enamel pearl [All Field]	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Cervical enamel projections	("neck"[MeSH Terms] OR "neck"[All Fields] OR "cervical"[All Fields]) AND ("dental enamel"[MeSH Terms] OR ("dental"[All Fields] AND "enamel"[All Fields]) OR "dental enamel"[All Fields] OR "enamel"[All Fields]) AND ("projection"[MeSH Terms] OR "projection"[All Fields] OR "projections"[All Fields] OR "forecasting"[MeSH Terms] OR "forecasting"[All Fields])	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Developmental grooves	grooves[All Fields]	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])

(Continues)

TABLE 1 (Continued)

Topic	Search strategy		Search strategy
Tooth and root fractures	"tooth fractures"[MeSH Terms] OR ("tooth"[All Fields] AND "fractures"[All Fields]) OR "tooth fractures"[All Fields]	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Root resorption	"Tooth Root/pathology"[MAJR] AND Root Resorption/pathology	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Tooth position	("malocclusion"[MeSH Terms] OR "malocclusion"[All Fields]) AND ("tooth"[MeSH Terms] OR "tooth"[All Fields]) AND position[All Fields])	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Root proximity	("tooth root"[MeSH Terms] OR ("tooth"[All Fields] AND "root"[All Fields]) OR "tooth root"[All Fields]) AND proximity[All Fields]	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])
Open contacts	"Diastema"[MAJR] OR Open contacts	AND	(Periodontitis OR Periodontal Diseases OR Gingivitis OR Gingival Diseases) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type])

prostheses.[47–49] In a prospective clinical trial where patients were instructed and motivated on adequate measures of self-performed plaque control, plaque levels and gingival inflammation were not significantly different between teeth that received crowns and controls.[50] Similarly, in a cohort of patients who were seen for periodontal maintenance every 1 to 6 months, no difference in plaque and gingival indices were found between crowned and non-crowned teeth regardless of the position of the crown margins,[51] a finding also reported by other studies.[52–54]

While porcelain veneers were not associated with changes in plaque levels and gingival inflammation for as long as 7 years after delivery,[55–59] gingival recession can be a common consequence of other fixed prosthodontic therapies.[60–62] Prosthodontic procedures required for the fabrication of fixed prostheses can negatively affect the periodontium. Procedures and/or materials such as crown preparation, gingival displacement during impression,[63,64] impressions, provisional prostheses,[65] and luting agents[66] may be contributing factors for the development of gingivitis, gingival recession, and periodontitis. The placement of provisional crowns causes an increase in plaque retention regardless of the resin material used for the prosthesis.[65] In another study[67] where all crown margins were designed in a subgingival location during crown preparation, only 82% of them were still located subgingivally at crown delivery. This suggests that the actual crown margin location was less of a contributing etiologic factor affecting the occurrence and magnitude of recession than the prosthetic procedures required to design and record the crown margin position. In a short-term randomized, multicenter, controlled trial, different methods of gingival displacement produced different magnitudes and frequency distributions of gingival recession, and most of the recession occurred before

final crown delivery.[68] The anatomy of the periodontium of teeth receiving crowns should be evaluated to minimize the likelihood of gingival recession because the presence of an initial shallow PD and narrow band of gingiva negatively influenced the level of periodontal attachment after crown delivery.[69] These studies point out the critical importance of including a complete periodontal assessment prior to prosthodontic manipulations when studying the response of the periodontium to indirect restorations.[60]

The available literature supports the conclusion that a direct restoration with subgingival margins can be associated with localized gingivitis and increases in PD. A direct or indirect restoration with overhanging margins can be associated with localized gingivitis, increase in PD, and interproximal bone loss, especially for larger overhangs. These changes are likely caused by the overhang acting as a plaque-retentive factor and causing a qualitative shift toward a subgingival cultivable microflora more characteristic of periodontitis.

From cross-sectional studies, it can be concluded, especially when self-performed plaque control and periodontal maintenance measures are not mentioned, that an indirect restoration subgingival margin is associated with gingivitis. However, in longitudinal studies, where self-performed plaque control and periodontal maintenance measures are described and patient compliance is achieved, subgingival prosthesis margins do not appear to act as plaque-retentive factors that cause gingivitis. Based on the available evidence, it appears that plaque control by the patient and compliance with periodontal maintenance is of paramount importance to maintain the health of the periodontium when subgingival margins are adopted in the prosthetic design. Permanent changes to the periodontium, such as gingival recession, could occur when subgingival margins are adopted for prosthesis design; however, they appear to be mostly related to trauma to the periodontium exerted by the procedures, instruments, and materials required to place and record the margins in a subgingival location, rather than the nominal position of the margin.

Dental materials

Different dental materials, their surface characteristics, and location in relation to the gingiva have been associated with variable periodontal responses.[70–73] However, this response could be potentially affected, not only by the type of material, but also by the surface characteristics, such as surface-free energy and roughness, among others, that act as confounding variables. For the latter, a minimum roughness threshold (Ra < 0.2 μm) has been suggested, with increases in plaque retention expected above this threshold, but no reduction for lower Ra values.[74] Similarly, when different alloys were used to fabricate onlays[75] and other types of prostheses,[50] they showed similar levels of plaque and gingival inflammation. Roughness changes, resulting from polishing, scaling, or patient-related factors are material-specific and data on resultant plaque accumulation as a function of the change in Ra is scarce.[76] Teeth restored with a variety of dental materials, when compared with enamel, had similar plaque levels, gingival inflammation, interleukin (IL)-1α, IL-1β, and IL-1ra levels, but most important, in a 10-day gingivitis experiment, showed no difference for the same parameters.[49,77] Similar clinical gingival reactions in periodontally healthy patients were also seen when comparing class V restorations of composite resin or calcium aluminate/silicate material.[78–82] These findings appear also valid when different restorative materials are used to rebuild part of the tooth anatomy during mucogingival surgical procedures.[83–88] Therefore, available evidence demonstrates that different dental materials act similarly to enamel as plaque-retentive factors to initiate gingivitis.

Metal ions and metal particles can also be released from dental alloys and can be found locally within plaque, the periodontum, and in several organs and tissues. While several of these ions (nickel [Ni], palladium [Pd], copper [Cu], titanium [Ti] among others) have been shown, via in vitro studies, to potentially affect cell count, viability, function, and the release of inflammatory mediators, their influence on gingivitis and periodontitis is largely unclear.[89] Metal ions and particles, especially Ni and Pd, have also been associated with hypersensitivity reactions which might clinically appear as gingivitis, localized in the area of gingival contact with the dental material that does not respond to adequate measures of plaque control, and contact stomatitis, often with a lichenoid-type appearance.[90–93] For patients who have shown allergic reactions to dental alloys, very limited evidence suggests that the replacement of these prostheses with zirconia-based protheses was associated with a resolution of the allergic reaction.[94]

Removable dental prostheses

In cross-sectional studies, where no information is present on the level of self-performed plaque control and periodontal maintenance or where clearly heterogeneous baseline periodontal conditions are present,[95] partial removable dental prostheses (RDPs) have been associated with increased prevalence of caries, gingivitis, and periodontitis.[96–100] A study has shown no changes in PD, but increases in plaque levels and gingival inflammation in patients wearing RDPs.[101] Other authors have reported that when the patient was adequately instructed on self-performed plaque control and seen at frequent periodic maintenance visits, there was a decrease in plaque levels and gingival inflammation.[102] A recent study showed no difference in PD, BOP, gingival recession, microbial count, and species between teeth that supported RDPs and teeth that did not.[103] Longitudinal studies of distal extension RDPs indicate that a favorable periodontal prognosis may be expected provided the following conditions are satisfied: 1) periodontal disease, if present, is treated and an adequate preprosthetic plaque control regimen established; 2) periodontal health and oral hygiene are maintained through self-performed plaque control measures[104] and periodic maintenance appointments,[105] and 3) patient's motivation is reinforced to enhance compliance to self-performed plaque control and periodontal maintenance.[106–112] Therefore, we can conclude that, if plaque control is established, the prostheses are correctly designed and regularly checked, and indicated maintenance procedures are performed,

RDPs do not cause greater plaque accumulation, periodontal loss of attachment, or increased mobility.[113–118] On the other hand, if patients do not adequately perform plaque control and attend periodic maintenance appointments, removable dental prostheses, including overdentures,[118–127] could act as plaque-retentive factors and indirectly cause gingivitis and periodontitis. In addition, especially distal extension RDPs, when not properly maintained and relined, have the potential to apply greater forces and torque to the abutment teeth, causing a traumatic increase in mobility.[107]

Tooth anatomy and position

Cervical enamel projections (CEP) and enamel pearls (EP)

Tooth anatomic factors, such as CEP and EP, have been associated with furcation invasion, increased PD, and loss of clinical attachment.[128,129] The extent of CEP extension toward the furcation area can be classified into three classes, with grade I described as "distinct change in cemento-enamel junction (CEJ) attitude with enamel projecting toward the furcation;" grade II, "the CEP approaching the furcation, but not actually making contact with it;" and grade III, "CEP extending into the furcation proper."[130] Prevalence of CEP for all extracted teeth varies, depending on the report, from 25% to 35.5% and 8% to 17% in mandibular and maxillary molars, respectively.[130–135] When controlling for the presence of furcation invasion (FI), CEP were found in 82.5% and 17.5% of molars with and without FI, respectively,[136] with prevalence for CEP associated with FI ranging from 63.2% to 90%[130,137,138] and only one study finding no greater significant association between CEP compared with FI.[134] While the prevalence of grade III CEP varies in the literature from 4.3% to 6.3%, these types of CEP might be more detrimental to the furcation periodontal tissues than grade I and II CEP.[136,139]

Enamel pearls are generally spheroidal in shape, occur in roughly 1% to 5.7% of all molar teeth,[140–142] vary in dimension from 0.3 to 2 mm, and occur most often isolated on a tooth, potentially localized in the furcation area of molars.[133,142–144] EP can act as a plaque-retentive factor when periodontitis progresses to the point that they become part of the subgingival microbial ecosystem.

Developmental grooves

The most frequent developmental groove appears to be the palatal groove, most often located in the maxillary lateral incisor with a prevalence of 1% to 8.5% at the subject level and 2.2% at the tooth level.[145] Forty-three percent of grooves do not extend more than 5 mm apical to the CEJ and only 10% are present 10 mm or more apical the CEJ.[146] The mechanism suggested for developmental grooves to initiate periodontal disease is related to plaque retention that causes localized gingivitis and periodontitis.[133,145,147–150] Grooves are also present on other teeth[151,152] and mostly in the interproximal areas, with few of these grooves extending to the tooth apex.[153]

Tooth and root fractures

Tooth fractures

If tooth fractures occur coronal to the gingival margin and do not extend to parts of the tooth surrounded by periodontal tissues, they do not initiate gingivitis or periodontitis, unless the surface characteristics of the fracture area predispose to greater plaque retention.

Root fractures

Root fractures can be classified based on the trajectory of the fracture (vertical, transverse, or oblique), their extent (complete or incomplete), location (apical, midroot, or cervical regions) and on the healing/repair mode.[154] While fractures located within the midroot and apical regions were shown in a 10-year study to have a very favorable prognosis (78% and 89% tooth survival, respectively), fractures located within the cervical one-third of the root had a significantly worse prognosis for tooth retention (33%).[154–156] Since fractures located within the cervical third of a root have a more likely possibility of being colonized by subgingival plaque, they can act as plaque-retentive factors and indirectly cause gingivitis and periodontitis. In addition, they can directly traumatize the surrounding periodontium due to mobility of the fractured tooth surfaces. Limited short-term evidence suggests that fractures located within the anatomic crown or slightly into the cervical third of the root can be successfully repaired with adhesive techniques and that periodontal parameters, such as plaque index, gingival index (GI), PD, and clinical attachment level, are not different than control teeth.[157–159] Vertical root fractures are defined as longitudinal fractures that might begin on the internal canal wall and extend outward to the external root surface. They occur most often on endodontically treated teeth, although they can be present on non-endodontically treated teeth, especially molars and premolars, as a result of apical extensions of coronal tooth fractures.[160] A localized pocket, with loss of attachment and bone is usually associated with the fractured tooth[161] and extends to variable lengths along the fracture line.[162,163] Narrow, deep, V- or U-shaped osseous defects are generally seen during surgical exposure of the fractured area with bone resorption and inflammation related to bacterial infection from the gingival margin and root canal system.[164,165]

Root resorption

Root resorption can be classified into surface, inflammatory, replacement resorption,[166,167] and depending on its location, as internal or external, cervical or apical.[168,169] When root resorption is located within the cervical third of the root, it can easily communicate with the subgingival microbial ecosystem. Plaque retention at such sites can cause gingivitis and periodontitis. Cemental tears are localized areas of cementum detachment from the underlying dentin and can potentially lead to localized periodontal breakdown, although the biologic mechanism involved has not been elucidated.[170,171]

Tooth position

Cross-bite,[172,173] misalignment/rotation of a tooth,[174] and crowding of the maxillary[175] and mandibular anterior sextant[176] have been shown to be associated with increased plaque retention[176] and gingivitis, greater PD, and bone[177] and clinical attachment loss.[178] However, other studies assessing the effect of crowding on the periodontium did not find an association with plaque retention and gingivitis.[179–181] Tooth position and periodontal biotype and their interaction[182] can also be factors that influence the likelihood of mucogingival deformities, as it has been shown that a thin periodontal biotype has a significantly thinner labial bone plate, narrower gingival width, and greater apico-coronal distance between the CEJ and the alveolar crest.[183] In subjects who exhibit trauma related to tooth brushing[184–187] or tooth malposition within the alveolar process,[187,188] a greater risk for gingival recession can be present. Tooth anatomy, and specifically the shape of the tooth and their approximation, have been shown to affect the height of the interproximal papilla.[189]

Root proximity

Root proximity (RP) in the maxilla is most prevalent between the first and second molar and between the central and lateral incisors; in the mandible, it is generally seen between the central and lateral incisors.[190,191] However, RP has been defined and measured in different ways in the literature, therefore producing inconsistent conclusions on its effect on the periodontum.[192,193] More recently, however, a longitudinal 10-year clinical study concluded that, while an interproximal root distance (IRD) of mandibular central and lateral incisors > 0.8 mm was not associated with a more apical position of the interproximal bone, an IRD > 0.8 mm was associated, even when controlled for age, smoking, plaque, and calculus, with interproximal crestal bone loss, and sites with IRDs < 0.6 mm were 28% and 56% more likely to lose > 0.5 mm and > 1.0 mm of bone during 10 years, respectively.[194] Based on the limited evidence, we are not able to conclude which are the biologic mechanisms underlying this increased bone loss.[194] To standardize the location and magnitude of RP, a classification has been proposed that defines the location of the measured site of RP (cervical, middle, or apical third of the root) and divides the severity of the RP into type 1: > 0.5 to ≤0.8 mm; type 2: > 0.3 to ≤0.5 mm; type 3: ≤0.3 mm.[190]

Open contacts

The presence of adequate proximal tooth contacts is considered important to prevent food impaction between teeth.[195] From a periodontal standpoint, while the presence of open contacts was not a factor directly associated with increased GI and PD, the statistically greater occurrence of food impaction at sites with open contacts was associated with increased PD in these areas.[196,197]

CONCLUSIONS

Tooth anatomic factors, root abnormalities and fractures, and tooth relationships in the dental arch and with the opposing dentition can enhance plaque retention. Restoration margins located within the gingival sulcus do not cause gingivitis if patients are compliant with self-performed plaque control and periodic maintenance. Tooth-supported and/or tooth-retained restorations and their design, fabrication, delivery, and materials have often been associated with plaque retention and loss of attachment. Hypersensitivity reactions can occur to dental materials. Restorations margins placed within the junctional epithelium and supracrestal connective tissue attachment can be associated with inflammation and, potentially, recession. However, the evidence in several of these areas, especially related to the biologic mechanisms by which these factors affect the periodontium, is inconclusive. This highlights the need for additional well-controlled animal studies to elucidate biologic mechanisms, as well as longitudinal, prospective human trials. Adequate periodontal assessment and treatment, instructions and motivation in self-performed plaque control, and compliance with maintenance protocols appear to be the most important factors to limit or avoid potential negative effects on the periodontium associated with fixed and removable prostheses.

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[1]Thomson Reuters, New York, NY.

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Periodontal manifestations of systemic diseases and developmental and acquired conditions: Consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions

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Abstract

Background: A variety of systemic diseases and conditions can affect the course of periodontitis or have a negative impact on the periodontal attachment apparatus. Gingival recessions are highly prevalent and often associated with hypersensitivity, the development of caries and non-carious cervical lesions on the exposed root surface and impaired esthetics. Occlusal forces can result in injury of teeth and periodontal attachment apparatus. Several developmental or acquired conditions associated with teeth or prostheses may predispose to diseases of the periodontium. The aim of this working group was to review and update the 1999 classification with regard to these diseases and conditions, and to develop case definitions and diagnostic considerations.

Methods: Discussions were informed by four reviews on 1) periodontal manifestions of systemic diseases and conditions; 2) mucogingival conditions around natural teeth; 3) traumatic occlusal forces and occlusal trauma; and 4) dental prostheses and tooth related factors. This consensus report is based on the results of these reviews and on expert opinion of the participants.

Results: Key findings included the following: 1) there are mainly rare systemic conditions (such as Papillon-Lefevre Syndrome, leucocyte adhesion deficiency, and others) with a major effect on the course of periodontitis and more common conditions (such as diabetes mellitus) with variable effects, as well as conditions affecting the periodontal apparatus independently of dental plaque biofilm-induced inflammation (such as neoplastic diseases); 2) diabetes-associated periodontitis should not be regarded as a distinct diagnosis, but diabetes should be recognized as an important modifying factor and included in a clinical diagnosis of periodontitis as a descriptor; 3) likewise, tobacco smoking – now considered a dependence to nicotine and a chronic relapsing medical disorder with major adverse effects on the periodontal supporting tissues – is an important modifier to be included in a clinical diagnosis of periodontitis as a descriptor; 4) the importance of the gingival phenotype, encompassing gingival thickness and width in the context of mucogingival conditions, is recognized and a novel classification for gingival recessions is introduced; 5) there is no evidence that traumatic occlusal forces lead to periodontal attachment loss, non-carious cervical lesions, or gingival recessions; 6) traumatic occlusal forces lead to adaptive mobility in teeth with normal support, whereas they lead to progressive mobility in teeth with reduced support, usually requiring splinting; 7) the term *biologic width* is replaced by *supracrestal tissue attachment* consisting of junctional epithelium and supracrestal connective tissue; 8) infringement of restorative margins within the supracrestal connective tissue attachment is associated with inflammation and/or loss of periodontal supporting tissue. However, it is not evident whether the negative effects on the periodontium are caused by dental plaque biofilm, trauma, toxicity of dental materials or a combination of these factors; 9) tooth anatomical factors are related to dental plaque biofilm-induced gingival inflammation and loss of periodontal supporting tissues.

Conclusion: An updated classification of the periodontal manifestations and conditions affecting the course of periodontitis and the periodontal attachment apparatus, as well as of developmental and acquired conditions, is introduced. Case definitions and diagnostic considerations are also presented.

KEYWORDS

anatomy, attachment loss, bruxism, classification, dental prostheses, dental restorations, diagnosis, genetic disease, gingival inflammation, gingival recession, gingival thickness, gingivitis, mucogingival surgery, occlusal trauma, periodontal disease, periodontitis, plastic periodontal surgery, systemic disease, tooth

A variety of systemic diseases and conditions can affect the course of periodontitis or have a negative impact on the periodontal attachment apparatus. Gingival recessions are highly prevalent and often associated with hypersensitivity, the development of caries and non-carious cervical lesions on the exposed root surface and impaired esthetics. Occlusal forces can result in injury of teeth and periodontal attachment apparatus. Several developmental or acquired conditions associated with teeth or prostheses may predispose to diseases of the periodontium.

The objectives of Workgroup 3 were to revisit the 1999 AAP classification for periodontal diseases and conditions, evaluate the updated evidence with regard to epidemiology and etiopathogenesis and to propose a new classification system together with case definitions and diagnostic considerations. In preparation, four position papers were provided, that had been accepted for publication. Discussions were based on these four reviews covering 1) periodontal manifestions of systemic diseases and conditions;[1] 2) mucogingival conditions around natural teeth;[2] 3) traumatic occlusal forces and occlusal trauma;[3] and 4) dental prostheses and tooth-related factors.[4] This consensus report is based on the results of these reviews and on expert opinions of the participants.

SYSTEMIC DISEASES AND CONDITIONS THAT AFFECT THE PERIODONTAL SUPPORTING TISSUES

Is it possible to categorize systemic diseases and conditions based on the underlying mechanisms of their effect on the periodontal supporting tissues?

Systemic diseases and conditions that can affect the periodontal supporting tissues can be grouped into broad categories as listed in Albandar et al.,[1] for example genetic disorders that affect the host immune response or affect the connective tissues, metabolic and endocrine disorders, and inflammatory conditions. In the future, it is anticipated that further refinement of these categories will be possible.

Are there diseases and conditions that can affect the periodontal supporting tissues?

There are many diseases and conditions that can affect the periodontal tissues either by 1) influencing the course of periodontitis or 2) affecting the periodontal supporting tissues independently of dental plaque biofilm-induced inflammation. These include:

1a. Mainly rare diseases that affect the course of periodontitis (e.g., Papillon Lefevre Syndrome, leucocyte adhesion deficiency, and hypophosphatasia). Many of these have a major impact resulting in the early presentation of severe periodontitis.

1b. Mainly common diseases and conditions that affect the course of periodontitis (e.g., diabetes mellitus). The magnitude of the effect of these diseases and conditions on the course of periodontitis varies but they result in increased occurrence and severity of periodontitis.

2. Mainly rare conditions affecting the periodontal supporting tissues independently of dental plaque biofilm-induced inflammation (e.g., squamous cell carcinoma, Langerhans cell histiocytosis). This is a more heterogeneous group of conditions which result in breakdown of periodontal tissues and some of which may mimic the clinical presentation of periodontitis.

The full list of these diseases and conditions is presented in Table 1, adapted from Albandar et al.[1]

Particularly relating to those common conditions identified in 1b) above:

Should diabetes-associated periodontitis be a distinct diagnosis?

Given the current global diabetes epidemic and the challenges with timely identification and/or achieving glycemic goals in a large percentage of affected individuals, this disease is of particular importance.[5] Because of differences in prevalence between type 1 and type 2 diabetes most of the evidence for its adverse effects on periodontal tissues is from patients with type 2 diabetes.[6] The level of hyperglycemia over time, irrespective of the type of diabetes, is of importance when it comes to the magnitude of its effect on the course of periodontitis.[7]

There are no characteristic phenotypic features that are unique to periodontitis in patients with diabetes mellitus. On this basis diabetes-associated periodontitis is not a distinct disease. Nevertheless, diabetes is an important modifying factor of periodontitis, and should be included in a clinical diagnosis of periodontitis as a descriptor. According to the new classification of periodontitis,[8,9] the level of glycemic control in diabetes influences the grading of periodontitis.

There is mounting evidence of specific mechanistic pathways in the pathogenesis of periodontitis in patients with diabetes.[10] In a more etiologically driven classification this should require further consideration in the future.

TABLE 1 Classification of systemic diseases and conditions that affect the periodontal supporting tissues (adapted from Albandar et al.[1])

Classification	Disorders	ICD-10 code
1.	**Systemic disorders that have a major impact on the loss of periodontal tissues by influencing periodontal inflammation**	
1.1.	**Genetic disorders**	
1.1.1.	**Diseases associated with immunologic disorders**	
	Down syndrome	Q90.9
	Leukocyte adhesion deficiency syndromes	D72.0
	Papillon-Lefèvre syndrome	Q82.8
	Haim-Munk syndrome	Q82.8
	Chediak-Higashi syndrome	E70.3
	Severe neutropenia	
	– Congenital neutropenia (Kostmann syndrome)	D70.0
	– Cyclic neutropenia	D70.4
	Primary immunodeficiency diseases	
	– Chronic granulomatous disease	D71.0
	– Hyperimmunoglobulin E syndromes	D82.9
	Cohen syndrome	Q87.8
1.1.2.	**Diseases affecting the oral mucosa and gingival tissue**	
	Epidermolysis bullosa	
	– Dystrophic epidermolysis bullosa	Q81.2
	– Kindler syndrome	Q81.8
	Plasminogen deficiency	D68.2
1.1.3.	**Diseases affecting the connective tissues**	
	Ehlers-Danlos syndromes (types IV, VIII)	Q79.6
	Angioedema (C1-inhibitor deficiency)	D84.1
	Systemic lupus erythematosus	M32.9
1.1.4.	**Metabolic and endocrine disorders**	
	Glycogen storage disease	E74.0
	Gaucher disease	E75.2
	Hypophosphatasia	E83.30
	Hypophosphatemic rickets	E83.31
	Hajdu-Cheney syndrome	Q78.8
1.2.	**Acquired immunodeficiency diseases**	
	Acquired neutropenia	D70.9
	HIV infection	B24
1.3.	**Inflammatory diseases**	
	Epidermolysis bullosa acquisita	L12.3
	Inflammatory bowel disease	K50, K51.9, K52.9
2.	**Other systemic disorders that influence the pathogenesis of periodontal diseases**	
	Diabetes mellitus	E10 (type 1), E11 (type 2)
	Obesity	E66.9
	Osteoporosis	M81.9
	Arthritis (rheumatoid arthritis, osteoarthritis)	M05, M06, M15-M19
	Emotional stress and depression	F32.9
	Smoking (nicotine dependence)	F17
	Medications	
3.	**Systemic disorders that can result in loss of periodontal tissues independent of periodontitis**	
3.1.	**Neoplasms**	
	Primary neoplastic diseases of the periodontal tissues	
	– Oral squamous cell carcinoma	C03.0 – 1
	– Odontogenic tumors	D48.0
	– Other primary neoplasms of the periodontal tissues	C41.0
	Secondary metastatic neoplasms of the periodontal tissues	C06.8
3.2.	**Other disorders that may affect the periodontal tissues**	
	Granulomatosis with polyangiitis	M31.3
	Langerhans cell histiocytosis	C96.6
	Giant cell granulomas	K10.1
	Hyperparathyroidism	E21.0
	Systemic sclerosis (scleroderma)	M34.9
	Vanishing bone disease (Gorham-Stout syndrome)	M89.5

Can obesity affect the course of periodontitis?

The relationship between obesity and metabolic status, including hyperglycemia, is complex and it is difficult to unravel their relative contributions to effects on periodontitis. Nevertheless, recent meta-analyses consistently show a statistically significant positive association between

obesity and periodontitis.[11,12] However there are relatively few studies with longitudinal design, and the overall effect appears to be modest.[13,14]

Can osteoporosis affect the course of periodontitis?

There is conflicting evidence regarding the association between osteoporosis and periodontitis. A recent systematic review concluded that postmenopausal women with osteoporosis or osteopenia exhibit a modest but statistically significant greater loss of periodontal attachment compared with women with normal bone mineral density.[15]

Can rheumatoid arthritis affect the course of periodontitis?

A recent meta-analysis found a statistically significant but weak positive association between rheumatoid arthritis and periodontitis.[16] There is some evidence that periodontitis may contribute to the pathogenesis of rheumatoid arthritis, and therefore, longitudinal studies are required to clarify this association.

Should smoking-associated periodontitis be a distinct diagnosis?

Tobacco smoking is a prevalent behavior with severe health consequences. Although tobacco use was once classified as a habit, it is now considered a dependence to nicotine and a chronic relapsing medical disorder (International Classification of Diseases, Tenth Revision [ICD-10 F17]).

It is well established that smoking has a major adverse effect on the periodontal supporting tissues, increasing the risk of periodontitis by 2- to 5-fold.[17] There are no unique periodontal phenotypic features of periodontitis in smokers. On this basis smoking-associated periodontitis is not a distinct disease. Nevertheless, tobacco smoking is an important modifying factor of periodontitis, and should be included in a clinical diagnosis of periodontitis as a descriptor. According to the new classification of periodontitis,[8,9] the current level of tobacco use influences the grading of periodontitis.

Case definitions and diagnostic considerations

1a. **Rare conditions that may have major effects on the course of periodontitis**. Periodontitis (see Workgroup 2 case definition, Papapanou et al.[8]) is a manifestation of these conditions. Cases are defined as periodontitis in the presence of the condition. The full list, case definitions, and diagnostic considerations are shown in Albandar et al.[1] (Tables 2 to 6).

1b. **Common conditions with variable effects on the course of periodontitis**.
Periodontitis associated with diabetes mellitus: Periodontitis (see Workgroup 2 case definition, Papapanou et al.,[8] Tonetti et al.[9]) and diagnosis of diabetes mellitus.
Periodontitis associated with smoking: Periodontitis (see Workgroup 2 case definition, Papapanou et al.,[8] Tonetti et al.[9]) and previous or current smoking in pack-years.

2. **Conditions affecting the periodontal apparatus independently of dental plaque biofilm-induced inflammation**
Periodontal attachment loss occurring in:
Neoplastic diseases
Other diseases

The full list, case definitions, and diagnostic considerations are shown in Albandar et al.[1] (Tables 9 and 10).

MUCOGINGIVAL CONDITIONS AROUND THE NATURAL DENTITION

This consensus focuses on single and multiple facial/lingual recessions that could be related to various periodontal conditions/diseases. Clinical aspects such as mucogingival conditions and therapeutic interventions that are associated with gingival recessions are evaluated. The accompanying narrative review[2] reports data supporting this consensus paper on nine focused questions, case definitions, and a novel classification for gingival recessions.

What is the definition of recession?

Recession is defined as an apical shift of the gingival margin caused by different conditions/pathologies. It is associated with clinical attachment loss. This may apply to all surfaces (buccal/lingual/interproximal).

What are the possible consequences of gingival recession and root surface exposure to oral environment?

Impaired esthetics
Dentin hypersensitivity
Caries/non-carious cervical lesions (NCCL)

Besides the esthetic impairment caused by the apical shift of the gingival margin, the group also highlights the impact of the oral environment on the exposed root surface. The prevalence of dentin hypersensitivity, cervical caries, and especially non-carious cervical lesions, is very high and the latter is increasing with age.

Is the development of gingival recession associated with the gingival phenotype?

The group strongly suggests the adoption of the definition "periodontal phenotype"[18] to describe the combination of gingival phenotype (three-dimensional gingival volume) and the thickness of the buccal bone plate (bone morphotype). Most papers use the term "biotype".

a. Biotype: (Genetics) group of organs having the same specific genotype.

b. Phenotype: Appearance of an organ based on a multifactorial combination of genetic traits and environmental factors (its expression includes the biotype).

The phenotype indicates a dimension that may change through time depending upon environmental factors and clinical intervention and can be site-specific (phenotype can be modified, not the genotype). Periodontal phenotype is determined by gingival phenotype (gingival thickness, keratinized tissue width), and bone morphotype (thickness of the buccal bone plate).

Thin phenotype increases risk for gingival recession. Thin phenotypes are more prone to develop increasing recession lesions.[19,20]

How can the periodontal phenotype be assessed in a standardized and reproducible way?

It can be assessed by using a periodontal probe to measure the gingival thickness (GT) observing the periodontal probe shining through gingival tissue after being inserted into the sulcus:

1) Probe visible: thin (≤1 mm).
2) Probe not visible: thick (> 1 mm).

Different types of probes are used to assess GT: CPU 15 UNC, HuFriedy,[21] SE Probe SD12 Yellow, American Eagle Instruments.[22]

Note: Probe visibility was tested in samples of subjects with unknown gingival pigmentation. It is unknown if the same outcomes are to be expected in populations with different gingival pigmentation. A novel electronic customized caliper has been recently proposed to measure the gingival thickness with a controlled force.[23]

Additional information on the three-dimensional gingival volume can be obtained by measuring the keratinized tissue width (KTW) from the gingival margin to the mucogingival junction. *Bone morphotypes* have been measured radiographically with cone-beam computed tomography (CBCT). The group does not recommend the application of CBCT in this context. There is evidence reporting a correlation between gingival thickness and buccal bone plate.[24,25] To date, periodontal phenotype cannot be assessed in full, while gingival phenotype (GT and KTW) can be assessed in a standardized and reproducible way.

Is there a certain amount (thickness and width) of gingiva necessary to maintain periodontal health?

Any amount of gingiva is sufficient to maintain periodontal health when optimal oral hygiene is attainable.

Does improper toothbrushing influence the development and progression of gingival recessions?

Data are inconclusive. Some studies reported a positive association, some a negative, and some no association.[26]

Does intrasulcular restorative margin placement influence the development of gingival recession?

Intrasulcular restorative/prosthetic cervical margin placement may be associated with the development of gingival recession particularly in a thin periodontal phenotype.

What is the effect of orthodontic treatment on the development of gingival recession?

1. Several studies report the observation of gingival recessions following orthodontic treatment (mainly on the effect of mandibular incisor proclination). The reported prevalence spans 5% to 12% at the end of treatment. Authors report an increase of the prevalence up to 47% in long-term observations (5 years).[27–30] One study reported a correlation between lower incisor proclination and thin phenotype.[31]
2. Direction of the tooth movement and the bucco-lingual thickness of the gingiva may play important roles in soft tissue alteration during orthodontic treatment.[32]

Do we need a new classification of gingival recession?

The group suggests the need for a new classification based upon anatomy.

Case definitions and diagnostic considerations

Mucogingival conditions

Within the individual variability of anatomy and morphology "normal mucogingival condition" can be defined as the "absence of pathosis (i.e. gingival recession, gingivitis, periodontitis)". There will be extreme conditions without obvious pathosis in which the deviation from what is considered "normal" in the oral cavity lies outside of the range of individual variability.[2]

a) Mucogingival condition with gingival recessions

A case with gingival recession presents with an apical shift of the gingival margin (*recession depth*). Relevant features contributing to the description of this condition are 1) the interdental clinical attachment level, 2) the gingival phenotype (*gingival thickness and keratinized tissue width*), 3) root surface condition (presence / absence of NCCL or caries), 4) detection of the CEJ, 5) tooth position, 6) aberrant frenum, and 7) number of adjacent recessions. Presence of recession can cause esthetic problems to the patients and be associated with dentin hypersensitivity.

b) Mucogingival condition without gingival recessions

A case without gingival recession can be described as the gingival phenotype (*gingival thickness and keratinized tissue width*), either at the entire dentition, or at individual sites. Relevant features

contributing to the description of this condition might be tooth position, aberrant frenum, or vestibular depth.

Gingival Recession

It is proposed to adopt a classification of gingival recession with reference to the interdental clinical attachment loss:[33]

- ***Recession Type 1 (RT1)***: Gingival recession with no loss of interproximal attachment. Interproximal CEJ is clinically not detectable at both mesial and distal aspects of the tooth.
- ***Recession Type 2 (RT2)***: Gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss (measured from the interproximal CEJ to the depth of the interproximal sulcus/pocket) is less than or equal to the buccal attachment loss (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).
- ***Recession Type 3 (RT3)***: Gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss (measured from the interproximal CEJ to the apical end of the sulcus/pocket) is higher than the buccal attachment loss (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).

Table 2 reports a diagnostic approach to classify gingival phenotype, gingival recession, and associated cervical lesions. This is a treatment-oriented classification supported by data included in the accompanying narrative review.[2]

OCCLUSAL TRAUMA AND TRAUMATIC OCCLUSAL FORCES

The group defined excessive occlusal force and renamed it *traumatic occlusal force*. *Traumatic occlusal force* is defined as any occlusal force resulting in injury of the teeth and/or the periodontal attachment apparatus. These were historically defined as excessive forces to denote that the forces exceed the adaptive capacity of the individual person or site. *Occlusal trauma* is a term used to describe the injury to the periodontal attachment apparatus, and is a histologic term. Nevertheless, the clinical presentation of the presence of occlusal trauma can be exhibited clinically as described in the case definition.

Does traumatic occlusal force or occlusal trauma cause periodontal attachment loss in humans?

There is no evidence that traumatic occlusal force or occlusal trauma causes periodontal attachment loss in humans.

Can traumatic occlusal force cause periodontal inflammation?

There is limited evidence from human and animal studies that traumatic occlusal forces can cause inflammation in the periodontal ligament.[3]

Does traumatic occlusal force accelerate the progression of periodontitis?

There is evidence from observational studies that traumatic occlusal forces may be associated with the severity of periodontitis.[34] Evidence from *animal* models indicate that traumatic occlusal forces may increase alveolar bone loss.[35,36] However, there is no evidence that traumatic occlusal forces can accelerate the progression of periodontitis *in humans*.

Can traumatic occlusal forces cause non-carious cervical lesions?

There is no credible evidence that traumatic occlusal forces cause non-carious cervical lesions.

What is the evidence that abfraction exists?

Abfraction, a term used to define a wedge-shaped defect that occurs at the cemento-enamel junction of affected teeth, has been claimed to be the result of flexure and fatigue of enamel and dentin. The existence of abfraction is not supported by current evidence.

Can traumatic occlusal forces cause gingival recession?

There is evidence from observational studies that occlusal forces do *not* cause gingival recession.[37,38]

Are orthodontic forces associated with adverse effects on the periodontium?

Evidence from animal models suggests that certain orthodontic forces can adversely affect the periodontium and result in root resorption, pulpal disorders, gingival recession and alveolar bone loss.[39,40] Conversely, there is evidence from observational studies that with good plaque control, teeth with a reduced but healthy periodontium can undergo successful tooth movement without compromising the periodontal support.[41,42]

Does the elimination of the signs of traumatic occlusal forces improve the response to treatment of periodontitis?

There is evidence from one randomized clinical trial that reducing tooth mobility may improve periodontal treatment outcomes.[43] There is insufficient clinical evidence evaluating the impact of eliminating signs of traumatic occlusal forces on response to periodontal treatment.

Should we still distinguish primary from secondary occlusal trauma in relation to treatment?

Primary occlusal trauma has been defined as injury resulting in tissue changes from traumatic occlusal forces applied to a tooth or teeth

TABLE 2 Classification of mucogingival conditions (gingival phenotype) and gingival recessions

Gingival site				Tooth site	
	REC Depth	GT	KTW	CEJ (A / B)	Step (+/-)
No recession					
RT1					
RT2					
RT3					

RT = recession type[33]
REC Depth = depth of the gingival recession
GT = gingival thickness
KTW = keratinized tissue width
CEJ = cemento-enamel junction (Class A = detectable CEJ, Class B = undetectable CEJ)
Step = root surface concavity (Class + = presence of a cervical step > 0.5 mm. Class – = absence of a cervical step > 0.5 mm)[44]

with normal periodontal support. This manifests itself clinically with *adaptive mobility* and is not progressive. Secondary occlusal trauma has been defined as injury resulting in tissue changes from normal or traumatic occlusal forces applied to a tooth or teeth with reduced support. Teeth with *progressive mobility* may also exhibit migration and pain on function. Current periodontal therapies are directed primarily to address etiology; in this context, traumatic occlusal forces. Teeth with progressive mobility may require splinting for patient comfort.

The group considered the term *reduced periodontium* related to secondary occlusal trauma and agreed there were problems with defining "*reduced periodontium*". A reduced periodontium is only meaningful when mobility is progressive indicating the forces acting on the tooth exceed the adaptive capacity of the person or site.

Case definitions and diagnostic considerations

1. *Traumatic occlusal force* is defined as any occlusal force resulting in injury of the teeth and/or the periodontal attachment apparatus. These were historically defined as *excessive forces* to denote that the forces exceed the adaptive capacity of the individual person or site. The presence of *traumatic occlusal forces* may be indicated by one or more of the following: fremitus, tooth mobility, thermal sensitivity, excessive occlusal wear, tooth migration, discomfort/pain on chewing, fractured teeth, radiographically widened periodontal ligament space, root resorption, and hypercementosis. Clinical management of traumatic occlusal forces is indicated to prevent and treat these signs and symptoms.
2. *Occlusal trauma* is a lesion in the periodontal ligament, cementum and adjacent bone caused by traumatic occlusal forces. It is a histologic term; however, a clinical diagnosis of occlusal trauma may be made in the presence of one or more of the following: progressive tooth mobility, adaptive tooth mobility (fremitus), radiographically widened periodontal ligament space, tooth migration, discomfort/pain on chewing, and root resorption.

As some of the signs and symptoms of traumatic occlusal forces and occlusal trauma may also be associated with other conditions, an appropriate differential analysis must be performed to rule out other etiologic factors.

The group agreed to a classification related to traumatic occlusal forces and occlusal trauma (Table 3).

DENTAL PROSTHESES AND TOOTH-RELATED FACTORS

Several conditions, associated with prostheses and teeth, may predispose to diseases of the periodontium and were extensively reviewed in a background paper.[4] The extent to which these conditions contribute to the disease process may be dependent upon the susceptibility of the individual patient.

What is the biologic width?

Biologic width is a commonly used clinical term to describe the apico-coronal variable dimensions of the supracrestal attached tissues. The supracrestal attached tissues are histologically composed of the junctional epithelium and supracrestal connective tissue attachment. *The term biologic width* should be replaced by *supracrestal tissue attachment*.

Is infringement of restorative margins within the supracrestal connective tissue attachment associated with inflammation and/or loss of periodontal supporting tissues?

Available evidence from human studies supports that infringement within the supracrestal connective tissue attachment is associated with inflammation and loss of periodontal supporting tissue. Animal studies corroborate this statement and provide histologic evidence that infringement within the supracrestal connective tissue attachment is associated with inflammation and subsequent loss of periodontal supporting tissues, accompanied with an apical shift of the junctional epithelium and supracrestal connective tissue attachment.

Are changes in the periodontium caused by infringement of restorative margins within supracrestal connective tissue attachment due to dental plaque biofilm, trauma, or some other factors?

Given the available evidence, it is not possible to determine if the negative effects on the periodontium associated with restoration margins located within the supracrestal connective tissue attachment is caused by dental plaque biofilm, trauma, toxicity of dental materials, or a combination of these factors.

For subgingival indirect dental restorations, are design, fabrication, materials, and delivery associated with gingival inflammation and/or loss of periodontal supporting tissues?

There is evidence to suggest that tooth supported/retained restorations and their design, fabrication, delivery, and materials can be associated with plaque retention and loss of clinical attachment. Optimal restoration margins located within the gingival sulcus do not cause gingival inflammation if patients are compliant with self-performed plaque control and periodic maintenance. Currently, there is a paucity of evidence to define a correct emergence profile.

Are fixed dental prostheses associated with periodontitis or loss of periodontal supporting tissues?

The available evidence does not support that optimal fixed dental prostheses are associated with periodontitis. There is evidence to suggest that design, fabrication, delivery and materials used for fixed dental prostheses procedures can be associated with plaque retention, gingival recession and loss of supporting periodontal tissues.

Are removable dental prostheses associated with periodontitis or loss of periodontal supporting tissues?

The available evidence does not support that optimal removable dental prostheses are associated with periodontitis. If plaque control is established and maintenance procedures performed, removable dental prostheses are not associated with greater plaque accumulation, periodontal loss of attachment and increased tooth mobility. However, if patients perform inadequate plaque control and do not attend periodic maintenance appointments, removable dental prostheses could act as dental plaque biofilm retentive factors, be associated with gingivitis/periodontitis, increased mobility and gingival recession.

Can tooth-related factors enhance plaque accumulation and retention and act as a contributing factor to gingival inflammation and loss of periodontal supporting tissues?

Tooth anatomical factors (cervical enamel projections, enamel pearls, developmental grooves), root proximity, abnormalities and fractures, and tooth relationships in the dental arch are related to dental plaque biofilm-induced gingival inflammation and loss of periodontal supporting tissues.

Can adverse reactions to dental materials occur?

Dental materials may be associated with hypersensitivity reactions which can clinically appear as localized inflammation that does not respond to adequate measures of plaque control. Additional diagnostic measures will be needed to confirm hypersensitivity. Limited in vitro evidence suggests selected ions liberated from dental materials may adversely affect cell viability and function.

TABLE 3 Classification of traumatic occlusal forces on the periodontium

1. Occlusal trauma
A. Primary occlusal trauma
B. Secondary occlusal trauma
C. Orthodontic forces

What is altered passive eruption?

Abnormal dentoalveolar relationships associated with altered passive tooth eruption is a developmental condition that is characterized by the gingival margin (and sometimes bone) located at a more coronal level. This condition may be clinically associated with the formation of pseudopockets and/or esthetic concerns.

Case definitions and diagnostic considerations

1. *Supracrestal attached tissues* are composed of the junctional epithelium and the supracrestal connective tissue attachment. This was formally referred to as the *biologic width*. The apico-coronal dimension of the supracrestal attached tissues is variable. Clinically, there is evidence that placement of restorative margins within the supracrestal connective tissues is associated with inflammation and loss of periodontal supporting tissues. Additional research is necessary to clarify the effects of placement of restorative margins within the junctional epithelium.
2. *Altered passive eruption* is a developmental condition with abnormal dento-alveolar relationships. Clinically, this condition is characterized by the gingival margin (and sometimes bone) located at a more coronal level, which leads to pseudopockets and esthetic concerns. Correction of this condition can be accomplished with periodontal surgery.

TABLE 4 Classification of factors related to teeth and to dental prostheses that can affect the periodontium

A. Localized tooth-related factors that modify or predispose to plaque-induced gingival diseases/periodontitis
1. Tooth anatomic factors
2. Root fractures
3. Cervical root resorption, cemental tears
4. Root proximity
5. Altered passive eruption
B. Localized dental prosthesis-related factors
1. Restoration margins placed within the supracrestal attached tissues
2. Clinical procedures related to the fabrication of indirect restorations
3. Hypersensitivity/toxicity reactions to dental materials

The workgroup agreed to a classification of dental prosthesis and tooth-related factors (Table 4).

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FIGURE 1 Participants of Workgroup 3

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2017 WORLD WORKSHOP

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Peri-implant health

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Abstract

Objective: The aim is to define clinical and histologic characteristics of peri-implant tissues in health and describe the mucosa–implant interface.

Importance: An understanding of the characteristics of healthy peri-implant tissues facilitates the recognition of disease (i.e., departure from health).

Findings: The healthy peri-implant mucosa is, at the microscopic level, comprised of a core of connective tissue covered by either a keratinized (masticatory mucosa) or non-keratinized epithelium (lining mucosa). The peri-implant mucosa averages about 3 to 4 mm high, and presents with an epithelium (about 2 mm long) facing the implant surface. Small clusters of inflammatory cells are usually present in the connective tissue lateral to the barrier epithelium. Most of the intrabony part of the implant appears to be in contact with mineralized bone (about 60%), while the remaining portion faces bone marrow, vascular structures, or fibrous tissue. During healing following implant installation, bone modeling occurs that may result in some reduction of the marginal bone level.

Conclusions: The characteristics of the peri-implant tissues in health are properly identified in the literature, including tissue dimensions and composition. Deviation from the features of health may be used by the clinician (and researcher) to identify disease, including peri-implant mucositis and peri-implantitis.

KEYWORDS

connective tissue biology, diagnosis, implantology, osseointegration

Peri-implant tissues are those that occur around osseointegrated dental implants. They are divided into soft and hard tissue compartments. The soft tissue compartment is denoted "peri-implant mucosa" and is formed during the wound healing process that follows implant/abutment placement.[1] The hard tissue compartment forms a contact relationship to the implant surface to secure implant stability.[2] Due to their histologic and anatomic features, peri-implant tissues carry out two basic functions: the mucosa protects the underlining bone, while the bone supports the implant. Indeed, the destruction of peri-implant tissues can jeopardize the implant success and survival,[3] and the understanding of the characteristics of healthy peri-implant tissues allows the recognition of disease. Thus, the aim of the present review was to define clinical and histologic characteristics of peri-implant tissues in health and describe the mucosa–implant interface.

A search in MEDLINE-PubMed was used to retrieve the evidence to support the present review. The following key words were used for the literature search: dental implants (Mesh) AND biological width OR mucosa OR soft tissue OR attachment OR keratinized mucosa OR peri-implant mucosa OR probing depth OR microbiota OR collagen fibers OR epithelium OR adhesion OR seal OR bone OR osseointegration AND humans OR animals. The two main reasons for exclusion of studies were: 1) not published in English, and 2) lack of detailed clinical, histologic, or microbiologic description of healthy peri-implant tissues.

PERI-IMPLANT MUCOSA

Most information regarding the structural features of the peri-implant mucosa is derived from animal studies using dog models.[4–15] In such studies implants were placed in the edentulous ridge (alternatively, the fresh extraction socket), the outer osseous part of which was covered with masticatory mucosa. It was also shown that the healed peri-implant mucosa on the buccal aspect averaged about 3 to 4 mm high when measured from the mucosal margin to the crest of the peri-implant bone. In addition, this mucosa contains a core of connective tissue, mainly comprised of collagen fibers and matrix elements (85%), comparatively few fibroblasts (3%), and vascular units (5%). The outer (oral) surface of the connective tissue is covered by an often orthokeratinized epithelium. The portion of the peri-implant mucosa that is facing the implant (abutment) contains two distinct parts, a "coronal" portion that is lined by a thin barrier epithelium (similar to the junctional epithelium of the gingiva) and sulcular epithelium, and a more "apical" segment in which the connective tissue appears to be in direct contact with the implant surface. This apical portion of the peri-implant mucosa is designated zone of connective tissue adhesion.

In the connective tissue immediately lateral to the barrier and sulcular epithelium, a delicate plexus of vascular structures, similar to the dentogingival vascular plexus,[16] is consistently present,[17] while the connective tissue adhesion zone appears to harbor only limited amounts of vascular structures. At implants placed into masticatory mucosa, the main collagen fiber bundles are anchored in the crestal bone and extend in a marginal direction parallel to the surface of the metal device. It is assumed that circular fibers may also be present in this type of peri-implant mucosa.

Moon et al.[18] analyzed under electron scanning microscope the zone of connective tissue adhesion confined to a 200-μm wide zone of the connective tissue facing the implant. The findings demonstrated that the adhesion includes two distinct layers: one inner layer, about 40 μm wide, which harbors large amounts of fibroblasts (32% of volume) that appear to be in intimate contact with the surface of the implant; and one outer layer, about 160 μm wide, that is dominated by collagen fibers (83%), smaller amounts of fibroblasts (11%), and larger volumes of vascular structures (3%).[18]

Valid histologic information is not currently available regarding the peri-implant mucosa when implants are placed in non-keratinized lining or alveolar mucosa.

MORPHOGENESIS OF THE MUCOSAL ADHESION

The formation of the mucosal adhesion was studied in a dog model.[1] One-piece implant devices were placed in the edentulous mandible of dogs, and healing was monitored using light microscopic examination of biopsies sampled at different intervals during a 3-month period. In the initial phase of the wound between the implant and cut connective tissue, a fibrin clot/coagulum formed that was infiltrated with mainly neutrophils and limited amounts of macrophages. The number of inflammatory cells subsequently subsided, and the wound surface became characterized by its dense layer of fibroblasts that appeared to be in intimate contact with the implant surface. In the 2nd to 3rd week of healing, the density of fibroblasts was reduced, the amount of collagen and matrix components increased, and epithelial cells, extending from the oral epithelium, had started to occupy marginal parts of the connective tissue wound. Collagen fibers in the previous wound area became organized in bundles after about 4 weeks. After 6 to 8 weeks the mucosal adhesion appeared mature, and the interface zone at tissue–implant was comprised of a combined epithelial and connective tissue adhesion to the implant surface. Since the build-up of the soft tissue adhesion did not change much after the first month, it is suggested that a homeostasis had been reached at this interval.[1]

DIMENSION OF THE PERI-IMPLANT MUCOSA

Animal studies

The dimension of the peri-implant mucosa, often called the biological width or dimension,[5] was examined in biopsies mainly obtained from studies in dogs.[19–26] Such measurements disclosed that a certain width of soft tissue may be required to cover the peri-implant bone. The studies referred to the length of the epithelium (from the peri-implant mucosa margin to the apical portion of the junctional epithelial) as about 2 mm, while the height of the zone of connective tissue adhesion exhibited more variation (between 1 and 2 mm). The experiments in the animal model included the study of different variables such as material used for the fabrication of the implant and/or the abutment, surgical placement protocol, implants/abutments with different surface texture,[5,19–23] as well as so-called implants with a "platform switching" implant/abutment design.[24–26] The results obtained documented that while abutments made of gold alloy and dental porcelain failed to establish appropriate soft tissue adhesion,[23] other variables had apparently limited effect on the dimensions of the peri-implant mucosa.

It should be noted, however, that although animal models may provide valuable data valid for proof-of-principle issues, they may not completely recreate the anatomic, physiologic, biomechanical/functional, or pathologic environment of the clinical conditions in humans.[27]

Human studies

Studies on the morphogenesis and morphology of the mucosa at implants in humans used block biopsies obtained from mini-implants or from soft tissue dissection techniques from conventional or specially designed abutments.[22,28–32] Tomasi et al.[31,32] presented a *de novo* biopsy technique and reported on the morphogenesis of the peri-implant mucosa at single implant sites in human volunteers. Soft tissue biopsies were sampled after 2, 4, 8, and 12 weeks of healing

following abutment connection. They reported that after 2 weeks large areas of the severed connective tissue were infiltrated with inflammatory cells, while after 4 weeks the infiltrated areas were smaller and a short barrier epithelium had formed in the interface zone. Sections representing later phases of observation exhibited continued healing of the connective tissue wound and the formation of a well-defined barrier and sulcular epithelium in the marginal portion of the soft tissue samples. The height of the peri-implant mucosa, measured along the profile of the soft tissue, increased during the healing phase from 2.7 mm at 2 weeks to between 3.0 and 3.5 mm after 4, 8, and 12 weeks. In the corresponding intervals the length of the epithelium varied between 2.2 and 2.0 mm, while the zone of connective tissue adhesion varied between 1.7 and 1.1 mm.

In summary, results from the available studies in man and from animal experiments are consistent and document that the peri-implant mucosa is about 3 to 4 mm high with an epithelium that is about 2 mm long.

PERI-IMPLANT TISSUES IN CLINICAL HEALTH

The gingiva and the peri-implant mucosa and their adhesion (seal) are consistently challenged by the oral environment, including the steady exposure to microorganisms in the biofilm present on the tooth and implant surfaces.[22,32–37] In the clinically normal peri-implant mucosa (and gingiva), the continuous host response includes both vascular and cellular events. Thus, distinct vascular structures occur in the connective tissue lateral to the epithelium, as well as small clusters of inflammatory cells (T- lymphocyte and B-lymphocyte). Macrophages seem to be present along the entire interface zone, while polymorphonuclear leukocytes occur mainly in the connective tissue immediately lateral to the epithelium.[32]

PROBING PERI-IMPLANT TISSUES

For many years it was incorrectly assumed that the tip of the periodontal probe in a probing depth (PD) measurement identified the apical base of the dento-gingival epithelium.[38] Later research documented, however, that this was not the case. At healthy sites the tip of the probe failed to reach the apical portion of the epithelial barrier, while at diseased sites the probe found the apical base of the inflammatory cell infiltrate. Hence, PD measurements assess the depth of probe penetration or the resistance offered by the soft tissue.[39–47]

The influence of the condition (health, disease) of the peri-implant mucosa on the outcome of the probing measurement was studied in animal models.[48–50] Lang et al.[49] reported that at sites with healthy mucosa or mucositis, the tip of the probe identified the apical border of the barrier epithelium with an error of approximately 0.2 mm, while at sites with peri-implantitis, the measurement error was much greater at 1.5 mm. Abrahamsson and Soldini,[50] in a subsequent study, stated that the probe penetration into the healthy soft tissues at the buccal surface of teeth and implants in dogs was alike and similar to the length of the junctional/barrier epithelium. It was assumed that probing the implant–mucosa interface would sever the soft tissue seal and jeopardize the integrity of the adhesion. This issue was examined in a dog study[51] that documented that already after 5 to 7 days following clinical probing, the soft tissue seal had regenerated to its full extent.

BONE SOUNDING

Bone sounding or transmucosal sounding (TS) is a measurement that is used to determine the height of the entire soft tissue cuff at various groups of teeth and implants. The dimensions of the peri-implant mucosa and the gingiva at adjacent tooth sites was studied by clinical measurements performed mainly in partially edentulous subjects who had been treated with implant-supported single-crown restorations. In such studies the brand of the periodontal probe used for the assessments was identified; PD as well as TS measurements were used to describe some features of the soft tissue.

Results from such studies[52–60] demonstrated that the PD was greater at proximal than at facial/buccal surfaces at both tooth and implant sites and greater at implant than at tooth sites. This shows that the soft tissue cuff around implants exhibits less resistance to probing than the gingiva at adjacent teeth. There are reasons to suggest that the lack of root cementum on the implant surface as well as the difference in the orientation of the collagen fibers in the two types of soft tissue may be associated with the variation observed in the "resistance to probing."

The TS measurements disclosed that the peri-implant mucosa was in most cases 1.0 to 1.5 mm higher than the corresponding gingiva at both buccal/facial and proximal sites. It was further demonstrated that patients with a "flat-thick" periodontal phenotype[61,62] exhibited greater peri-implant mucosa dimensions than subjects that belonged to the "scalloped-thin" biotype.[57,63] In addition, the height of the papilla between an implant-supported restoration and a natural tooth was reported to be ≤5 mm[52,56,64,65] and related to the connective tissue adhesion level at the adjacent approximal tooth surfaces.[57,66] The corresponding dimension between two adjacent implant restorations averaged 3 mm[64,67] and apparently was dependent on the outline of the crest of the supporting bone.

KERATINIZED MUCOSA (KM)

KM is a term used to describe the masticatory mucosa that is present at many, but not all, implant sites. KM extends from the margin of the peri-implant mucosa to the movable lining (oral) mucosa. KM is comprised of a lamina propria (fibrous connective tissue that contains fibroblasts and equal amounts of type I and type III collagen) that is covered by an orthokeratinized squamous epithelium. The width of the KM at the facial/buccal side of teeth is, as a rule, about 1 mm

greater than at contralateral implant sites.[54,59,60] It is suggested that loss of crestal bone following tooth extraction is the main reason for dimunition of the KM. The thickness of facial KM, determined with a probe at the base of the PD, is greater at implants than at teeth (2.0 mm vs 1.1 mm, respectively).[54]

The need for a minimum amount of keratinized mucosa to maintain peri-implant tissue health is apparently a controversial issue.[68–72] Several studies failed to associate the lack of a minimum amount of KM with mucosal inflammation,[73–80] while other studies suggested that plaque build-up and marginal inflammation were more frequent at implant sites with < 2 mm of KM.[81–85]

BONE TISSUE AROUND IMPLANTS

Bone tissue in the edentulous ridge

In a study involving partially edentulous subjects, hard tissue biopsies were sampled from the maxilla and the mandible with the use of trephine drills.[86] The bone tissue was found to include a blend of mainly lamellar bone (46%) and bone marrow (23%) with less amounts of fibrous (12%) and osteoid (4%) tissue. Bone marrow was the dominant tissue element in the anterior maxilla, while dense lamellar bone characterized the anterior portion of the mandible. The cortical cap was consistently comprised of lamellar bone and was wider in the mandible than in the maxilla (1.8 mm vs 0.8 mm, respectively) and substantially more narrow in the anterior maxilla than in the anterior mandible.

Osseointegration

The term osseointegration was coined by Brånemark et al.[87] and was described as bone-to-implant contact on the light microscopic level. Later, Albrektsson and Sennerby[2] defined osseointegration as, "a direct functional and structural connection between living bone and the surface of a load-carrying implant."

In animal experiments[88,89] the process of hard tissue healing around implants made of c.p.titanium was described. The individual device had the shape of a solid screw with a modified surface configuration and U-shaped invaginations (wound chambers) that allowed the ingrowth of bone. The wound chambers were first occupied with a coagulum that after 4 days had been replaced with granulation tissue that contained inflammatory cells and also numerous mesenchymal cells and newly formed vessels. After about 1 week of healing, fingerlike projections of woven bone occurred around vascular structures in the center of the chambers and also in direct contact with small areas of the implant. After 2 to 4 weeks the chambers were filled with woven bone extending from the old bone to reach the surface of the titanium device. In the 6- to 12-week interval the woven bone was replaced with lamellar bone and marrow and bone-to-implant contact had been established. At the end of the experiment about 60% of the moderately rough implant surface was occupied with mineralized bone and the marginal bone-to-implant contact was located about 0.3 mm from the abutment/implant level. Additional preclinical studies[90,91] have confirmed that rough surfaces enhance early bone formation and bone-to-implant contact. Findings from studies in man[92–97] confirmed the animal results by documenting that the amount of direct bone (mineralized tissue)-to-implant contact was about 60% of the circumference of the implanted device after a healing period of 6 weeks to 3 months.

Crestal bone-level change

Following implant installation and loading, modeling of the bone occurs, and during this process some crestal bone height is lost. Studies in animals have demonstrated the location of the implant–abutment interface (microgap) determines the amount of this initial marginal bone loss.[26,98–100] Thus, the crestal bone reduction that occurs in this healing phase apparently varies between brands and seems to be related to the design of the implant system used.[101–112] After this initial period about 75% of implants experience no additional bone loss but osseointegration takes place. Most implant sites that exhibit crestal bone loss of > 1 mm appear to be associated with soft tissue inflammation although some sites may have an apparently healthy peri-implant mucosa.[3]

MAJOR DIFFERENCES BETWEEN HEALTHY PERI-IMPLANT AND PERIODONTAL TISSUES

The implant device lacks tooth characteristic structures such as root cementum, periodontal ligament, and bundle bone (alveolar bone proper).[113] The dento-alveolar and the dento-gingival fiber bundles connect the soft tissues with the tooth (root cementum), while no such fiber bundles are apparent in the peri-implant tissues. At periodontally healthy sites, the margin of the gingiva follows the outline of the cemento-enamel junction, while at a corresponding implant site the mucosal margin follows the contour of the crestal bone (multiple implants) or relates to the connective tissue adhesion at adjacent teeth (single implants). The tooth is mobile within its socket, while the implant is rigidly anchored (ankylosed) to the surrounding host bone.

CONCLUSIONS

The healthy peri-implant mucosa is comprised of a core of connective tissue covered by either a keratinized or non-keratinized epithelium. Most of the intrabony part of the implant is in contact with mineralized bone, while the remaining portion faces bone marrow, vascular structures, or fibrous tissue. The characteristics of peri-implant tissues in health are properly identified in the literature. According to the available definitions[114] of peri-implant mucositis and peri-implantitis, the absence of signs of clinical inflammation is necessary for concluding that a site has peri-implant health.

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2017 WORLD WORKSHOP

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Peri-implant mucositis

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objectives: This narrative review was prepared for the 2017 World Workshop of the American Academy of Periodontology and European Federation of Periodontology to address key questions related to the clinical condition of peri-implant mucositis, including: 1) the definition of peri-implant mucositis, 2) conversion of peri-implant health to the biofilm-induced peri-implant mucositis lesion, 3) reversibility of peri-implant mucositis, 4) the long-standing peri-implant mucositis lesion, 5) similarities and differences between peri-implant mucositis at implants and gingivitis at teeth, and 6) risk indicators/factors for peri-implant mucositis.

Methods: A literature search of MEDLINE (PubMed) and The Cochrane Library up to and including July 31, 2016, was carried out using the search strategy (peri-implant[All Fields] AND ("mucositis"[MeSH Terms] OR "mucositis"[All Fields])) OR (periimplant[All Fields] AND mucosits[All Fields]). Prospective, retrospective, and cross-sectional studies and review papers that focused on risk factors/indicators for peri-implant mucositis as well as experimental peri-implant mucositis studies in animals and humans were included.

Findings: Peri-implant mucositis is an inflammatory lesion of the soft tissues surrounding an endosseous implant in the absence of loss of supporting bone or continuing marginal bone loss. A cause-and-effect relationship between experimental accumulation of bacterial biofilms around titanium dental implants and the development of an inflammatory response has been demonstrated. The experimental peri-implant mucositis lesion is characterized by an inflammatory cell infiltrate present within the connective tissue lateral to the barrier epithelium. In long-standing peri-implant mucositis, the inflammatory cell infiltrate is larger in size than in the early (3-week) experimental peri-implant mucositis lesion. Biofilm-induced peri-implant mucositis is reversible at the host biomarker level once biofilm control is reinstituted. Reversal of the clinical signs of inflammation may take longer than 3 weeks. Factors identified as risk indicators for peri-implant mucositis include biofilm accumulation, smoking, and radiation. Further evidence is required for potential risk factors, including diabetes, lack of keratinized mucosa, and presence of excess luting cement.

Conclusions: Peri-implant mucositis is caused by biofilm accumulation which disrupts the host–microbe homeostasis at the implant–mucosa interface, resulting in an inflammatory lesion. Peri-implant mucositis is a reversible condition at the host

biomarker level. Therefore, the clinical implication is that optimal biofilm removal is a prerequisite for the prevention and management of peri-implant mucositis. An understanding of peri-implant mucositis is important because it is considered a precursor for peri-implantitis.

KEYWORDS
peri-implant disease, peri-implant mucositis, peri-implantitis, risk factor, risk indicator

Peri-implant diseases, including peri-implant mucositis and peri-implantitis, were first defined and described at the First European Workshop on Periodontology in Ittingen in 1993.[1] Following this, there have been numerous workshops addressing the definition, prevalence, and treatment of these diseases.[2,3] Peri-implant mucositis is considered to be the precursor of peri-implantitis. The objective of this narrative review was to address key questions related to peri-implant mucositis, including: 1) the definition of peri-implant mucositis, 2) conversion of peri-implant health to the biofilm-induced peri-implant mucositis lesion, 3) reversibility of peri-implant mucosits, 4) the long-standing peri-implant mucositis lesion, 5) similarities and differences between peri-implant mucositis at implants and gingivitis at teeth, and 6) risk indicators/factors for peri-implant mucositis.

MATERIALS AND METHODS

A literature search of MEDLINE (PubMed) and The Cochrane Library up to and including July 31, 2016, was carried out using the search strategy (peri-implant[All Fields] AND ("mucositis"[MeSH Terms] OR "mucositis"[All Fields])) OR (periimplant[All Fields] AND mucositis[All Fields]), resulting in 224 papers. Prospective, retrospective, and cross-sectional studies and review papers focused on risk factors/indicators for peri-implant mucositis as well as experimental peri-implant mucositis studies in animals and humans were included. Following discussion, the current authors agreed on the studies to be included in this narrative review based on their relevance to the questions, outlined above, addressing the topic of peri-implant mucositis.

TABLE 1 Similarities and differences between biofilm-induced gingivitis and peri-implant mucositis

	Gingivitis	Peri-implant mucositis
Definition	Gingival inflammation without periodontal attachment loss	Peri-implant mucosal inflammation in absence of continuous marginal peri-implant bone loss
Clinical signs	Redness, swelling, and bleeding on gentle probing	Redness, swelling, bleeding on gentle probing, and suppuration
Experimental inflammation in humans	Increase in bleeding sites during experimental gingivitis[12,13]	Experimental peri-implant mucositis leads to greater increase in bleeding sites compared with experimental gingivitis.[12,13]
Reversibility in humans	Experimental gingivitis clinically reversible after reinstitution of biofilm control[14] Resolution of host biomarkers in gingival crevicular fluid following 21 days of reinstituted biofilm control[12,13]	Experimental peri-implant mucositis may take longer than 3 weeks for clinical reversibility.[12,13] Resolution of host biomarkers in peri-implant crevicular fluid following 21 days of reinstituted biofilm control[12,13]
Analysis of human biopsies	Experimental biofilm accumulation results in increased proportions of inflammatory cells in connective tissue[11]	Increased proportions of inflammatory cells in connective tissue similar to those found in experimental gingivitis[11]
Short- vs. long-standing inflammation	3-week and 3-month experimental biofilm accumulation results in similar intensity of inflammatory responses in gingiva of dogs[17,72]	3-month experimental biofilm accumulation in dogs results in a more pronounced inflammatory response in peri-implant mucosa compared with inflammatory response in the gingiva[17] Inflammatory lesions from long-standing mucositis in humans[20] considerably larger compared with those of short-term (3-week) experimental mucositis lesions[11]
Variability in humans	High and low responders to experimental biofilm accumulation[73]	High and low responders to experimental biofilm accumulation not yet identified

DEFINITION OF PERI-IMPLANT MUCOSITIS

Peri-implant mucositis has been defined in previous workshops as an inflammatory lesion of the mucosa surrounding an endosseous implant without loss of supporting peri-implant bone.[1–3] The important criteria for the definition of peri-implant mucositis are inflammation in the peri-implant mucosa and the absence of continuing marginal peri-implant bone loss. The clinical sign of inflammation is bleeding on probing, while additional signs may include erythema, swelling, and suppuration (Table 1). The clinical case definition of peri-implant mucositis has been addressed in another review prepared for this workshop.

CONVERSION FROM HEALTHY PERI-IMPLANT MUCOSA TO PERI-IMPLANT MUCOSITIS

Healthy peri-implant mucosa is characterized by the presence of an oral epithelium extending into a non-keratinized barrier epithelium with basal lamina and hemidesmosomes facing the implant or abutment surface.[4] In the connective tissue adjacent to the epithelial barrier, inflammatory cell infiltrates representing the host's defense against the bacterial challenge are present. In healthy peri-implant mucosal conditions, the barrier epithelium and the presence of scattered inflammatory cells constitute the soft tissue seal separating the peri-implant attachment from the oral cavity.[5–9]

Peri-implant mucositis develops from healthy peri-implant mucosa following accumulation of bacterial biofilms around osseointegrated dental implants. A cause-and-effect relationship between experimental accumulation of bacterial biofilms around titanium dental implants and the development of an inflammatory response (i.e., experimental peri-implant mucositis) has been demonstrated in humans.[10–13]

In an early study by Pontoriero et al.,[10] twenty partially edentulous patients received dental implants following successful completion of periodontal therapy. After 6 months of supervised oral hygiene, the peri-implant mucosa was characterized by the absence of obvious signs of clinical inflammation. Following this period, the patients were asked to abolish oral hygiene practices for 3 weeks. At the end of this period, optimal biofilm control was reinstituted. At all examinations the following clinical parameters were assessed around the implants: plaque index (PI), gingival index (GI), sulcus bleeding index (SBI), probing depths (PD), and marginal recession (REC). The 3-week period of abolished oral hygiene practices revealed the development of visible signs of mucosal inflammation, such as swelling, redness, and bleeding. This cause-and-effect relationship between the accumulation of bacterial biofilms and the development of peri-implant mucositis is consistent with the results obtained in the experimental gingivitis model by Löe et al.[14] In another study by Zitzmann et al.[11] involving 12 partially edentulous patients the inflammatory. The inflammatory response to the experimental bacterial challenge was characterized by the enumeration of the proportions of T- and B-cells in peri-implant tissues. Biopsies harvested around implants in a clinically healthy situation and after 21 days of experimental biofilm accumulation indicated that the connective tissue surrounding the implants displayed an increased volume of T- and B-lymphocytes as a consequence of abolished oral hygiene practices.[11] It was also noted that the size of the inflammatory cell infiltrate and the number of several immune cell populations was not significantly different when comparing biopsies from gingiva at teeth and biopsies from peri-implant mucosa.[11]

Outcomes of a comparative study in humans by Salvi et al.[12] indicated that 3 weeks of experimental biofilm accumulation resulted in a higher proportion of bleeding sites in the peri-implant mucosa when compared with that in the gingiva. In that study, the PI at tooth sites was significantly elevated when compared with that at implant sites after 3 weeks of abolished oral hygiene.[12] However, the increase of the GI at tooth sites was significantly lower compared with that at implant sites, indicating that a comparable bacterial challenge yielded a more severe inflammatory response at implant sites.

A recent study, by Meyer et al.,[13] compared clinical and biologic responses during experimental gingivitis and peri-implant mucositis in subjects aged ≥70 years. Although less biofilm accumulation was observed at implant sites, the peri-implant mucosa yielded a higher proportion of bleeding sites compared with that observed in the gingiva,[13] thus confirming the results by Salvi et al.[12] obtained in a younger patient sample.

IS BIOFILM-INDUCED PERI-IMPLANT MUCOSITIS A REVERSIBLE DISEASE?

Although a cause–effect relationship between experimental biofilm accumulation and the development of experimental peri-implant mucositis was claimed in the two studies mentioned previously,[10,11] the case for a true cause–effect relationship would be strengthened by the proof of reversibility to pre-experimental levels of mucosal health. In the study by Salvi et al.,[12] the GI at implant sites dropped significantly less compared with that at tooth sites following 3 weeks of reinstituted oral hygiene practices. Moreover, pre-experimental levels of GI were not reached at implant sites 21 days after reinstitution of self-performed biofilm control.[12] This indicated that resolution of experimental peri-implant mucositis in humans may take longer than 3 weeks (Table 1). In contrast to the study by Salvi et al.,[12] all clinical parameters assessed in an elderly patient sample (i.e., ≥70 years) returned to pre-experimental levels after 3 weeks of reinstituted biofilm control, thus documenting reversibility of experimentally induced peri-implant mucositis.[13]

Resolution of experimental peri-implant mucositis was achieved in both studies at the host biomarker level, as identified by the decrease to pre-experimental values of crevicular fluid pro-inflammatory biomarkers.[12,13] These outcomes[12,13] corroborated the findings of a study in which levels of interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta2 (TGF-β2) were determined in crevicular fluid samples of 25 subjects before and

after a 3-week period of abolished oral hygiene and after 69 days of re-established oral hygiene practices.[15] While TNF-α and TGF-β2 levels did not change during the experimental period, IL-1β yielded a significant increase after 3 weeks of abolished oral hygiene and was reversed to pre-experimental levels after 69 days.[15] Although the period of reinstituted oral hygiene was shorter at 3 weeks in the studies by Salvi et al.[12] and Meyer et al.,[13] IL-1β crevicular fluid levels returned to pre-experimental values, thus confirming the outcomes obtained by Schierano et al.[15]

EXPERIMENTAL PERI-IMPLANT MUCOSITIS MODELS VERSUS LONG-STANDING PERI-IMPLANT MUCOSITIS LESIONS

Experimental studies in humans and animals have demonstrated that *de novo* biofilm accumulation results in an inflammatory lesion within the peri-implant mucosa with migration of leukocytes through the barrier epithelium and the establishment of an inflammatory infiltrate with an increased proportion of T- and B-cells in the connective tissue adjacent to the barrier epithelium.[6,8,10,16]

Animal models

Experimental peri-implant mucositis models have evaluated the response of the peri-implant mucosa to both early (3 weeks) and long-standing (90 days) periods of undisturbed biofilm accumulation.[16,17] In these dog studies, comparisons were made between the response of the gingiva at teeth and the peri-implant mucosa at implants. Clinical examinations, biofilm sampling, and biopsies were obtained at both the early and long-standing inflammatory lesions. At 3 weeks there was abundant biofilm accumulation, and both the gingiva and the peri-implant mucosa showed clinical signs of inflammation. Histology showed an inflammatory cell infiltrate within the connective tissue which was found in the marginal portion of the soft tissues, immediately adjacent to the barrier epithelium at implants and the junctional epithelium at teeth.[16] In contrast, after a longer period (90 days) of undisturbed biofilm accumulation, the peri-implant mucositis lesions contained a smaller number of fibroblasts than the gingival counterparts, and the area occupied by the inflammatory infiltrate was greater in the peri-implant mucositis lesions than the gingivitis lesions, although it did not extend beyond the barrier epithelium.[17]

Ericsson et al.,[18] in an experimental dog study, obtained biopsies of peri-implant mucosa after 9 months of biofilm accumulation and showed an inflammatory infiltrate located within the marginal portion of the peri-implant mucosa. In another experimental study in the dog model, long-standing biofilm-associated lesions of 5 months duration were established in the peri-implant mucosa adjacent to three different implant systems.[19] The findings of this study confirmed that the size and apical extension of the inflammatory infiltrate did not extend beyond the barrier epithelium for all three implant systems used.

Human studies

Experimental studies in humans have evaluated the response to 3 weeks of biofilm accumulation, corresponding to the time frame of the experimental gingivitis study by Löe et al.,[14] where reversibility of the inflammatory lesion around teeth was demonstrated after reinstitution of biofilm control after 3 weeks. There are studies reporting on human biopsies of peri-implant tissues where long-standing peri-implant mucositis lesions were evaluated.[20,21] Gualini et al.[20] described the immunohistochemical features of peri-implant mucositis lesions obtained from 10 partially edentulous subjects with implants in function between 2 and 5 years. Clinically, the degree of redness and swelling of the inflamed tissues varied; however, all sites bled on gentle probing. In all biopsies the histologic sections showed a small and well-defined inflammatory infiltrate in the connective tissue lateral to the barrier epithelium. The lesions included 7.3% T-cells (CD3 positive) and 4.1% B-cells (CD19 positive). Elastase-positive polymorphonuclear neutrophils (PMN) occured within the barrier epithelium and in the connective tissue compartment immediately lateral to the barrier epithelium. The area of the inflammatory lesions corresponded to 0.36 mm^2, considerably larger than the size of the lesions observed in the experimental short-term (3 week) peri-implant mucositis study by Zitzmann et al.[11] and histologic samples taken mainly from clinically healthy sites.[6,8] These studies confirmed the findings of Seymour et al.[21] who also evaluated biospies of nine subjects with long-standing peri-implant mucositis and found an increase in size of the inflammatory lesion compared to clinically healthy sites.[21]

Peri-implant mucositis may be present for extensive periods of time without progression to peri-implantitis. Conversion of the peri-implant mucositis lesion to peri-implantitis in humans is difficult to study in an experimental design for obvious ethical reasons. However, in a longitudinal study of patients diagnosed with peri-implant mucositis, those with a lack of adherence to supportive peri-implant therapy had a higher incidence of peri-implantitis at 5 years.[22] Hence, sites with peri-implant mucositis should be considered at increased risk for the development of peri-implantitis.

RISK INDICATORS/FACTORS FOR PERI-IMPLANT MUCOSITIS

At a previous World Workshop on Periodontology the definition of a risk factor was agreed as, "an environmental, behavioral or biologic factor confirmed by temporal sequence, usually in longitudinal studies, which if present, directly increases the probability of a disease occurring and, if absent or removed reduces that probability."[23] To identify a true risk factor, prospective studies are required.[24–26] The majority of studies available are cross-sectional or retrospective in design and, therefore, in this review paper the term "risk" refers to a factor which is associated with peri-implant mucositis or a risk indicator.

TABLE 2 Evidence for factors as risk indicators for peri-implant mucositis

Risk indicator	Publication	Summary	Odds ratio (95% CI), multivariate analysis	Significance
Plaque biofilm presence	Roos-Jansaker et al.[28]	218 subjects, 9- to 14-year follow-up, multivariate analysis	1.9 (1.2 –2.9)	$P = 0.004$
Plaque score: poor = median plaque score > 1 and < 2	Ferreira et al.[30]	212 subjects all non-smokers, 6-month to 5-year follow-up, multinomial regression analysis	1.9 (1.2 – 2.3)	$P = 0.0021$
Plaque score: very poor = median plaque score ≥2	Ferreira et al.[30]	212 subjects all non-smokers, 6-month to 5-year follow-up, multinomial regression analysis	2.9 (2.0 – 4.1)	$P = 0.0027$
Full-mouth plaque score 0.30 – 0.43	Konstandinitis et al.[36]	186 subjects, minimum 5-year follow-up, multilevel analysis	1.15 (1.01 – 1.33)	$P < 0.04$
Full-mouth plaque score > 0.43	Konstandinitis et al.[36]	186 subjects, minimum 5-year follow-up, multilevel analysis	1.36 (1.18 – 1.58)	$P < 0.001$
Periodontal BOP > 30% sites affected	Ferreira et al.[30]	212 subjects all non-smokers, 6-month to 5-year follow-up, multinomial regression analysis	3.2 (2.0 – 3.3)	$P = 0.0025$
Presence of keratinized peri-implant mucosa	Roos-Jansaker et al.[28]	218 subjects, 9- to 14-year follow-up, multivariate analysis	1.6 (1.1 – 2.3)	$P = 0.008$
Smoking	Roos-Jansaker et al.[28]	218 subjects, 9- to 14-year follow-up, multivariate analysis	2.8 (1.2 – 6.2)	$P = 0.02$
Smoking	Karbach et al.[27]	100 subjects, 1- to 19-year follow-up, cancer patients, multivariate logistic regression analysis	3.0 (1.14 – 7.92)	$P = 0.26$
Smoking	Rinke et al.[29]	89 subjects, mean observation period 68.2 ± 24.8 months, multiple logistic regression analysis	3.77 (1.2 – 11.86)	$P = 0.023$
Radiation therapy	Karbach et al.[27]	100 subjects, 1- to 19-year follow-up, cancer patients, multivariate logistic regression analysis	2.9 (1.08 – 7.83)	$P = 0.035$
Male gender	Ferreira et al.[30]	212 subjects all non-smokers, 6-month to 5-year follow-up, multinomial regression analysis	1.7 (1.5 – 2.9)	$P = 0.0027$
Diabetes	Ferreira et al.[30]	212 subjects all non-smokers, 6-month to 5-year follow-up, significant association in univariate analysis but not in multinomial regression analysis	NA	NS
Time in function	Ferreira et al.[30]	212 subjects all non-smokers, 6-month to 5-year follow-up, significant association in univariate analysis but not in multinomial regression analysis	NA	NS
Time in function	Máximo et al.[33]	113 subjects, mean follow-up 3.4 years, weak correlation Pearson correlation coefficient (r = 0.44, $P = 0.0058$)	NA	NS

NA, not applicable; NS, not significant; CI, confidence interval

General risk indicators/factors

Factors which may affect host susceptibility to biofilm-induced peri-implant mucositis have been investigated. Cigarette smoking has been identified as a risk indicator for peri-implant mucositis in three studies (Table 2).[27–29] There is also evidence for radiation therapy as a risk indicator for peri-implant mucositis.[27] There is some evidence for diabetes mellitus as a risk indicator for peri-implant mucositis.[28,30] Poorly controlled diabetes mellitus (HbA1c levels > 10.1) was shown to be associated with increased bleeding on probing at implants.[31] While a history of cardiovascular disaease has been associated with an increased risk of peri-implantitis, there is no evidence for an association with peri-implant mucositis.[32] Máximo et al.[33] reported a significant but weak correlation (r = 0.44, Pearson χ^2 test) between peri-implant mucositis and increased time of loading of the implant. However, this study did not account for confounding factors, and the reported association may have been due to the increased time in function without regular removal of the biofilm.

Similarly, in a recent cross-sectional study conducted in 193 patients with implants in function for at least 12 months (range, 1 to 9 years), an association between peri-implant mucositis and age and time of prosthesis in function was reported.[34] However, a clear distinction between peri-implant mucositis and peri-implantitis was not described. Ferreira et al.[34] also reported an association with peri-implant mucositis and systemic disease. However, the systemic diseases described included "diabetes mellitus, hormonal changes, menopause, chemotherapy, thyroid alterations, cardiac problems, and alcohol use," and thus the results of the study are difficult to interpret.

Major local risk indicators/factors

Oral hygiene

Outcomes of cross-sectional clinical studies have clearly indicated that biofilm accumulation is associated with the presence of peri-implant mucositis around osseointegrated dental implants.[30,35,36] Ferreira et al.[30] reported on 212 patients treated with three different implant systems and diagnosed with peri-implant mucositis. All implants had been in function for a period ranging from 6 months to 5 years. The modified plaque index[37] was recorded, and the full-mouth plaque scores were stratified as good (median score ≤1), poor (median score > 1 and < 2), and very poor (median score ≥2). The authors reported a significant dose-dependent association between plaque scores and peri-implant mucositis. The prevalence of peri-implant mucositis was reported as 64.6% at patient level and 62.6% at implant level.[30] Outcomes of another study involving 218 patients with 999 implants in function for a period of 9 to 14 years indicated that plaque scores were significantly associated with the presence of peri-implant mucositis.[35]

Mechanical biofilm control should be considered the standard of care for management of peri-implant mucositis administered either by the patient[38] or the oral healthcare professional.[39]

Compliance/lack of compliance with supportive implant therapy (SIT)

Among patients not adhering to regular supportive implant therapy (SIT), peri-implant mucositis was reported to be a common finding with a prevalence of 48% during an observation period of 9 to 14 years.[28,35,40] Conversely, outcomes of a prospective cohort study with a 5-year follow-up indicated that implants placed in patients with treated periodontal conditions and adhering to an SIT program yielded a 20% prevalence of peri-implant mucositis.[41] In that study, upon diagnosis of peri-implant mucositis, all implants with the exception of one were successfully treated according to a cumulative anti-infective protocol.[42] Findings from a 3-month randomized placebo-controlled clinical trial revealed that mechanical debridement with or without local application of chlorhexidine gel in conjunction with optimal self-performed biofilm control completely resolved bleeding on probing around 38% of implants diagnosed with peri-implant mucositis.[43]

In partially edentulous patients, pre-existing peri-implant mucositis in conjunction with lack of adherence to SIT was associated with a higher incidence of peri-implantitis during a 5-year follow-up period.[22] The outcomes of that study yielded a 5-year incidence of peri-implantitis of 18.0% in the group of patients with SIT and of 43.9% in the group without SIT, respectively.[22] The logistic regression analysis revealed that lack of adherence to SIT within the overall patient sample was significantly associated with the onset of peri-implantitis with an odds ratio of 5.92.[22] Hence, therapy of peri-implant mucositis should be considered a prerequisite for the prevention of peri-implantitis.

Materials and surface characteristics of implant components

Evidence for the influence of implant surface roughness on the incidence of peri-implant mucositis in humans is limited.[44] A 12-month comparative analysis in humans between machined titanium abutments (Ra = 0.2 μm) and highly polished ceramic abutments (Ra = 0.0 6 μm) indicated that further reduction in surface roughness had no impact on bleeding on probing (BOP) scores.[45] A study in humans investigated the association between abutment surfaces of varying roughness and the early inflammatory response of the peri-implant mucosa.[46] Although a statistically significant difference among patients was observed with respect to biofilm accumulation on the abutment surfaces and inflammatory cells, no association was observed between the inflammatory response and abutment surface roughness after an observation period of 4 weeks.[46]

Compared with implants and abutments made of titanium, more beneficial properties in terms of biocompatibility have recently been claimed for implants and abutments made of zirconium dioxide (ZrO_2). It has to be noted, however, that in clinical studies no significant differences in BOP scores[47,48] or slightly higher BOP scores[49,50] were reported around ZrO_2 compared with titanium abutments.

Design of implant-supported prostheses

Accessibility for biofilm removal around implant-supported prostheses plays an important role in the prevention and management of peri-implant diseases. Implants with supramucosal restoration margins yielded significantly greater reductions in probing depths following treatment of peri-implant mucositis compared with those with submucosal restoration margins.[43] This finding corroborates previous observations on the association between subgingival restoration margins at natural teeth and periodontal inflammation and attachment loss.[51–53]

Outcomes of a clinical retrospective study indicated that high proportions of implants diagnosed with peri-implantitis were associated with inadequate biofilm control or lack of accessibility for oral hygiene measures, while peri-implantitis was rarely detected at implants supporting cleansible prostheses or when proper biofilm control was performed.[54] Consequently, oral hygiene instructions should be individually adapted to patients treated with dental

implants because peri-implant mucositis may be considered a precursor for peri-implantitis. Furthermore, whenever possible, margins of implant-supported prostheses should be placed at or above the peri-implant mucosal margin to facilitate access for biofilm control. Implant-supported reconstructions impairing access for biofilm removal should be adjusted or replaced by cleansible prostheses.

Dimensions of keratinized peri-implant mucosa

The effect of the dimensions of peri-implant keratinized mucosa as a risk indicator for peri-implant mucositis was investigated in several studies in humans. While some studies reported higher rates of peri-implant mucositis at implants lacking or surrounded by an inadequate width (<2 mm) of keratinized mucosa,[55–60] other studies found no association[61–63] or a postive association.[28] Collectively, evidence for the presence or minimum width of keratinized mucosa around implants to maintain soft tissue health and stability remains controversial. In clinical situations of adequate self-performed biofilm control around implants, presence or grafting of keratinized mucosa to maintain peri-implant health does not seem to be essential.

Excess cement

Excess cement has been associated with clinical signs of peri-implant mucositis.[44,64–66] Patients restored with single-unit crowns with excess cement displayed more signs of peri-implant mucositis compared with those restored with single-unit crowns without excess cement.[64] In addition, peri-implant mucositis was more prevalent in patients with cemented prostheses compared with those with screw-retained prostheses.[65] Therefore, to avoid cement excess, restoration margins should be located at or above the peri-implant mucosal margin or restorations should be cemented on individualized abutments allowing proper cement removal.

SIMILARITIES AND DIFFERENCES BETWEEN RISK INDICATORS/FACTORS FOR PERIODONTAL DISEASES VERSUS PERI-IMPLANT MUCOSITIS

A recent systematic review summarized potential risk indicators for peri-implant mucositis and identified biofilm accumulation and smoking as risk indicators.[44] In addition, a cross-sectional study showed that plaque score was a risk indicator for peri-implant mucositis in a dose-dependent manner (Table 2).[36] Data from the 2009–2012 National Health and Nutrition Examination Survey (NHANES) identified cigarette smoking as a modifiable risk indicator for all levels of periodontitis severity.[67] Uncontrolled diabetes, male gender, and age were also identified as risk indicators for periodontal disease.[67] Thus, there are similarities in risk indicators for peri-implant mucositis and periodontal disease, although there is still limited information available regarding risk for peri-implant mucositis.

Non–biofilm-induced mucositis conditions

Mucosal diseases such as oral lichen planus (OLP) have been suggested to negatively affect the ability of the epithelium to attach to titanium surfaces. Hence, it may be postulated that peri-implant mucosa affected by such conditions would also respond differently than a healthy peri-implant mucosa to a bacterial challenge, resulting in a faster breakdown of the peri-implant soft tissue seal. The prevalence of peri-implant mucositis was assessed in patients diagnosed with oral lichen planus (OLP) and compared with that of control patients.[68] The results indicated that the presence of OLP was not associated with a higher prevalence of peri-implant mucositis.[68] These results were confirmed in a cross-sectional study failing to report significant differences in the prevalence of peri-implant mucositis in patients with dental implants and diagnosed with or without OLP.[69] However, in patients diagnosed with OLP and gingival desquamation, a significantly higher prevalence of peri-implant mucositis was observed.[68] This higher prevalence of peri-implant mucositis reported in the study by Hernandez et al.[68] may be associated with higher plaque scores, with the stomatologic condition per se or with both.

It has been suggested that susceptible patients may suffer from allergic/adverse reactions to materials such as titanium and titanium alloys;[70] however, the evidence remains very limited.[71]

CONCLUSIONS

Peri-implant mucositis is an inflammatory lesion of the peri-implant mucosa in the absence of continuing marginal bone loss. Peri-implant mucositis is primarily caused by a disruption of the host–microbe homeostasis at the implant–mucosa interface and is a reversible condition at the host biomarker level. Optimal biofilm control in experimental peri-implant mucositis studies may take longer than 3 weeks for complete resolution at the clinical level. Factors associated with peri-implant mucositis include biofilm accumulation, smoking, and radiation therapy. Regular supportive peri-implant therapy with biofilm removal is an important preventive strategy against the conversion of health to peri-implant mucositis and also against the progression of peri-implant mucositis to peri-implantitis.

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2017 WORLD WORKSHOP

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Peri-implantitis

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Abstract

Objectives: This narrative review provides an evidence-based overview on peri-implantitis for the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.

Methods: A literature review was conducted addressing the following topics: 1) definition of peri-implantitis; 2) conversion from peri-implant mucositis to peri-implantitis, 3) onset and pattern of disease progression, 4) characteristics of peri-implantitis, 5) risk factors/indicators for peri-implantitis, and 6) progressive crestal bone loss in the absence of soft tissue inflammation.

Conclusions:

1) Peri-implantitis is a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone.
2) The histopathologic and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood.
3) The onset of peri-implantitis may occur early during follow-up and the disease progresses in a non-linear and accelerating pattern.

4a) Peri-implantitis sites exhibit clinical signs of inflammation and increased probing depths compared to baseline measurements.

4b) At the histologic level, compared to periodontitis sites, peri-implantitis sites often have larger inflammatory lesions.

4c) Surgical entry at peri-implantitis sites often reveals a circumferential pattern of bone loss.

5a) There is strong evidence that there is an increased risk of developing peri-implantitis in patients who have a history of chronic periodontitis, poor plaque control skills, and no regular maintenance care after implant therapy. Data identifying "smoking" and "diabetes" as potential risk factors/indicators for peri-implantitis are inconclusive.

5b) There is some limited evidence linking peri-implantitis to other factors such as: post-restorative presence of submucosal cement, lack of peri-implant keratinized mucosa and positioning of implants that make it difficult to perform oral hygiene and maintenance.

6) Evidence suggests that progressive crestal bone loss around implants in the absence of clinical signs of soft tissue inflammation is a rare event.

KEYWORDS

diagnosis, implantology, peri-implantitis, systematic reviews and evidence-based medicine

INTRODUCTION

Biological complications affecting osseointegrated implants are a topic of major interest in contemporary dentistry. Such complications mainly refer to inflammatory conditions associated with a bacterial challenge.[1–3] Two clinical varieties may be distinguished: peri-implant mucositis and peri-implantitis. While the presence of an inflammatory lesion is a feature both conditions have in common, only the latter form presents with loss of supporting bone.[4] It is anticipated that mucositis precedes peri-implantitis.[3]

This review addresses the following topics: 1) definition of peri-implantitis; 2) conversion from peri-implant mucositis to peri-implantitis, 3) onset and pattern of disease progression, 4) characteristics of peri-implantitis, 5) risk factors/indicators for peri-implantitis, and 6) progressive crestal bone loss in the absence of soft tissue inflammation.

METHODS

Search strategy and data extraction

An electronic and manual search was conducted for each of the addressed topics. The PubMed database of the US National Library of Medicine, the Excerpta Medica database (Embase) by Elsevier, and the Web of Knowledge of Thomson Reuters were screened for relevant articles (i.e. experimental studies in animals and humans/ observational studies, randomized/ controlled clinical studies, systematic reviews/ meta-analyses, consensus reports). Data from identified and relevant publications were extracted and, if indicated, presented in evidence tables. Overall findings were summarized in a narrative manner.

OBSERVATIONS AND DISCUSSION

Current definition of peri-implantitis

Peri-implantitis is a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and progressive loss of supporting bone.[1,4]

In the clinical setting, soft tissue inflammation is detected by probing (bleeding on probing, BOP), while progressive bone loss is identified on radiographs. Studies on peri-implantitis require case definitions and threshold values to distinguish 1) health from disease and 2) mucositis from peri-implantitis. It should be noted that, while case definitions for peri-implantitis vary considerably between studies,[5] the definition of the disease remains.

Conversion from peri-implant mucositis to peri-implantitis

Mirroring the progression of gingivitis to periodontitis, peri-implant mucositis is assumed to precede peri-implantitis.[3] Currently, features or conditions characterizing the conversion from peri-implant mucositis to peri-implantitis have not been identified.

The peri-implant soft tissue reactions to plaque formation have been extensively evaluated in both animal[6–13] and human studies.[14–16] Thus, plaque formation consistently resulted in an inflammation of the peri-implant soft tissues,[14–16] associated with clinical signs of inflammation, such as redness and edema.[7]

Zitzmann et al. (2002) examined human biopsies after a plaque formation period of 21 days.[13] The histologic analysis revealed the establishment of a B and T cell-dominated inflammatory cell infiltrate (ICT) in the soft tissue lateral to the barrier epithelium, occupying an area of approximately 0.14 mm[2,16]

Similar findings were made in animal studies, presenting with a varying apical extension of the inflammatory lesion.[7,9,10,12] At most of the implant sites investigated, the lesion was located lateral to the barrier epithelium and separated from the crestal bone by a zone of healthy connective tissue. However, at some sites in one study, the subepithelial connective tissue was infiltrated with inflammatory cells (i.e. CD68 positive cells), thus decreasing the zone of healthy connective tissue above the peri-implant bone.[7] At 16 weeks of plaque formation, the distance between the apical extension of the ICT and the crestal bone varied between 1.0 and 1.9 mm. At only one implant site did the ICT reach the crestal bone.[7] The exact histopathologic mechanisms resulting in apical extension of the ICT and associated crestal bone loss have yet to be determined.

Clinically, the conversion from mucositis to peri-implantitis was evaluated in one retrospective observational study including 80 patients initially suffering from peri-implant mucositis.[17] Over 5 years, the incidence of peri-implantitis was lower in subjects enrolled in a regular maintenance program (18%) than among patients without regular maintenance care (43%). In the "maintained" group, "BOP+ at >50% of all implant sites" (OR 37) and "probing depth (PD) ≥4 mm at >5% of sites" (OR 20) were associated with peri-implantitis. In the "not maintained" group, the associated factors were PD (OR 26) and the presence of periodontitis (OR 11). In the entire patient group, the conversion to peri-implantitis was correlated with BOP (OR 18) and PD scores (OR 16), the lack of regular maintenance therapy (OR 6), as well as the presence of periodontitis (OR 9).

The histopathologic and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood.

Onset and pattern of disease progression

Progression of experimentally induced peri-implantitis

The so-called "ligature model" is often used to study experimental peri-implantitis in animals.[18,19] The protocol comprises a phase of active tissue breakdown around osseointegrated implants, including plaque formation and placement of ligatures in a submucosal position.[20] The ligature breaks the mucosal seal to the implant and promotes submucosal bacterial biofilm formation. The ensuing inflammatory lesion initiates tissue destruction, including bone loss. Also

after the removal of the ligatures and under continuous plaque formation, progression of disease may occur.[22] This model thus mimics naturally occurring peri-implantitis. When compared to experimentally induced periodontitis, lesions associated with experimental peri-implantitis demonstrate larger inflammatory cell infiltrates and more rapid and pronounced bone loss.[21] After a period of several weeks of plaque formation subsequent to ligature removal, spontanoues progression of peri-implantitis was associated with severe inflammation and tissue destruction.[22] Disease progression was influenced by implant surface characteristics with more pronounced breakdown at implants with modified than with non-modified surfaces.[21,23]

Clinical studies on onset and progression of peri-implantitis

Prospective studies evaluating onset and progression of naturally occurring peri-implantitis could not be identified and are for obvious ethical reasons not feasible. However, retrospective observational studies employing *multilevel growth curve models* provided statistical estimates on onset and pattern of peri-implantitis associated bone loss.[24,25] Fransson et al. evaluated 182 patients with a total of 419 implants (machined/turned surfaces, no bone grafting procedures, fixed restorations) that presented with progressive bone loss.[25] For these implants, bone levels were assessed using intra-oral radiographs obtained between the 1-year examination and a follow-up period of 5 to 23 years (mean: 11.1 years). The average bone loss was 1.7 mm and cumulative percentages of implants with bone loss ≥1 mm, ≥2 mm, or ≥3 mm were 68%, 32% and 10%, respectively. A multilevel growth curve model revealed that the pattern of bone loss was non-linear, accelerating and demonstrating an increased variance over time that was attributed to subject heterogeneity. This was confirmed in a retrospective analysis by Derks et al.[24] Results indicated that the onset of peri-implantitis may occur early, as the majority of implants demonstrated first signs of bone loss (>0.5 mm) already after the second (52%) and third year (66%) in function.[24] At the subject level, these calculations amounted to 70% and 81%, respectively.

When evaluating the above studies, it must be kept in mind that the onset of peri-implantitis was estimated on the basis of radiographic bone loss alone, not considering other clinical parameters.[24,25] Nevertheless, these analyses suggest that peri-implantitis may commence early during follow-up and that the progression of peri-implantitis appears to be faster than what is observed in periodontitis.[26–28]

The concept of a potentially early onset of peri-implantitis is further supported by findings from studies evaluating peri-implant conditions already after comparatively short follow-up periods (≤2 years). A cross-sectional analysis of 238 patients with a total of 512 implants revealed that peri-implantitis (case definition: BOP+ and changes in radiographic bone level compared to baseline) was frequently noted in all implant age groups investigated.[29] At the implant level, its frequency amounted to n = 18 at 1 to 12 months of follow-up, n = 34 at 12 to 48 months and n = 12 at >48 months, respectively. For the diagnosis of peri-implant mucositis, the number of affected implants in respective age groups was n = 25, n = 157 and n = 32, respectively. Becker et al. recently studied the incidence of biological complications at zirconia implants over a 2-year period in 52 patients.[30] BOP values significantly increased from 21% at baseline (i.e. 10 to 12 weeks after implant placement) to 38% and 64% at 6 and 12 months, respectively. Based on the given case definition (BOP+ and changes in the radiographic bone level compared to baseline), 18 patients were diagnosed with initial peri-implantitis between 12 and 24 months.[30]

Characteristics of peri-implantitis

Histopathologic characteristics of naturally occurring peri-implantitis

The histopathologic features of naturally occurring peri-implantitis lesions have been extensively assessed in human biopsy materials.[31–39]

When compared with peri-implant mucositis, the lesions at peri-implantitis sites (case definition: BOP+, suppuration, radiographic bone loss) harbored more neutrophil granulocytes and larger "proportions of B cells (CD19+)".[35] Similar to periodontitis, the lesions at peri-implantitis sites were also dominated by plasma cells and lymphocytes,[33,34,36] but characterized by larger proportions of polymorphonuclear leukocytes and macrophages.[31,38] Recently, it was also shown that the size of peri-implantitis lesions (case definition: interproximal implant sites with BOP+ and PD ≥7 mm) was more than twice as large as that noted at periodontitis sites (3.5 mm^2 vs. 1.5 mm^2).[39] Moreover, peri-implantitis lesions were characterized by larger area proportions, numbers and densities of plasma cells, macrophages and neutrophils, as well as a higher density of vascular structures outside and lateral to the cell infiltrate.[39] Another study using immunohistochemical analysis of harvested soft tissue biopsies showed that IL-1α was a dominant osteoclast activating cytokine at peri-implantitis sites.[37] It must be emphasized that the above analyses of human peri-implant tissue biopsies did, for ethical reasons, not include the osseous component of the sites.

Microbiologic and immunologic characteristics of naturally occurring peri-implantitis

Using conventional DNA probe and cultural analyses, common periodontopathogenic bacteria have been isolated at both healthy and diseased implant sites,[40] and the distribution of the detected species did not markedly differ by clinical implant status (i.e. healthy, peri-implant mucositis, peri-implantitis).[41] However, when compared with healthy implant sites alone, peri-implantitis was associated with higher counts of 19 bacterial species, including *Porphyromonas gingivalis* and *Tannerella forsythia*.[42] Moreover, observational studies have indicated that peri-implantitis was more frequently linked with opportunistic pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* (*S. aureus*),[43,44] fungal organisms (e.g. *Candida albicans*, *Candida boidinii*, *Penicillum spp*., *Rhadotorula laryngis*, *Paelicomyces spp*.),[43,45,46] and viruses (i.e. human cytomegalovirus, Epstein-Barr virus),[47] thus pointing to a rather complex and heterogenous infection.[48,49] It should be

emphasized that the submucosal microbiota of peri-implantitis lesions have not been extensively studied using culture-independent techniques. Thus, the microbial picture associated with peri-implantitis should be regarded as incomplete.

Most recent systematic reviews have focused on the correlations between various cytokines (i.e. proinflammatory/ anti-inflammatory/ osteoclastogenesis-related) and chemokines measured in the peri-implant crevicular fluid (PICF) and the clinical condition at implant sites.[50,51] Most of the included studies focused on the assessment of IL-1β and tumor necrosis factor alpha (TNF-α). Based on a meta-analysis,[50] the release of IL-1β was reported to be significantly increased at mucositis and peri-implantitis sites, when compared with healthy implant sites. However, no significant difference in IL-1β levels was noted between peri-implant mucositis and peri-implantitis sites. Peri-implantitis sites were also associated with a significant increase in TNF-α levels over healthy implant sites.[50] In contrast, the majority of included studies failed to identify any significant differences in the levels of either IL-4, IL-10, or osteoclastogenesis-related (RANKL) cytokines between healthy and peri-implantitis sites.[51] Accordingly, the systematic reviews indicated that the assessment of proinflammatory cytokines (mainly IL-1β) in the PICF might be of beneficial value to differentiate between peri-implant health and disease, but inappropriate to determine the onset of peri-implantitis.

Clinical characteristics of naturally occurring peri-implantitis

Clinical signs of inflammation including redness, edema, mucosal enlargement, BOP+ with or without suppuration along with increases in PD and radiographic bone loss are commonly used in case definitions for peri-implantitis.[31,33–39]

Implant sites diagnosed with peri-implantitis commonly show increased PD. In a study evaluating 588 patients with 2,277 implants after a function time of 9 years, PD ≥6 mm was recorded at 59% of all implants presenting with moderate/severe peri-implantitis (case definition: BOP+ and bone loss >2 mm).[52] Out of the implants classified as healthy (case definition: BOP-) or diagnosed with mucositis (case definition: BOP+ but no bone loss >0.5 mm), 3% and 16% showed PD ≥6 mm, respectively. It was also noted that the frequency of implants demonstrating PD ≥6 mm increased with increasing severity of peri-implantitis.

In a cross-sectional analysis, Schwarz et al. evaluated a total of 238 patients (n = 512 implants) after a median function time of 23 months (1 to 80 months).[29] At peri-implant mucositis sites (case definition: BOP+ on at least one aspect of the implant), the frequency of BOP scores mainly ranged between 33% and 50%, while the peak was 67% at peri-implantitis sites (case definition: BOP+ and/or suppuration and changes in the radiographic bone level compared to baseline). Diseased implant sites were associated with higher frequencies of 4 to 6 mm PD than implants with a healthy peri-implant mucosa, with an equal distribution between mucositis and peri-implantitis sites. PD values of ≥7 mm were only observed at one implant diagnosed with peri-implantitis.[29]

In this context, it must be realized that the determination of what constitutes a physiological PD at implant sites is difficult. A recent analysis described a high degree of variation in the vertical mucosal thickness measured at healthy implant sites, ranging from 1.6 to 7.0 mm (i.e. mucosal margin to the crestal bone level).[53] One cross-sectional analysis also evaluated and compared the horizontal mucosal thickness (hMT) at healthy and diseased implant sites. Median hMT were significantly increased at diseased-, when compared with healthy implant sites (1.1 mm), but were similar at mucositis and peri-implantitis sites (i.e. 1.7 vs. 1.6 mm), respectively. In all groups investigated, these values did not markedly differ by implant location (i.e., upper/lower jaws) or position (i.e., anterior/posterior sites).[54]

Several consensus statements pointed towards suppuration as a common finding at sites diagnosed with peri-implantitis.[1,4] One study examined 197 implants in 97 patients demonstrating progressive bone loss on radiographs.[55,56] The authors compared these implants with 285 implants in the same patients not exhibiting bone loss. It was observed that, while 94% of the implants presenting with bone loss also were positive for BOP, suppuration on probing was identified at 19%. Only 5% of implant sites without bone loss showed suppuration.

Clinical studies also reported on the configuration of peri-implantitis defects.[57–59] In 79% of all sites investigated, naturally occurring peri-implantitis lesions featured a combined supra- (Class II) and intrabony (Class I) defect configuration.[58] The intrabony component most frequently (55%) exhibited circumferential bone loss with maintenance of the buccal and lingual contours of the supporting crestal bone (i.e. Class Ie). This was followed by buccal dehiscence-type defects revealing a semicircular defect to the middle of the implant body (i.e. Class Ib) (16%), and buccal dehiscence-type defects with circular bone resorption in the presence (i.e. Class Ic) (13%), or absence (i.e. Class Id) (10%) of the lingual bone plate. The lowest frequency was noted for isolated buccal dehiscence-type defects (i.e. Class Ia) (5%).[58] Similar intraoperative findings were also reported by Serino et al.[57] The majority (66%) of the implants investigated (n = 59) exhibited a uniform bone loss at all four aspects.[57] The remaining peri-implantitis defects mainly featured a more advanced bone loss at the buccal site. These data were recently confirmed in a cross-sectional analysis, also pointing to an uniform bone loss at all four implant aspects with a high frequency of Class Ie defects (15/46, 33%).[59] Based on the above studies, it is assumed that peri-implantitis lesions commonly progress circumferentially around the affected implants.

Studies reporting on clinical characteristics of implants diagnosed with peri-implantitis are summarized in Table 1.

Periapical peri-implantitis

Apart from peri-implant infections at sites with deepened probing depths, a number of case series also reported on the occurrence of periapical peri-implantitis lesions. The affected implants were commonly characterized by a periapical radiographic radiolucency with or without concomitant clinical signs of inflammation, such as redness, edema, fistula and/ or abscess formation.[60–72] These clinical and radiographic

TABLE 1 Clinical characteristics of peri-implantitis

Study	Type of study	Study sample	Case definition/inclusion criteria	Findings
Fransson et al. 2005[56] and 2008[55]	Cross-sectional 5 to 20 years mean: 9.4 years	82 patients 197 implants identified with progressive bone loss 285 implants with no progressive bone loss	Progressive bone loss Bone level ≥3 threads & bone loss >0.6 mm	Clinical examination PD ≥6 mm/Suppuration (% of implants) No progressive bone loss: 12%/5% Progressive bone loss: 35%/19%
Schwarz et al. 2007[58]	Cross-sectional	24 patients 40 implants diagnosed with moderate to advanced peri-implantitis	Case definition PD >6 mm BOP/SUP+ Bone loss	Intraoperative assessment Combination of intrabony and supracrestal defects; circumferential-type intrabony defects most frequent (55.3%).
Serino et al. 2013[57]	Cross-sectional	29 patients 89 implants diagnosed with peri-implantitis	Case definition PD >4 mm BOP/SUP+ Bone loss ≥2 mm	Clinical examination and intraoperative assessment Circumferential-type bone defects most frequent (66.0%).
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 137 patients diagnosed with mucositis 62 patients diagnosed with moderate/severe peri-implantitis	Case definition BOP/SUP+ Bone loss >2 mm	Clinical examination PD ≥6 mm (% of implants) Healthy: 3% Mucositis: 16% Moderate/severe peri-implantitis: 59%
Garcia-Garcia et al. 2016[59]	Cross-sectional	25 patients 46 implants diagnosed with peri-implantitis	Case definition BOP/SUP+ Bone level >2 mm	Radiographic and intraoperative assessment Circumferential-type intrabony defects most frequent (32.6%).
Schwarz et al. 2017[54]	Cross-sectional	60 patients 229 implants diagnosed with moderate to advanced peri-implantitis	Case definition BOP/SUP+ Bone loss	Clinical assessment with validated ultrasonic A-sacnner Horizontal mucosal thickness (median) Healthy sites 1.1 mm Mucositis: 1.7 mm Peri-implantitis: 1.61 mm
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients 216/512 implants diagnosed with mucositis 46/512 implants diagnosed with peri-implantitis	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	Clinical examination Higher BOP scores at peri-implantitis sites when compared to mucositis sites. Similar PD scores.

signs of inflammation were noted between 2 to 8 weeks[68,71] and up to 4 years[65] after implant placement. The majority of the studies reported a direct correlation between retrograde peri-implantitis and the existence of periapical endodontic lesions at adjacent teeth.[61–63,65,67,68,70,72]

Oral-mucosal lesions mimicking peri-implantitis

Case reports have described a variety of oral-mucosal lesions at dental implants that may mimic peri-implant diseases. Such lesions include primary malignant tumors (i.e. oral squamous cell carcinoma)[73–76] or metastases[77] as well as giant cell and pyogenic granuloma.[78–86]

While these pathologic conditions share several clinical features with peri-implant diseases, they reveal distinct differences to a non-specific inflammation at the histopathologic level.[86]

Risk factors/indicators for peri-implantitis

Interventional studies of longitudinal design are required to identify true risk factors for a disease. Observational studies, cross-sectional or retrospective in nature, may only describe risk indicators.

In the following text, potential risk factors/indicators with substantial evidence are addressed in dedicated sections, while factors with limited evidence are summarized under "Areas of future research".

History of periodontitis

Periodontitis is a common disease. Its severe form ranks 6th among the most prevalent disorders.[87] In a recent survey carried out in the United States, Eke et al. reported that roughly 50% of the adult population (aged ≥30 years) presented with periodontitis.[88] In individuals aged ≥65 years, the corresponding number was 68%. Studies reporting on the potential association between history of periodontitis (chronic or aggressive) and peri-implantitis are described in Table 2.

In two 10-year longitudinal studies, peri-implantitis was assessed and correlated with a history of periodontitis. Karoussis et al. provided implant therapy to 45 patients without a history of periodontitits.[89] A total of eight patients were treated with implants after having successfully completed periodontal therapy. The 10-year incidence of peri-implantitis (case definition: PD ≥5 mm, BOP+ and annual bone loss >0.2 mm) in the non-periodontitis group was 6% (implant level) compared to 29% in subjects with a history of periodontitis. Roccuzzo et al. followed 101 patients provided with dental implants after having been categorized as 1) periodontally not compromised, 2) moderately compromised and 3) severely compromised.[90,91] The authors reported that both the frequency of implant sites demonstrating PD ≥6 mm (2%, 16%, 27%, respectively) and bone loss ≥3 mm (5%, 11%, 15%, respectively) differed significantly between groups. The results also showed that treatment of peri-implantitis was more time consuming in patients with a history of periodontitis. In a follow-up study of 80 patients presenting with mucositis at baseline, the incidence of peri-implantitis over 5 years was assessed by Costa et al.[17] The authors observed an overall incidence of peri-implantitis of 31%. Patients suffering from periodontitis at the final examination had significantly higher odds to also have developed peri-implantitis when compared to individuals without periodontitis (OR 9).

A number of cross-sectional studies reported on prevalence of peri-implantitis and analyzed associations with either a history of periodontitis or current periodontitis. In a study including 216 patients were evaluated 9 to 14 years after implant therapy, Roos-Jansåker et al. reported that implants placed in patients with a history of periodontits had significantly higher odds (OR 5) for peri-implantitis when compared to implants in patients without.[92,93] Koldsland et al. reported similar findings after examining 109 subjects with 1 to 16 years of follow-up.[94,95] Thus, patients with a history of periodontitis were found to be at higher risk for peri-implantitis (OR 6). Several subsequent studies confirmed this association with varying degrees of strength.[96–100] Other studies correlated current periodontitis with peri-implantitis, also reporting strong associations.[52,101,102] In fact, Daubert et al. found that severe periodontitis at follow-up was the strongest indicator for peri-implantitis of all variables examined, presenting with an unadjusted risk ratio of 7.[101] Derks et al., in a 9-year follow-up including 588 patients reported an odds ratio of 4 for patients with current periodontitis.[52]

While the majority of publications is in general agreement when examining the association between periodontitis and peri-implantitis, it should also be noted that conflicting reports exist.[29,103–106] Thus, Marrone et al. examined 103 patients with implant-supported restorations in function for at least 5 years.[103] Neither current periodontitis nor history of periodontitis were statistically significant predictors for peri-implantitis. Also Rokn et al., in a cross-sectional study on 134 patients failed to demonstrate a higher risk for peri-implantitis in patients with a history of periodontitis.[104] Disagreement between studies may be explained by differences in case definitions for 1) (history of) periodontitis and 2) peri-implantitis (see Table 2).

Conclusion: There is strong evidence from longitudinal and cross-sectional studies that a history of periodontitis constitutes a risk factor/indicator for peri-implantitis.

Smoking

Smoking has been strongly associated with chronic periodontitis, attachment loss as well as tooth loss,[107,108] Studies reporting on the potential association between smoking and peri-implantitis are described in Table 3.

Lindquist et al. reported that smokers presented with substantially more crestal bone loss than non-smokers.[109] In line with this observation, several subsequent studies observed a strong association between smoking and peri-implantitis. In a 10-year cohort study, Karoussis et al. found that 18% of all implants in smokers developed peri-implantitis, while only 6% of implants in non-smokers were affected.[89] Three cross-sectional studies confirmed these findings, reporting odds ratios of 32,[110] 3,[30] and 5,[93] respectively.

The majority of publications, however, failed to identify smoking as a risk factor/indicator for peri-implantitis. Aguirre-Zorzano et al.

TABLE 2 History of periodontitis and peri-implantitis

Study	Type of study	Study sample	History of periodontitis	Peri-implantitis	Association
Karoussis et al. 2003[89]	Cohort study 8-12 years	53 patients 8 patients with history of periodontitis 45 patients with no history of periodontitis	Case definition for periodontitis not specified. Successfully treated prior to implant therapy.	Case definition PD ≥5 mm BOP+ Annual bone loss >0.2 mm	10-year incidence of peri-implantitis (implant level) History of periodontitis: 28.6% No history of periodontitis: 5.8%
Ferreira et al. 2006[102]	Cross-sectional 0.5-5 years mean: 3.5 years	212 patients 30 patients with current periodontitis 182 patients with no current periodontitis	Case definition ≥4 teeth with PD ≥4 mm and CAL ≥3 mm (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) Periodontitis: OR 3.1
Roos-Jansåker et al. 2006[92,93]	Cross-sectional 9-14 years mean: 11.0 years	216 patients Number of patients with/without history of periodontitis not reported	Case definition % remaining teeth with bone loss ≥4 mm (prior to implant therapy) Categories: 0-30% and 31-100%	Case definition BOP/SUP+ Bone loss ≥1.8 mm	Odds for peri-implantitis (implant level) History of periodontitis: OR 4.7
Máximo et al. 2008[100]	Cross-sectional ≥1 year mean: 3.4 years	113 patients 33 edentulous patients 21 patients with no history of periodontal bone loss 59 patients with history of periodontal bone loss	Case definition Number of quadrants showing crestal bone loss (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level ≥3 threads	Peri-implantitis most common in patients presenting with periodontal bone loss in all 4 quadrants.
Koldsland et al. 2010[94] & 2011[95]	Cross-sectional 1-16 years mean: 8.4 years	103 patients 24 patients with history of periodontitis (6 patients with current periodontitis) 77 patients with no history of periodontitis	Case definition for current periodontitis ≥2 teeth with PD ≥5 mm, BOP % bone loss ≥6 mm (at final examination) Definition for history of periodontitis Tooth loss due to periodontitis and bone loss ≥4 mm at ≥30% of remaining teeth.	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	Odds for peri-implantitis (implant level) History of periodontitis: OR 6.2
Roccuzzo et al. 2010[91] & 2012[90]	Cohort study 10 years	101 patients 28 patients not periodontally compromised 37 patients moderately compromised 36 patients severely compromised	Case definition for periodontitis not specified. Based on clinical examination at baseline. Periodontally compromised patients categorized according to number and depth of periodontal pockets.	Case definition for peri-implantitis not reported. Number of sites with increased PD and bone loss as well as patients treated for peri-implantitis by means of systemic antibiotics and/or surgery are presented.	Association between (i) % of sites with PD ≥6 mm, (ii) % of sites with bone loss ≥3 mm, (iii) % of patients treated for peri-implantitis and baseline periodontal status.
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	203 patients Number of patients with/without history of periodontitis not reported	Case definition for periodontitis not specified. Patient-reported.	Case definition PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.
Costa et al. 2012[17]	Cohort study 5 years	80 patients with mucositis 28 patients with current periodontitis 52 patients with no current periodontitis	Case definition ≥4 teeth with PD ≥4 mm and CAL ≥3 mm (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) Periodontitis: OR 9.2

(Continues)

TABLE 2 (Continued)

Study	Type of study	Study sample	History of periodontitis	Peri-implantitis	Association
Casado et al. 2013[96]	Cross-sectional 1-8 years mean: 5.6 years	215 patients 88 with history of periodontitis 127 with no history of periodontitis	Case definition Bone loss and PD ≥4 mm at ≥30% of remaining sites (prior to implant therapy). Patient records.	Case definition BOP+ Annual bone loss >0.2 mm (1 mm for first year)	Odds for peri-implantitis (patient level) History of periodontitis: OR 4.0
Marrone et al. 2013[103]	Cross-sectional 5-18 years mean: 8.5 years	103 patients 62 patients with history of periodontitis (15 patients with current periodontitis) 41 patients with no history of periodontitis	Case definition for current periodontitis BOP ≥25% & PD ≥5 mm (at final examination). Definition for history of periodontitis not reported.	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Renvert et al. 2014[98]	Cross-sectional mean: 10.1 years	270 patients 137 with history of periodontitis 133 with no history of periodontitis	Case definition for periodontitis not specified. Based on patient records, interview and clinical examination.	Case definition PD ≥4 mm BOP/SUP+ Bone level >2 mm	Odds for peri-implantitis (patient level) History of periodontitis: OR 4.5
Daubert et al. 2015[101]	Cross-sectional 9-15 years mean: 10.9 years	96 patients Number of patients with current severe periodontitis not reported	Severe periodontitis defined as the presence of periodontitis with attachment loss ≥5 mm (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	Risk for peri-implantitis (implant level) Severe periodontitis: RR 7.3
de Araujo Nobre et al. 2015[97]	Case-control ≥1 year	1275 patients 198/255 cases with history of periodontitis 57/1020 controls with history of periodontitis	Tooth loss due to periodontitis.	Case definition PD ≥5 mm BOP+ Bone loss ≥2 mm	Odds for peri-implantitis (patient level) History of periodontitis: OR 19.0
Canullo et al. 2016[105]	Cross-sectional mean: 5.1 years	534 patients 140 patients with current periodontitis 394 patients with no current periodontitis	Case definition >30% of remaining teeth with BOP, presence of PD ≥4 mm and bone loss (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone level >3 mm	No association.
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 140 patients with current periodontitis 352 patients with not current periodontitis 96 edentulouspatients	Case definition ≥2 teeth exhibiting BOP/SUP+, attachment loss ≥2 mm and PD ≥6 mm (at final examination)	Case definition BOP/SUP+ Bone loss >2 mm	Odds for peri-implantitis (patient level) Periodontitis: OR 4.1
Rokn et al. 2017[104]	Cross-sectional 1-11 years mean: 4.4 years	134 patients 17 patients with history of periodontal treatment 117 patients with no history of periodontal treatment	Case definition for periodontitis not specified.	Case definition BOP/SUP+ Bone level >2 mm	No association.
Dalago et al. 2017[99]	Cross-sectional 1-14 years	183 patients 33 patients with history of periodontitis 150 with no history of periodontitis	Case definition Tooth loss, bone loss >5 mm, mobility degree III and/or PD >4 mm (prior to implant therapy)	Case definition PD >5 mm BOP/SUP+ Bone level >2 mm	Odds for peri-implantitis (implant level) History of periodontitis: OR 2.2
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients 39 with history of periodontitis 199 with no history of periodontitis	Case definition for periodontitis not specified.	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	No association.

TABLE 3 Smoking and peri-implantitis

Study	Type of study	Study sample	Smoking	Peri-implantitis	Association
Karoussis et al. 2003[89]	Cohort study 8-12 years	53 patients 41 non-smokers 12 smokers	Patient-reported Smoker: smoking at time of implant installation.	Case definition PD ≥5 mm BOP+ Annual bone loss >0.2 mm	Incidence of peri-implantitis (implant level) Non-smokers: 6.0% Smokers: 17.9%
Roos-Jansåker et al. 2006[92,93]	Cross-sectional 9-14 years mean: 11.0 years	216 patients Number of smokers/former smokers not reported.	Patient-reported Smoker: smoking at final examination.	Case definition BOP/SUP+ Bone loss ≥1.8 mm	Odds for peri-implantitis (implant level) Smoking OR 4.6
Máximo et al. 2008[100]	Cross-sectional ≥1 year mean: 3.4 years	113 patients 60 never-smokers 32 former smokers 21 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD ≥5 mm BOP/SUP+ Bone level ≥3 threads	No association.
Koldsland et al. 2010[94] & 2011[95]	Cross-sectional 1-16 years mean: 8.4 years	103 patients 87 non-smokers 16 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	No association.
Rinke et al. 2011[110]	Cross-sectional 2-11 years mean: 5.7 years	89 patients 72 non-smokers 17 smokers	Patient-reported Smoker: smoking at final examination and former smokers (cessation <5 years).	Case definition PD ≥4 mm BOP+ Bone loss ≥3.5 mm	Odds for peri-implantitis (patient level) Smoker: OR 31.6
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	203 patients Number of smokers not reported.	Patient-reported Smoker: smoking at final examination.	Case definition PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.
Casado et al. 2013[96]	Cross-sectional 1-8 years mean: 5.6 years	215 patients 194 non-smokers 21 smokers	Patient-reported Smoker: smoking at final examination.	Case definition BOP+ Annual bone loss >0.2 mm (1 mm for first year)	No association.
Marrone et al. 2013[103]	Cross-sectional 5-18 years mean: 8.5 years	103 patients 83 non-smokers 20 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Renvert et al. 2014[98]	Not reported	270 patients 155 non-smokers 110 smokers	Patient-reported Smoker: smoking at final examination and former smokers (cessation ≤10 years).	Case definition PD ≥4 mm BOP/SUP+ Bone level >2 mm	Signficant association in unadjusted but not in adjusted analysis.
Aguirre-Zorzano et al. 2015[111]	Cross-sectional 6 months - 17 years mean: 5.3 years	239 patients 164 non-smokers 75 smokers	Patient-reported Smoker: smoking at final examination.	Case definition BOP+ Bone loss >1.5 mm	No association.
Daubert et al. 2015[101]	Cross-sectional 9-15 years mean: 10.9 years	96 patients 89 non-smokers 7 smokers	Patient-reported at time of implant installation and final examination. Smoker: smoking at initial/final examination. Calculation of pack/years.	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	No association between peri-implantitis and (i) smoking status at initial/final examation, (ii) pack/years.
de Araujo Nobre et al. 2015[97]	Case-control ≥1 year	1275 patients 95/255 cases are smokers 242/1020 controls are smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD ≥5 mm BOP+ Bone loss ≥2 mm	No association.

(Continues)

TABLE 3 (Continued)

Study	Type of study	Study sample	Smoking	Peri-implantitis	Association
Canullo et al. 2016[105]	Cross-sectional mean: 5.1 years	534 patients 393 non-smokers 141 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD ≥4 mm BOP/SUP+ Bone level >3 mm	No association.
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 467 non-smokers 121 smokers	Patient-reported Smoker: smoking at time of implant installation.	Case definition BOP/SUP+ Bone loss >2 mm	Signficant association in unadjusted but not in adjusted analysis.
Rokn et al. 2017[104]	Cross-sectional 1-11 years mean: 4.4 years	134 patients 126 non-smokers 8 smokers	Patient-reported Smoker: smoking at final examination.	Case definition BOP/SUP+ Bone level >2 mm	No association.
Dalago et al. 2017[99]	Cross-sectional 1-14 years	183 patients 162 non-smokers 21 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD >5 mm BOP/SUP+ Bone level >2 mm	No association.
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients 204 non-smokers 34 smokers	Patient-reported Smoker: smoking at time of implant installation.	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	Odds for peri-implantitis (patient level) Smoking: OR 2.7

examined 239 implant-carrying individuals after a mean follow-up time of about 5 years and found an overall prevalence of peri-implantitis of 15%.[111] Smokers were not at higher risk. Results from other cross-sectional studies confirmed their findings.[95,96,99–101,103–106] It should be observed that three different studies reported on an association between smoking and peri-implantitis in their respective initial univariate analyses.[52,97,98] However, in the following calculations with adjustments for confounding and interaction (multivariate analyses), smoking was not retained as a relevant predictor for peri-implantitis. This indicates that smoking may be confounded by other background variables, e.g. history of periodontitis. The reasons for the conflicting findings and the apparent weak association between smoking and peri-implantits are currently not understood but may be related to differences in categorization of smokers and non-smokers. Thus, criteria for the factor "smoking" varied considerably from study to study. Furthermore, all of the identfied studies relied solely on patient-reported information for the assessment of smoking status.

Conclusion: There is currently no conclusive evidence that smoking constitutes a risk factor/indicator for peri-implantitis.

Diabetes

Diabetes mellitus comprises a group of metabolic diseases where type 1 describes an autoimmune destruction of insulin-producing β-cells and type 2 is characterized by insulin resistance.[112] The global prevalence of diabetes in the adult population is estimated at around 8%,[113,114] and the disorder has been identified as a risk factor for periodontitis.[115,116] Table 4 summarizes studies on its potential association with peri-implantitis.

A number of authors have indicated that patients with diabetes are at higher risk for peri-implantitis. Thus, Ferreira et al. recorded peri-implantitis in 24% of individuals who either medicated for glycaemic control or presented with fasting blood sugar ≥126 mg/dL at the final examination[102] In contrast, only 7% of non-diabetic patients were diagnosed accordingly. The authors reported an OR of 1.9. Recent findings from a study involving 96 patients with 225 implants demonstrated, after a mean follow-up of 11 years, a 3-fold risk (Risk ratio 3, implant level) for peri-implantitis in subjects who were diagnosed with diabetes at time of implant placement.[101] This analysis, however, was not adjusted for potential confounding. Tawil et al. followed 45 patients with diabetes for a mean of 42 months (range 1 to 12 years).[117] In subjects with a mean HbA1c level ≤7%, no implants were diagnosed with peri-implantitis. In patients with elevated HbA1c levels (7% to 9%), six out of 141 implants developed peri-implantitis.

A number of studies failed to identify diabetes as a risk for peri-implantitis. In the retrospective study by Costa et al., patients with diabetes diagnosed with mucositis were not at higher risk to develop peri-implantitis when compared to non-diabetics.[17] Similarly, a lack of assocation between peri-implantitis and diabetes was reported in the majority of available cross-sectional studies.[52,93,98–100,103,104,106] It should be pointed out that the assessment of diabetes in all but three studies[17,102,117] was solely based on patient-reported information. In two of the three reports an association was found between diabetes[102] or HbA1c levels[117] and peri-implantitis.

TABLE 4 Diabetes and peri-implantitis

Study	Type of study	Study sample	Diabetes	Peri-implantitis	Association
Ferreira et al. 2006[102]	Cross-sectional 0.5-5 years mean: 3.5 years	212 patients 183 non-diabetic patients 29 patients with diabetes	Fasting blood sugar ≥126 mg/dl or intake of anti-diabetic medicine (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Peri-implantitis (patient level) Diabetes: OR 1.9
Roos-Jansåker et al. 2006[92,93]	Cross-sectional 9-14 years mean: 11.0 years	216 patients Number of patients with/without diabetes not reported.	Patient-reported (at final examination) Diabetes considered in factor "General disease"	Case definition BOP/SUP+ Bone loss ≥1.8 mm	No association.
Máximo et al. 2008[100]	Cross-sectional ≥1 year mean: 3.4 years	113 patients 111 non-diabetic patients 2 patients with diabetes	Patient-reported (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level ≥3 threads	No association.
Tawil et al. 2008[117]	Cohort study 1-12 years mean: 3.5 years	45 patients with diabetes 22 patients with HbA1c level ≤7% 22 patients with HbA1c level 7% to 9% 1 patient with HbA1c level >9%	Regular assessments of HbA1c levels during pre- and postoperative period.	Case definition for peri-implantitis not reported.	Peri-implantitis (implant level) HbA1c level ≤7%: 0% HbA1c level 7% - 9%: 4.3% HbA1c level >9%: 9.1%
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	203 patients Number of patients with/without diabetes not reported.	Patient-reported (at final examination)	Case definition PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.
Costa et al. 2012[17]	Cohort study 5 years	80 patients with mucositis 69 non-diabetic patients 11 patients with diabetes	Fasting blood sugar ≥126 mg/dL or intake of anti-diabetic medicine (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	No association.
Marrone et al. 2013[103]	Cross-sectional 5 to 18 years mean: 8.5 years	103 patients 96 non-diabetic patients 7 patients with diabetes	Patient-reported (at final examination)	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Renvert et al. 2014[98]	Not reported	270 patients 259 non-diabetic patients 11 patients with diabetes	Patient-reported (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone level >2 mm	Association in unadjusted (OR 6.1, $P = 0.09$) but not in adjusted analysis.
Daubert et al. 2015[101]	Cross-sectional 9 to 15 years mean: 10.9 years	96 patients 91 non-diabetic patients 5 patients with diabetes	Patient records/Patient-reported (prior to implant therapy)	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	Risk for peri-implantitis (implant level) Diabetic at baseline: RR 3.0 (unadjusted analysis)

(Continues)

TABLE 4 (Continued)

Study	Type of study	Study sample	Diabetes	Peri-implantitis	Association
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 254 non-diabetic patients 14 patients with diabetes	Patient records/Patient-reported (prior to implant therapy)	Case definition BOP/SUP+ Bone loss >2 mm	No association.
Rokn et al. 2017[104]	Cross-sectional 1 to 11 years mean: 4.4 years	134 patients 130 non-diabetic patients 4 patients with diabetes	Patient records/Patient-reported	Case definition BOP/SUP+ Bone level >2 mm	No association.
Dalago et al. 2017[99]	Cross-sectional 1 to 14 years	183 patients 167 non-diabetic patients 16 patients with diabetes	Patient records/Patient-reported (prior to implant therapy)	Case definition PD >5 mm BOP/SUP+ Bone level >2 mm	No association.

Conclusion: Available evidence is inconclusive as to whether diabetes is a risk factor/indicator for peri-implantitis.

Poor plaque control/lack of regular maintenance therapy

As demonstrated in classical studies on periodontal diseases, lack of regular maintenance therapy is associated with tooth mortality and clinical attachment loss at teeth.[26,118–121] These findings have highlighted the importance of self-performed and professionally-administered infection control measures in the prevention of periodontal diseases. Studies on the potential association between poor plaque control or lack of regular maintenance therapy and peri-implantitis are presented in Table 5.

Results from one longitudinal study including patients diagnosed with mucositis indicated the importance of plaque control in the prevention of peri-implantitis.[17] The analysis showed that the incidence of peri-implantitis over a 5-year period was lower in patients attending maintenance therapy (18%) when compared to individuals without supportive care (44%). These findings are in aggreement with Roccuzzo et al.[90] The authors reported that patients who, during a 10-year period, failed to adhere to the recommended maintenance therapy required substantially more treatment for peri-implantitis (41%) than those attending the follow-up visits (27%). Results from a cross-sectional study are also in agreement. Patients complying to maintenance therapy following implant therapy during a mean obersvation time of 3.8 years were less likely to be diagnosed with peri-implantitis than non-compliers (OR 0.14).[122]

Cross-sectional reports assessing self-performed plaque control and its association with peri-implantitis demonstrated a strong correlation. In four studies, poor plaque control at the final examination was the strongest statistical predictor for peri-implantitis with ORs ranging from 5 to 14.[29,102,104,111] A more modest assocation (ORs 3 to 4) was described by one additional cross-sectional[105] and one case-control study.[97]

Contradictory data have also been reported. A total of four publications were identified that failed to observe correlations between cross-sectional assessments of plaque scores and peri-implantitis.[93,95,103,106] In this context, it should be considered that a one-time assessment of plaque may not necessarily reflect the long-term level of self-performed plaque control.

Other factors related to oral hygiene measures at implants may also be considered. Recently, Souza et al. reported that brushing at implant sites with keratinized mucosa (KM) <2 mm was associated with considerably more discomfort when compared to brushing at sites with KM ≥2 mm.[123] The authors also noted higher scores for plaque and bleeding at sites with reduced KM. Serino and Ström evaluated the accessibility of implant-supported restorations for oral hygiene measures in patients diagnosed with peri-implantitis.[124] The authors noted that only few sites with access for oral hygiene were affected (18%), while 65% of the non-cleansable sites showed peri-implantitis.

TABLE 5 Poor plaque control/lack of regular maintenance therapy and peri-implantitis

Study	Type of study	Study sample	Plaque control/maintenance therapy	Peri-implantitis	Association
Ferreira et al. 2006[102]	Cross-sectional 0.5 to 5 years mean: 3.5 years	212 patients 43 patients with good plaque control 123 patients with poor plaque control 46 patients with very poor plaque control	Plaque score (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) Poor plaque control: OR 3.8 Very poor plaque control: OR 14.3
Roos-Jansåker et al. 2006[92,93]	Cross-sectional 9 to 14 years mean: 11.0 years	216 patients Number of patients with/without good plaque control not reported.	Presence of plaque at implant level (at final examination)	Case definition BOP/SUP+ Bone loss ≥1.8 mm	No association.
Koldsland et al. 2010[94] & 2011[95]	Cross-sectional 1 to 16 years mean: 8.4 years	103 patients 10 patients with plaque score ≥30% 93 patients with plaque score <30%	Plaque score and presence of plaque at implant level (at final examination) Recall visits Patient-reported	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	No association.
Rinke et al. 2011[110]	Cross-sectional 2 to 11 years mean: 5.7 years	89 patients 58 patients attending recommended maintenance visits 31 patients not attending recommended maintenance visits	Maintenance therapy	Case definition PD ≥4 mm BOP+ Bone loss ≥3.5 mm	Odds for peri-implantitis (patient level) Regular maintenance therapy: OR 0.09
Dvorak et al. 2011[106]	Cross-sectional 1 to 24 years mean: 6.0 years	177 patients Number of patients with/without good plaque control not reported.	Presence of plaque at implant level (at final examination)	Case definition PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.
Costa et al. 2012[17]	Cohort study 5 years	80 patients with mucositis 39 patients with maintenance therapy 41 patients without maintenance therapy	Maintenance therapy Patient-reported and patient records Plaque index (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) No maintenance therapy: OR 1.8
Roccuzzo et al. 2010[91] and 2012[90]	Cohort study 10 years	101 patients 79 patients adhering to maintenance therapy 22 patients not adhering to maintenance therapy	Maintenance therapy	Case definiton for peri-implantitis not reported. Treatment for peri-implantitis (surgery and/or systemic antibiotics).	Treatment for peri-implantitis (patient level) Adherence to maintenance therapy: 27% Non-adherence to maintenance therapy: 41%

(Continues)

TABLE 5 (Continued)

Study	Type of study	Study sample	Plaque control/maintenance therapy	Peri-implantitis	Association
Marrone et al. 2013[103]	Cross-sectional 5 to 18 years mean: 8.5 years	103 patients 16 patients with plaque score ≥30% 87 patients with plaque score <30%	Plaque index (at final examination)	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Aguirre-Zorzano et al. 2015[111]	Cross-sectional 6 months to 17 years mean: 5.3 years	239 patients 50 patients with plaque score ≥25% 189 patients with plaque score <25%	Plaque index (at final examination)	Case definition BOP+ Bone loss >1.5 mm	Odds for peri-implantitis (implant level) Plaque ≥25%: OR 5.4
de Araujo Nobre et al. 2015[97]	Case-control ≥1 year	1275 patients Plaque present in 108/255 cases Plaque present in 67/1020 controls	Presence of plaque at patient level (at final examination)	Case definition PD ≥5 mm BOP+ Bone loss ≥2 mm	Odds for peri-implantitis (patient level) Plaque: OR 3.6
Canullo et al. 2016[105]	Cross-sectional mean: 5.1 years	534 patients Number of patients with/without good plaque control not reported.	Plaque index (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone level >3 mm	Odds for peri-implantitis (patient level) Plaque >30%: OR 3.4
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 474 patients attending annual maintenance visits 101 patients not attending annual maintenance visits	Recall visits Patient records	Case definition BOP/SUP+ Bone loss >2 mm	No association.
Rokn et al. 2017[104]	Cross-sectional 1 to 11 years mean: 4.4 years	134 patients Number of patients with/without good plaque control not reported.	Plaque index (at final examination)	Case definition BOP/SUP+ Bone level >2 mm	Odds for peri-implantitis (implant level) Plaque index (categorization not reported): OR 5.4
Schwarz et al. 2017[29]	Cross-sectional 1 month to 6.7 years mean: 2.2 years	238 patients Number of patients with/without good plaque control not reported.	Plaque index (at final examination)	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	Odds for peri-implantitis (patient level) Plaque ≥33%: OR 9.3
Monje et al. 2017[122]	Cross-sectional 3 to 4.5 years mean: 3.8 years	115 patients Patients categorized according to frequency of maintenance visits	Plaque index (at final examination) Recall visits Patient records on early marginal bone loss	Case definition BOP/SUP+ Changes in the radiographic bone level (≥2 mm) compared to baseline (i.e. prosthesis installation) Alternative case definitions were further explored (i.e. ≥3 mm and ≥4 mm with signs of inflammation)	Prevalence of peri-implantitis: Regular compliers: 72.7% were healthy, 4.5% had peri-implantitis. Non-compliers: 53.5% were healthy, and 23.9% had peri-implantitis (OR=0.14)

Conclusion: There is evidence that poor plaque control and lack of regular maintenance therapy constitute risk factors/indicators for peri-implantitis.

Areas of future research

Keratinized mucosa

The evidence that there is a need of a keratinized mucosa (KM) to maintain peri-implant health is still limited.[125,126] Previous systematic reviews have indicated that a KM of <2 mm was associated with more plaque accumulation and peri-implant soft tissue inflammation when compared with implants that were surrounded by a KM of ≥2 mm.[126,127] In particular, a meta- analysis pointed to statistically significant differences in terms of plaque scores, modified gingival index, mucosal recession and attachment loss in favour of sites with a wider KM.[127]

These findings were also supported by recent observational studies.[105,123,128–130] In a cross-sectional analysis, Ladwein et al. evaluated 211 patients (n = 967 implants) after a mean observation period of 8 years.[130] Implant sites lacking KM were associated with significantly higher plaque scores, marginal bleeding and BOP scores than sites with KM. However, no significant differences were noted with regard to PD and radiographic bone levels.

Another cross-sectional analysis of 36 patients (n = 110 implants) after an observation period of at least 6 months also pointed to significantly more plaque, marginal bleeding and mucosal inflammation as well as greater mucosal recession at sites where KM was ≤2 mm.[129] Souza et al. observed that implant sites with a KM of <2 mm had significantly higher plaque and BOP scores and were associated with an increased brushing discomfort than implant sites with a KM of ≥2 mm.[123] This finding was also supported by data from another cross-sectional analysis (n = 60 patients) indicating that implants with a KM of <2 mm revealed a significantly higher levels of plaque accumulation as well as increased BOP+ and PD values when compared with implant sites with a KM of ≥2 mm.[128] Canullo et al. reported that periodontally healthy patients diagnosed with peri-implantitis (53 out of 534 patients) had higher plaque and BOP scores as well as higher percentages of implants with a KM of <2 mm.[105] Recently, in a cross-sectional analysis at 10 years after implant placement, Rocuzzo et al. reported that, even in patients with a sufficient oral hygiene, the absence of KM was associated with higher plaque scores.[131]

Conclusion: While studies suggest that the absence or a reduced width of KM may negatively affect self-performed oral hygiene measures, there is limited evidence that this factor constitutes a risk for peri-implantitis.

Excess cement

Several observational studies have reported on a correlation between excess cement and the prevalence of peri-implant diseases. Employing a variety of different case definitions, it was suggested that the presence of excess cement was closely linked to the occurrence of either peri-implant mucositis or peri-implantitis.[132–136] However, the proportions of diseased implant sites showing showing excess cement varied considerably among studies and ranged between 9% and 81%. Accordingly, several implant sites showing excess cement exhibited no disease.[132–136] Furthermore, cement-retained restorations were not found to be at higher risk for peri-implantitis when compared to screw-retained reconstructions.[52,101,103,137] Nevertheless, a systematic review emphasized that the rough surface structure of cement remnants may facilitate retention and biofilm formation.[138]

Conclusion: It is suggested that excess cement is a potential risk factor/indicator for peri-implantitis.

Genetic factors

Gene polymorphisms may affect gene expression, protein production and cytokine secretion.[139] Several observational studies have addressed the potential association between various gene polymorphisms and the occurence of peri-implantitis, with the majority focussing on IL-1.[140–144] Based on a cross-sectional analysis, Gruica et al. reported that 64 out of 180 patients revealed a positive IL-1 composite gene polymorphism (IL-1α +4845; IL-1β +3954) and a total of 34 patients (51 implants) were associated with biological complications (unclear case definition) at 8 to 15 years after implant therapy.[141] An association between a positive IL-1 composite gene polymorphism and the occurrence of biological complications was, however, observed only in a subgroup of heavy smokers (≥20 cigarettes per day). In another cross-sectional analysis, Laine et al. identified a significantly higher prevalence of IL-1 receptor antagonist (IL-1RA) polymorphisms in patients that were diagnosed with peri-implantitis (case definition: BOP+ and/or suppuration, bone loss >3 threads at machined implants) when compared with patients showing healthy control implants (57% vs. 33%; OR 3).[140] Similar findings were reported by Hamdy and Ebrahem, showing that a positive IL-1 composite gene polymorphism (IL-1α -889; IL-1β +3954) was significantly higher among patients suffering from peri-implantitis.[143] However, this association was not confirmed in other cross-sectional analyses.[142,144,145] Recent observational studies have also pointed to a potential association with gene polymorphisms of osteoprotegerin,[146,147] IL-6,[148] CD14-159 C/T and TNFα -308 A/G.[149]

Conclusion: While prospective clinical studies and studies with sufficient sample size are still lacking, the available evidence points to a potential influence of various gene polymorphisms in the pathogenesis of peri-implantitis.

Systemic conditions

The association of systemic conditions (other than diabetes) with peri-implantitis has rarely been studied and is therefore unclear. A cross-sectional study reported a higher risk for peri-implantitis in patients diagnosed with cardiovascular disease (OR 9) and rheumatoid arthritis (OR 7).[98] Koldsland et al. evaluated cardiovascular disease but failed to observe an association with peri-implantitis.[95] Roos-Jansåker et al.,[93] Casado et al.,[96] and Canullo et al.[105] combined different systemic diseases into one parameter and found no

elevated risk for peri-implantitis in their respective analyses. Other studies considered osteoporosis,[100,106] osteopenia,[100,106] thyroid disease,[99,106] hepatitis,[99,103] BMI[100] as well as radiation and chemotherapy.[97] No association with peri-implantitis was observed. It may be questioned whether existing studies evaluating risk factors/indicators for peri-implantitis are adequately powered to detect associations with rare disorders.

Conclusion: Evidence suggesting systemic conditions (other than diabetes) to be a risk factor/indicator for peri-implantitis is limited.

Iatrogenic factors

The Consenus report of the 7th European Workshop on Periodontology recognized that the onset and progression of peri-implantitis may be influenced by iatrogenic factors such as "inadequate restoration-abutment seating, overcontouring of restorations or implant-malpositioning".[1] It appears reasonable that the implant position and design of the suprastructure should facilitate access for self-performed oral hygiene and professionally administered plaque removal.[3] However, studies examining the role of iatrogenic factors in the development of peri-implant diseases are still scarce.

In a restrospective analysis, it was suggested that peri-implantitis was linked with malpositioning (OR 48) and bone augmentation (OR 2).[150] The potential association between bone augmentation procedures and peri-implantitis was also addressed in two cross-sectional studies. [105,151] Canullo et al. reported that in patients (n = 53) diagnosed with peri-implantitis (case definition: BOP+ and/or suppuration, PD ≥4 mm, radiographic bone level >3 mm), 18% of the diseased implants had received a bone grafting procedure at installation while the percentage of healthy implants sites with a history of bone augmentation was significantly smaller (7%).[105]

In another cross-sectional study, Schwarz et al. evaluated the impact of the outcome of guided bone regeneration in dehiscence-type bone defects on peri-implant health.[151] The residual defect height was assessed 4 months following grafting. After 4 years of follow-up, it was observed that implants with residual defects of >1 mm were at a higher risk of developing peri-implant disease.

Conclusion: In the absence of sufficient data, it appears reasonable to suggest that implant position and design of the suprastructure may influence the access for home care- and professionally administered plaque removal.

Occlusal overload

In the presence of plaque, the potential influence of excessive occlusal overload[152] and lateral static load[153] on peri-implantitis has been addressed in animal studies. In particular, employing the ligature model in dogs, Kozlovsky et al. subjected titanium abutments connected to machined implants to either a supra- (i.e. overload), or infra-occlusion (i.e. unloaded) over a period of 12 weeks.[152] At control sites (i.e. implants with plaque control), overload was associated with an improved osseointegration over unloaded implants. No data on changes of crestal bone levels were presented. In the study by Gotfredsen et al., implants with mucositis and experimental peri-implantitis were exposed to lateral static load by means of expansion screws.[153] There was no difference in terms of bone level changes between loaded and unloaded implants. Lateral load did not induce bone loss at mucositis sites. These findings were supported by Heitz-Mayfield et al.,[154] since in their study occlusal overload at implant sites with plaque control in the dog did not result in increased PD or BOP scores over unloaded (i.e. no crowns) control implants at 8 months.

Cross-sectional analysis revealed that clinical signs of occlusal overload (e.g. abutment fracture, loss of retention, chipping, dynamic occlusal measurements) were identified at three out of 207 implants with healthy peri-implant conditions, whereas the ratio changed to 27/125 at peri-implantitis sites (OR 19).[150] It should be noted that only patients diagnosed with peri-implantitis were considered in the analysis. In a population of 183 patients with a total of 916 implants, Dalago et al.[99] identified that wear facets on the implant supported crowns were associated with peri-implantitis (OR 2).

Conclusion: There is currently no evidence that occlusal overload constitutes a risk factor/indicator for the onset or progression of peri-implantitis.

Titanium particles

In an analysis of archive material of human biopsies, it was reported that the inflammatory cell infiltrate at peri-implantitis sites occasionally (i.e. seven out of 36 biopsies) revealed residues of particles featuring titanium peaks in the energy dispersive x-ray spectroscope.[32] Similar findings were also reported by Fretwurst et al.,[155] since metal particles (i.e. titanium and iron) were identified in nine out of 12 human hard and soft tissue biopsies taken at peri-implantitis sites. Both studies, however, were lacking tissue biopsies retrieved from clinically healthy implant sites (e.g. taken during the removal of malpositioned or fractured implants).

In a cytological analysis of oral smears taken from the peri-implant mucosa of 30 patients, Olmedo et al. identified metal-like particles at both healthy and diseased (i.e. peri-implantitis) implant sites.[156] However, the titanium concentration appeared to be higher in patients suffering from peri-implantitis.

Conclusion: At the time being, the available evidence does not allow for an evaluation of the role of titanium or metal particles in the pathogenesis of peri-implant diseases.

A number of additional factors have been associated with peri-implantitis in case reports, finite-element analyses or pre-clinical research (e.g. bone compression necrosis,[157,158] over-heating,[159] micromotion,[160] and biocorrosion[161]). The importance of such factors should be evaluated in future research.

Does progressive crestal bone loss around implants occur in the absence of soft tissue inflammation?

It is important to distinguish between initial physiological bone remodeling and progressive crestal peri-implant bone loss, with the latter implying that a pathological process is ongoing. The initial

remodeling of the crestal bone is considered to be a physiological process following implant placement.[1] This process is influenced by a variety of biological (e.g. mucosal thickness[162]), technical (e.g. prosthetic connections[163]) and surgical (e.g. implant positioning[164,165]) factors.

Observational studies have indicated that crestal bone level changes at implants are commonly associated with clinical signs of inflammation. In a retrospective analysis, Fransson et al. evaluated the prevalence of subjects with progressive bone loss (bone level >3 threads and bone loss ≥0.6 mm with year 1 as baseline) at machined/turned implants.[56] Between 5 and 23 years after loading, the prevalence of progressive bone loss amounted to 28% at the subject- and 12% at the implant level. In an analysis of a subgroup of these patients, clinical signs of inflammation (i.e. BOP+, suppuration, PD >6 mm) were more frequent at sites demonstrating "progressive bone loss".[55] In particular, the percentages of BOP+, suppuration and PD ≥6 mm at implant sites without progressive bone loss were 91%, 5%, and 12% compared to 94%, 19%, and 35% at implant sites with progressive bone loss.

In another cross-sectional analysis including 427 patients, Derks et al. observed that, over a 9-year period, bone loss (>0.5 mm) had occurred at 629 (40%) out of 1,578 implants.[52] Of these 629 implants, 393 (63%) also presented with soft tissue inflammation (BOP+) at the final examination. At implants presenting with more pronounced bone loss (>1, >2, >3, >4 mm), BOP+ was recorded at 72%, 80%, 87%, and 88%, respectively.

Similarly, a prospective analysis of implants with a modified surface over a period of 10 years indicated, that crestal bone level changes (>0.5; >1.0; >2.0 mm) were commonly associated with clinical signs of inflammation (BOP+).[166,167]

Conclusion: Evidence suggests that progressive crestal bone loss around implants in the absence of clinical signs of soft tissue inflammation is a rare event.

CONCLUSIONS

1) Peri-implantitis is defined as a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone.
2) The histopathologic and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood.
3) The onset of peri-implantitis may occur early during follow-up and the disease progresses in a non-linear and accelerating pattern.

4a) Peri-implantitis sites exhibit clinical signs of inflammation and increased probing depths compared to baseline measurements.

4b) At the histologic level, compared to periodontitis sites, peri-implantitis sites often have larger inflammatory lesions.

4c) Surgical entry at peri-implantitis sites often reveals a circumferential pattern of bone loss.

5a) There is strong evidence that there is an increased risk of developing peri-implantitis in patients who have a history of chronic periodontitis, poor plaque control skills and no regular maintenance care after implant therapy. Data identifying "smoking" and "diabetes" as potential risk factors/indicators for peri-implantitis are inconclusive.

5b) There is some limited evidence linking peri-implantitis to other factors such as: post-restorative presence of submucosal cement, lack of peri-implant keratinized mucosa and positioning of implants that make it difficult to perform oral hygiene and maintenance.

6) Evidence suggests that progressive crestal bone loss around implants in the absence of clinical signs of soft tissue inflammation is a rare event.

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2017 WORLD WORKSHOP

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The etiology of hard- and soft-tissue deficiencies at dental implants: A narrative review

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objective: The objective of the present paper was to review factors and conditions that are associated with hard and soft-tissue deficiencies at implant sites.

Importance: Hard- and soft-tissue deficiencies at dental implants are common clinical findings. They can lead to complications and compromise implant survival and, hence, may require therapeutic interventions. It is, therefore, important to understand the etiology of hard and soft-tissue deficiencies. Based on this understanding, strategies should be developed to correct hard and soft-tissue deficiencies with the aim of improving clinical outcomes of implant therapy.

Findings: A large number of etiological factors have been identified that may lead to hard and soft-tissue deficiencies. These factors include: 1) systemic diseases and conditions of the patients; 2) systemic medications; 3) processes of tissue healing; 4) tissue turnover and tissue response to clinical interventions; 5) trauma to orofacial structures; 6) local diseases affecting the teeth, the periodontium, the bone and the mucosa; 7) biomechanical factors; 8) tissue morphology and tissue phenotype; and 9) iatrogenic factors. These factors may appear as an isolated cause of hard and soft-tissue defects or may appear in conjunction with other factors.

Conclusions: Hard- and soft-tissue deficiencies at implant sites may result from a multitude of factors. They encompass natural resorption processes following tooth extraction, trauma, infectious diseases such as periodontitis, peri-implantitis, endodontic infections, growth and development, expansion of the sinus floor, anatomical preconditions, mechanical overload, thin soft tissues, lack of keratinized mucosa, malpositioning of implants, migration of teeth, lifelong growth, and systemic diseases. When more than one factor leading to hard and/or soft-tissue deficiencies appear together, the severity of the resulting condition may increase. Efforts should be made to better identify the relative importance of these etiological factors, and to develop strategies to counteract their negative effects on our patient's wellbeing.

KEYWORDS

gingival thickness, implantology, osseointegration, osseous defects

INTRODUCTION

The use of dental implants is considered a predictable therapeutic option for the rehabilitation of partially or fully edentulous patients providing long-term function and esthetics.[1–4] Tissue deficiencies at implant sites are common clinical findings.[5,6] Their presence may lead to an increase in marginal bone loss, soft-tissue inflammation, and soft-tissue recession.[7,8] These complications are difficult to treat and may threaten the survival of the implant. Hard-tissue defects at implant sites encompass intra-alveolar, dehiscence, fenestration, horizontal ridge, and vertical ridge defects.[9] Soft-tissue defects include volume and quality deficiencies, i.e. lack of keratinized tissue.[10] These tissue deficiencies may result from a large number of reasons. The aim of the present paper is to describe the factors associated with and/or causing soft- and hard-tissue deficiencies of dental implants.

Some factors need to be considered related to implant therapy within the context of this review. The aim of implant therapy is to provide patients with teeth for function and esthetics in good health. To use implants as anchoring elements for artificial teeth, the implants need to be placed in a position amenable to prosthetic reconstruction. This position may not be within the available bony envelope even in situations, where the bone volume is sufficient for placing implants. The prosthetically ideal position is determined by several factors: 1) the treatment plan, which takes into consideration the aim of prosthetic therapy; 2) the volume and the morphology of the host bone in the area; 3) the morbidity associated with the overall treatment; 4) the costs of the treatment; and 5) the desires of the patient. Hence, although avoidable, bone defects are often the consequence of placing the implant in the prosthetically driven position in ridges with sufficient bone and soft tissue.

Moreover, implants are available in different forms and shapes. For the purpose of this review treatment with rotational symmetric, screw-type implants with diameters of 3.5 to 4.5 mm and lengths of 8 to 14 mm is considered.

Due to ethical reasons, many of the factors described in the present review cannot be studied in randomized controlled clinical trials. Hence, evidence of lower levels like cohort, prospective or cross-sectional study designs or observational studies need to be included in the analysis of the available data. Furthermore, cause and effect are difficult to establish for most of the factors, which only allows describing associations between the factors and the hard and soft tissue defects.

METHODS

Electronic searches of the Medline (PubMed) database were performed and complimented by manual searches of relevant recent articles representing original research or review papers. The following basic search terms were applied: hard tissue, bone, soft tissue, mucosa, soft-tissue thickness, keratinized mucosa, tooth extraction, tooth loss, tooth fracture, trauma, periodontitis, peri-implantitis, endodontic lesion, periapical lesion, sinus floor, sinus floor expansion, growth, development, tooth migration, malpositioning, mechanical overload, systemic disease and combined with defect, deficiencies. Data from both clinical and preclinical studies were considered. Papers taken into account had to report evidence on the etiology of hard- and soft-tissue deficiencies of dental implants. No further restrictions were applied. The criteria regarding the methodology of the studies included were broad thus allowing information originating from experimental pre-clinical and clinical trials to case series to be used for this review. Since this review is of narrative nature no formal evidence-based quality assessment was performed of the studies included. The search was limited to the English language. Owing to the heterogeneity of the data no statistical analysis was performed.

OBSERVATIONS AND DISCUSSION

Hard-tissue deficiencies prior to implant placement

Hard-tissue deficiencies prior to implant placement encompass situations, where the available amount of bone does not allow placing a standard implant fully embedded in the local host bone (Table 1).

TABLE 1 Factors affecting hard- and soft-tissue deficiencies at dental implants

Hard-tissue deficiencies prior to implant placement
Tooth loss
Trauma from tooth extraction
Periodontitis
Endodontic infections
Longitudinal root fractures
General trauma
Bone height in the posterior maxilla (area of the sinus floor)
Systemic diseases
Hard-tissue deficiencies after implant placement
Defects in healthy situations
Malpositioning of implants
Peri-implantitis
Mechanical overload
Soft-tissue thickness
Systemic diseases
Soft-tissue deficiencies prior to implant placement
Tooth loss
Periodontal disease
Systemic diseases
Soft-tissue deficiencies after implant placement
Lack of buccal bone
Papilla height
Keratinized tissue
Migration of teeth and life-long skeletal changes

Tooth loss

Resorbed edentulous ridges may show various forms, whereas certain overall patterns have been identified in 24 maxillary and 99 mandibular completely edentulous dry skulls.[11] Generally speaking the resorption pattern of the mandible is centrifugal and that of the maxilla is centripetal. This resorption process may reach a degree, where the circumference of the mandible is further buccal than that of the maxilla. The investigators surmised that implant placement in such situations is not possible without bone augmentation to correct the bone deficiencies.[11] Many studies have investigated ridge resorption on a longitudinal basis between tooth extraction and up to 12 months thereafter.[12] Changes of the alveolar ridge were studied in 24 patients between tooth extraction and implant placement demonstrating loss of ridge profile.[13] Still another study with 16 extraction sites with spontaneous healing demonstrated vertical and horizontal loss of bone dimensions after full flaps.[14] Multiple additional studies have been published assessing the changes in alveolar bone dimensions between tooth extraction and 3 to 12 months thereafter.[15,16] These resorption processes have been examined longitudinally in animal experiments and have been summarized.[17,18] It has been shown, however that the bone profile of people wearing removable dentures is continuously reduced over time under the denture bases.[19,20]

Evidence: There is a high level of evidence from well-performed prospective clinical studies by various groups of investigators describing the process of loss of alveolar bone occurring following tooth extraction. Some cross-sectional observational studies describe a pronounced loss of alveolar bone and overall ridge profile over long periods of edentulous individuals. Very scarce data is available comparatively studying the prevalence and the severity of hard tissue defects at different time points following tooth extraction.

Trauma from tooth extraction

Trauma during tooth extraction may affect bone healing at the extraction site. In a recent study in five beagle dogs raising of flaps lead to higher resorption rates and hence to smaller dimensions of alveolar process compared to flapless extraction.[21] In a clinical study, 21 patients were either treated with a widely mobilized flap design or a limited papilla sparing flap design.[22] One year after crown placement, the loss of crestal bone on the adjacent teeth had amounted to 1.1 mm in the widely mobilized flap design and to 0.3 mm in the limited flap design. The clinical and preclinical data of these two studies agree. The status of the buccal bone was assessed in 53 sites in 30 patients.[23] Bone dehiscence, plate fracture and complete plate loss occurred in 28%, 9%, and 4% of sites, respectively. In 73 out of 301 tooth extractions a traumatic event (fracture of crowns, roots, or alveolar bone) occurred during the extraction procedure.[24] Of these 73 sockets 18 developed a healing complication. A previous study compared 36 histologic samples of disturbed wound healing with 185 of undisturbed healing.[25] The results showed decreased connective tissue formation in the sites with disturbed wound healing. The investigators concluded that this disturbed wound healing will eventually lead to lower amounts of bone volume in the area of the previous extraction socket. In an experimental study in eight rabbits the buccal wall of the alveolus was deliberately removed in half or the sites (experimental group) and left intact in the control group.[26] Micro CT analysis showed decreased amounts of bone width in the experimental group in the previous socket area.

Evidence: Some data from preclinical studies exist assessing the effect of trauma to the healing process of the alveolar process. Clinical investigations reporting on hard- and soft- tissue defects resulting from traumatic tooth extraction are scarce.

Periodontitis

Chronic periodontitis has been defined as "an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment, and bone loss. It is characterized by pocket formation and/or gingival recession".[27] As periodontitis progresses the tooth supporting bone of the alveolar process is continuously resorbed adjacent to the teeth.[28] In a group of 20 patients, who had lost teeth due to periodontal disease, implant placement was not possible due to a lack of bone volume at the sites.[29] In a control group of 10 patients implants could be placed without bone augmentation in sites, where teeth had been lost due to aplasia, endodontic infections, or trauma.

Evidence: Controlled clinical studies are largely lacking comparing the need for bone regeneration, when teeth are lost due to periodontal disease or to other reasons. Many studies reporting bone regeneration procedures describe the reasons for tooth extraction, which also include periodontal disease.

Endodontic infections

Loss of supporting periodontal and surrounding bone at teeth may also result from infectious processes other than marginal periodontal disease namely by apical periodontitis.[30] Endodontic infections are a common clinical finding leading to resorption of periapical bone.[31–35] Whereas the marginal bone may still be intact, the bone resorption around the apex of the tooth may reach a degree clinically affecting the feasibility of implant placement using standard procedures. The bone deficiencies may render implant placement more difficult. Moreover, depending on the degree of bone resorption implant placement may not be possible at all.[36] Few controlled studies with small patient samples have compared the outcome of implants immediately placed into extraction sockets of teeth exhibiting apical periodontitis to implants replacing teeth without apical periodontitis.[16,37,38]

Evidence: Scarce evidence from controlled clinical studies (three studies, 1- to 5-year observation rates, < 50 patients) indicates that at sites with periapical infections survival (96% cumulative survival rate > 5 years) and complication rates of implant are similar to implants placed in non-infected sites.

Longitudinal root fractures

Furthermore, longitudinal root fractures may lead to bone resorption and thus cause hard-tissue deficiencies at implants.[39] Pattern

and amount of bone resorption are depending on factors like the type of the fracture, the extent and the duration until a therapeutic intervention.[39–41] Evidence based data is largely missing for early diagnosis of vertical root fractures.[42] Epidemiologic studies have reported vertical root fractures to account for around 10% of reasons for extractions of endodontically treated teeth.[43] At the time of tooth extraction and implant placement varying extents of bone deficiencies may be present.[44]

Evidence: Information is very scarce assessing the extent of bone destruction caused by vertical root fractures and the bone defects resulting, when implants are placed. Available data are limited to describing the occurrence of bone destruction associated with longitudinal root fractures. In addition, some prevalence data exist for longitudinal root fractures of endodontically treated teeth.

General trauma

A frequent clinical reason making it necessary to place implants is trauma. Trauma may affect teeth alone or may affect teeth, mucosa, bone along with intraoral and perioral tissues.[45] When the alveolar process and/or the body of the mandible and the maxilla are involved, a reduced volume of bone available for implant anchorage will result.[46]

Evidence: Trauma as a cause of loss of tissue is obvious. Analysis regarding frequency and extent of soft- and hard- tissue defects in such situations compared to normal ones is missing. There are no data on survival and complications of implants in prosthetically optimal position versus implants in suboptimal position following surgical reconstruction of the lost tissues.

Bone height in the posterior maxilla (area of the sinus floor)

The height of the bone in the posterior maxilla is bordered by the floor of the sinus and by the crest of the alveolar bone. Often times the height of this bone is insufficient for the placement of implants of standard length and consequently bone defects will result.[6,47–50] With the progressing age of patients the floor of the maxillary sinus expands in the caudal direction thus decreasing the bone height.[51] This process is more pronounced when teeth are extracted (average loss of height 2.2 mm) as compared to dentate sites (average 1.8 mm).[48] Additional findings support these data reporting lower height in edentulous regions (average height 7.1 mm) as compared to dentate regions (average height 9.7 mm).[50] As a consequence, oral surgical interventions will become necessary[52,53] thus allowing implant placement.[54]

Evidence: There is a high level of evidence describing the frequent presence of bone defects at implant sites in the posterior maxilla.

Systemic diseases

Some systemic diseases are associated with abnormal and incomplete tooth and bone formation during growth and development like ectodermal dysplasia.[55] When tooth development does not take place, the alveolar process is not formed at all or is reduced in its volume.[56] The resulting bone deficits may reach different degrees of magnitude. With increasing amounts of lacking bone, implant treatment becomes more and more difficult and bone grafts harvesting with associated patient morbidity becomes necessary.[57,58] Twenty-four patients received 88 implants after tumor resection in the maxilla.[59] All patients needed to be reconstructed with bone transplants prior to implant placement. At a median of 99 months of follow-up time, the cumulative survival rate amounted to 89%. As a treatment option short implants were tested in a recent study.[60] At the 5-year examination, the survival rate ranged from 74% to 95%.

Evidence: As stated above for trauma lack of bone formation as a cause of lack of tissue is obvious. Again, analysis regarding frequency and extent of soft- and hard-tissue defects in patients suffering from malformation or substantial loss of bone is missing. Similarly, there are no data on survival and complications of implants in prosthetically optimal position versus implants in suboptimal position following surgical reconstruction of the lost tissues.

Hard-tissue deficiencies after implant placement

Hard-tissue deficiencies after implant placement may generally be placed into two categories: bone deficiencies associated with healthy situations, and those associated with diseases and malfunctions.

Defects in healthy situations

Defects of the alveolar process also exist, when teeth are present. The prevalence of dehiscence and fenestrations defects in modern skulls has been described to amount to 4.1% and 9.0%, respectively.[61] After tooth removal and implant placement, bone defects will result. Defects existing in healthy anatomical situations encompass dehiscence defects, fenestration defects, and infrabony defects.[9,62,63]

In addition, at intact ridges the prosthetically correct implant positions may not be within the bony envelope. Lingual undercuts are a frequent finding in the mandibular anterior and the premolar and molar areas. The prevalence of undercuts has been reported in cross-sectional studies to range from 36% to 66% in the posterior area[63–65] and from 2.4% to 8% in the anterior area.[64,66] Recently, a variant of mandibular anatomy has described and termed “hourglass” shape.[67] Ten out of 719 patients in need of full mandibular reconstruction exhibited this variant of mandibular shape.[67]

Evidence: Well-conducted cross-sectional clinical studies exist describing the frequency of bony undercuts in the mandible possibly leading to bone defects at implants in these sites. No valid data are available describing the prevalence of clinical conditions with these defect situations.

Malpositioning of implants

A factor, which has been given increased attention recently, is malpositioning of implants. In a group of 125 implants malpositioning

was identified as the most important factor with an odds ratio of 48 associated signs and symptoms of peri-implant tissue breakdown.[68] Malpositioning as the reason for explantation was reported in 22 (14%) out of 151 implants scheduled for removal.[69] Buccal mucosal recession was observed to be significantly associated with more buccal implant positioning in a prospective cohort study including 30 implants placed in esthetic sites.[70] These findings were corroborated in a retrospective study with 42 single implants in the esthetic zone reporting a significant association of buccal mucosal recession with buccal implant positioning.[71] Another retrospective study photographically analyzed the level of the mucosal margin at 85 single tooth implants in the esthetic zone compared with the reference central incisor.[72] Again mucosal recession was associated with buccal implant position. Similarly, a multivariate analysis performed in a group of 93 patients with single implant reconstructions found a correlation between the bucco-oral position of the implant and the height of the buccal crest 4 months after implant placement.[73] Thus, each 1 mm that the implant was placed more buccally from the center of the alveolus resulted in a more apical position of the buccal crest of 0.22 mm.

Evidence: Few prospective cohort studies report in a structured manner on the effect of implant positioning on the hard and soft tissues at the implant site. In addition, several reports of single or multiple cases deal with reconstructive difficulties when dealing with malpositioned implants. These include fabrication of specific prosthetic parts, leaving certain implants unrestored and surgical interventions to remove implants or reposition them in a more favorable prosthetic location.

Peri-implantitis

Peri-implantitis includes the following components: "changes in the level of crestal bone, presence of bleeding on probing and/or suppuration; with or without concomitant deepening of peri-implant pockets".[74] Peri-implantitis leads to the loss of hard and soft tissue at implant sites (for details see the review on this topic of this workshop).

Mechanical overload

Mechanical overload has been described as another possible factor leading to hard-tissue deficiencies at implants.[75] Mechanical overload may be categorized into two different entities: loading forces preventing the implant to osseointegrate during the healing phase, and loading forces destroying a previously established osseointegration. The absence of micromotion is not a prerequisite for successful osseointegration. It has been shown that during the phase of bone integration of an implant micromotions of less than 50 μm to 150 μm are still amendable to successful bone integration.[76] Excessive strain can lead to bone resorption, whereas magnitudes below this strain result in bone apposition. The clinically responsible parameters for the pathway of overload of already integrated implants have not been identified thus far.[77–81]

Evidence: The evidence for overload of osseointegrated implants leading to hard and/or soft tissue defects is very scarce. There is a complete lack of well-structured studies testing overload in a clinical environment. The evidence for loss of osseointegration due to overload is limited to anecdotal reports of single or multiple cases.

Soft-tissue thickness

It has recently been investigated whether the thickness of the soft tissues influences the behavior of the crestal bone during tissue integration of implants. Twenty-three implants were placed in 19 patients.[82] The implants were divided into two groups related to soft tissue thickness. At the one-year follow-up examination the marginal bone loss at the implants in the thin group was in the magnitude of 1.5 mm, whereas the thick group only measured around 0.3 mm. Implant abutment connections were evaluated in another study.[83] In addition, the investigators analyzed the effects of the buccal soft tissue thickness on marginal bone level changes in 32 patients. They found a significant correlation between soft tissue thickness and bone loss with more loss (0.3 mm versus 0.1 mm) at thin soft tissue sites at the 1-year examination. The findings that thin soft tissues lead to increased marginal bone loss were confirmed in a recent study.[84] In addition to the thin and thick tissue-groups the investigators followed a third group with about 30 patients, where they increased the thin soft tissue at implant placement by grafting. The results showed bone loss, which was not different from the thick soft tissue-group.[84] Using a different implant system, patients were also stratified into three groups of about 30 patients each.[85] Groups 1 and 2 exhibited thin soft tissues, whereas group 2 received grafts for increasing the thickness and group 1 did not. Group 3 had thick soft tissues. One year after implant placement group 1 had lost significantly more marginal bone (about 1.2 mm) than groups 2 and 3 (about 0.2 mm), which were no different from each other.[85] Yet another study stratified the patients according to mucosal thickness into two groups of 40 patients each. At the 1-year examination after implant placement, the group with thin tissues showed 1.2 mm and the group with thick tissues 0.2 mm of crestal bone loss.[86] These clinical results are in line with a previous preclinical study, where thinning out of the mucosa at implant sites lead to increased marginal bone loss.[87] It has been hypothesized that one of the reasons for this is the reestablishment of the biological width around implants penetrating the mucosa.[88,89] Since this biologic width usually exceeds 2 mm for titanium and zirconia dental implants[90] a resorption of the crestal bone is postulated to take place to generate space for connective tissue and epithelium adherence to the implant surface. These studies combined suggest that thin soft tissues covering the surgical sites can be a reason for hard-tissue deficiencies at implants.

Evidence: There is a significant amount of controlled prospective studies with medium size patient samples indicating that thin soft tissues lead to increased marginal bone loss compared to thick soft tissues at implants. The majority of the data, however, have been published by one specific group of researchers.

Systemic diseases

Hard-tissue deficiencies after implant placement may also result from systemic diseases, from bone diseases, from the intake of

medications, and from certain forms of therapies. Most notably the prolonged medication of high doses of bisphosphonates[91] increases the risk of bone necrosis of the jaws in conjunction with implant therapy.[92,93] In addition, high dose radiotherapy in the jawbone regions may lead to impaired bone turnover and thus to bone loss at implants.[94,95] In addition, increased bone loss as well as soft-tissue recession has been noted in some papers on long-term results, when patients underwent radiotherapy.[96]

Evidence: There is some evidence from case reports and case series demonstrating that implants in patients suffering from certain systemic diseases suffer from increased rates of hard tissue deficiencies.

Soft-tissue deficiencies prior to implant placement

Soft-tissue deficiencies prior to implant placement encompass the following situations: the available amount of soft tissue does not 1) easily allow soft-tissue coverage of bone volume augmentations; 2) allow tension free primary coverage of the site of implant placement; or 3) allow tension free adaptation of the keratinized soft-tissue flap around the neck of the placed implant (Table 1).

Tooth loss

As stated above with respect to hard-tissue deficiencies, the changes to the ridge occurring after tooth loss are the most common reason leading to soft-tissue deficiencies prior to implant placement. At the same time as the bony profile of the alveolar ridge is reduced in size following tooth loss, the covering soft tissue is also reduced. When implants are to be placed after bone and soft-tissue healing are completed, a diminished amount of soft tissue to cover the site of implantation and concomitant bone regeneration can be an important clinical problem.[90]

Extraction sockets left for spontaneous healing exhibited vertical and horizontal loss of ridge volume as assessed on study casts. Significant vertical but not horizontal resorption was confirmed in a study with 10 extraction sockets in five patients.[97] Silicone impressions at 101 sites taken before and 3 months after tooth extraction for combined assessment of ridge dimensions including both hard and soft tissues revealed only small changes to the ridge.[98] When assessing study cast in 44 patients immediately after tooth extraction of posterior teeth with full thickness flaps and 12 months later, the magnitude of change to the outer contour of the alveolar process has been estimated to amount to 50% in bucco-lingual direction with the resorption being clearly more pronounced at the buccal compared to the lingual surfaces.[99] The crestal resorption during this same time frame was in the magnitude of 1 to 2 mm. The patterns of resorption more than 12 months after tooth extraction have not been studied in detail.

Evidence: There is a high level of evidence from well-performed prospective clinical studies by various groups of investigators describing the process of loss of covering soft tissues occurring following tooth extraction.

Periodontal disease

When left untreated, periodontitis will lead to loss of periodontal support including recession of the soft tissues and resorption of the tooth-supporting bone.[28] Chronic periodontitis has been defined as "an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment and bone loss. It is characterized by pocket formation and/or gingival recession".[27] In cases of recession the available soft tissue is reduced compared to a healthy situation.

Evidence: Controlled clinical studies are largely lacking comparing the effect of the soft tissue available, when teeth are lost due to periodontal disease or to other reasons. Few studies reporting regenerative procedures after tooth extraction also assess the amount of soft tissue present in a comparative manner between sites with and without periodontal disease.

Systemic diseases

Some systemic diseases are associated with abnormal and incomplete bone formation, e.g. osteogenesis imperfecta.[100,101] The reduced bone formation may result in a bone volume too small to place implants. The soft tissues cover the bone volume present. When more bone volume is needed for implant placement, bone augmentation will be necessary. The available soft tissue may then be insufficient to cover the new bone volume during the regeneration surgery. This lack of soft tissue may render implant treatment more challenging.

Evidence: to date there is scarce data looking into means to increase the amount of soft tissue to facilitate the coverage of bone augmentation sites.

Soft-tissue deficiencies after implant placement

Lack of buccal bone

The lack of buccal bone at implants has been reported to be associated with decreased height of facial soft tissues.[102,103] Twenty-four patients received dental implants immediately placed into extraction sockets.[102] Guided bone regeneration (GBR) was performed and single crowns were inserted. Seven years later, cone-beam computed tomography (CBCTs), were taken to assess the labial bone. Of the 14 patients attending the follow-up examination five exhibited no buccal bone, whereas nine showed intact buccal bone plates. In the sites with intact radiographic buccal bone height, the facial mucosa was at clinically normal levels, i.e. the bone fully covered the implant surface intended for bone contact. In the situations with a lack of buccal bone at the implant, the investigators reported an average facial recession of 1 mm.[102] A large variability of the height of the buccal bone was observed in 17 of 20 patients attending a 10-year examination following immediate implant placement concomitant with GBR.[103] The mean distance from the buccal implant shoulder as assessed on CBCTs amounted to 1.6 mm, whereas the range reached from 0.1 mm

to 14.9 mm. In a recent study, 18 implants completely surrounded by native bone were compared with 10 implant exhibiting bone defects treated by GBR.[104] Assessments of buccal soft tissue contours were done prior to implant placement and 3 years thereafter. During this time, the buccal contour increased to a significantly higher degree (mean 1.2 mm) in the GBR sites compared to the native bone sites (0.6 mm). In 20 patients presence of the buccal bone plate was observed 6 years following implant placement and concomitant bone augmentation.[105] The soft tissues esthetics reached high scores using the pink esthetic score (mean 8.25, range 5 to 10). In a group of 22 patients with buccal bone defects smaller than 6 mm, 11 were randomly assigned to no bone augmentation treatment.[7] Although, the bone height slightly decreased, the soft tissue levels remained stable over the 18-month period with no difference compared to the 11 sites with initial GBR to correct the bone defects. In another study 24 bone defects at implant sites were treated with GBR.[8] Four months later the remaining defect sizes were assessed and classified as absent, minimal up to 1 mm, or advanced > 1 mm. Four years later a follow-up examination was performed. Whereas the probing pocket depths were similar in all three groups the values for mucosal recession and for bleeding on probing were higher in the defect groups compared to the group with complete bone coverage of the implant.[8]

Evidence: There are conflicting results from controlled prospective clinical studies and from cohort studies reporting whether or not the buccal bone plate will remain stable over time and will support the soft tissue buccal to the implant.

Papilla height

Another major soft-tissue deficiency is the reduced papilla height between two adjacent implants.[106,107] This situation can cause significant esthetic problems in the visible area. In 33 patients, 136 measurements of papilla height between two implants were performed. The mean papilla height from the bone crest to the top of the papilla amounted to 3.4 mm with a large variability reaching from 1 to 7 mm.[108] This is considerably less than the previously reported value of the normal papilla height of 5 to 6 mm between two adjacent teeth.[109] The papillae at single tooth implants were assessed in 27 implants in 26 patients. The mean papilla height at the 52 sites available for measurement amounted to 3.9 mm between a single implant and an adjacent tooth.[110]

Evidence: Clinical cross-sectional and some longitudinal studies indicate that the papilla height between implants and teeth is affected by the level of the periodontal tissues at the teeth. The height of the papilla between implants is determined by the bone crest between the implants. These processes, however, are not well understood due to the lack of well-controlled studies.

Keratinized tissue

The need for an adequate band of keratinized tissue at implant sites has been discussed controversially in the past.[111] The possible association between the width of the keratinized mucosa at implant was studied in a group of 39 patients.[112] Patients had been treated 5 to 10 years before this examination. In addition to the width of the keratinized mucosa mobility of the mucosal margin was assessed. The statistical analysis failed to reveal an association between the width of the keratinized mucosa or the mobility of the marginal mucosa at the implant sites regarding plaque accumulation, gingivitis, bleeding on probing, or probing pocket.[112] Over a period of at least 3 years, 339 implants were longitudinally followed in 69 patients.[113] Subgroups were made according to the amount of keratinized mucosa present. Results revealed no difference regarding changes in marginal bone levels. The gingival index (0.9 vs 0.8) and the modified plaque index (1.5 vs 1.3) were, however, higher in the subgroup with keratinized mucosa of < 2 mm compared with the subgroup with > 2 mm.[113] In another clinical study thirty patients were identified with < 1 mm of keratinized mucosa at implant sites.[114] Half of the patients underwent surgery for widening of the band of keratinized mucosa and half did not. After an observation period of 10 years a significant difference in gain of keratinized mucosa was present (intervention group 3.1 mm, non-intervention group 0 mm). None of the clinical parameters studied (Quigley-Hein plaque index, bleeding on probing, probing pocket depth, presence of peri-implantitis) were different between the two groups.[114] In contrast, 58 patients with 307 implants completed the 5-year examination of a study assessing the relationship between the width of the keratinized mucosa at implants and some clinical parameters in edentulous mandibles with fixed reconstructions.[115] At sites with < 2 mm compared with > 2 mm of keratinized mucosa the investigators reported higher plaque scores (0.7 vs 0.4) and bleeding tendencies (0.2 vs 0.1) at lingual sites and more recession (0.7 vs 0.1) at buccal sites. No additional differences were reported.[115] Fifteen edentulous patients with mandibular overdentures on four implants were stratified according to the presence or absence of keratinized mucosa at the buccal aspects of the implants.[116] The 19 implants in 15 patients with at least 2 mm of keratinized mucosa had significantly lower plaque (0.3 vs 0.6) and gingival indices (0.1 vs 0.6) than the 17 implants in 15 patients without keratinized mucosa.[116]

When primary coverage of an implant site is aimed at following tooth extraction, a buccal flap is normally raised, advanced and placed in contact with the lingual flap. In 11 patients, ridge preservation was performed and the site was either closed by advancing the buccal flap or not covered to allow for open healing.[117] The 6-month reevaluation revealed the mucogingival junction to be displaced coronally to a significantly greater extent in the group with flap closure (3.8 mm) compared to the control group (1.2 mm). This lack of keratinized tissue is normally more pronounced at the buccal aspect compared to the lingual one.

Evidence: There are numerous prospective, controlled clinical trials assessing the associations between clinical and radiographic parameters and the presence or absence of a band of keratinized mucosa at implant sites. To date, the results are inconclusive regarding the effect on long-term health and maintenance of dental implants exhibiting these clinical conditions. The effects of clinical manipulations on the position of the mucogingival junction have only scarcely been studied and are, hence, poorly understood.

Migration of teeth and life-long skeletal changes

Discrepancies between implants and teeth may develop due to tooth wear and changes in the anatomy of face and jawbones in adults long after the patient has finished growth and development.[118] This will cause discrepancies of the facial tissue heights between the implant crowns and the natural teeth. Similar to tooth wear these changes occur slowly and take time to manifest clinically. With the increased use of osseointegrated implants over longer periods of time these problems are expected to increase. Changes in the maxillary and mandibular arches occur continuously. From an original sample of 89 boys and 86 girls aged > 3 years, 15 men and 16 women could be reexamined at 45 years of age.[119] Between 13 to 45 years of age the maxillary arch length decreased an average of 5.7 mm in males and 4.6 mm in females. During the time period from 8 to 45 years of age the mandibular arch length decreased on average by 7.4 mm in males and 8.3 mm in females. In another study, 14 females with implants bilaterally in the maxillary molar region and at least one implant in the incisor region were longitudinally followed in the age range from 9 to 25 years.[120] During the observation period the results showed an average eruption of the maxillary incisors of 6 mm downward and 2.5 mm forward. The maxillary first molars experienced an average eruption of 8 mm downward and 3 mm forward underscoring the continuous skeletal changes over time.[120] Wear facets at approximal surfaces of molars and premolars were studied in a sample of 376 skulls.[121] Tooth wear was a common finding and increasing with age. In addition, various patterns of wear were identified. The position of single implant reconstructions was studied in a group of 82 patients, of which 47 were available for examination 18 years after implant reconstruction.[122] In 40% of the patients the implant reconstruction showed signs of infraposition compared to the adjacent teeth. In a recent retrospective study, 174 implants in 128 patients were examined for interproximal contact loss after implant restoration times ranging from 3 months to 11 years.[123] More than half (53%) of the reconstructions showed interproximal contact loss. Seventy-eight of these open contacts were located mesially and 22% distally. Eight implant reconstructions exhibited mesial and distal interproximal contact loss.[123] Over an observation period of 16 years tooth movements were examined adjacent to 28 single-tooth implants.[124] Tooth movements included vertical and palatal displacements and occurred in some but not all patients. In a sample of 146 implants in 105 patients loss of the interproximal contact was examined prospectively over time.[125] During the observation period, 43% of 186 interproximal contacts were lost with a significantly greater incidence at the mesial (52%) compared to the distal (16%) aspect. Using the pooled data, the investigators calculated that half of the interproximal contacts might be lost in 5.5 years of function.

Evidence: Whereas migration of teeth adjacent to implants is well documented in prospective and in cross-sectional studies, the clinical consequences regarding hard- and soft-tissue defects are poorly examined and understood.

CONCLUSIONS

Hard- and soft-tissue deficiencies at implant sites may result from a multitude of factors. They encompass natural resorption processes following tooth extraction, trauma, infectious diseases such as periodontitis, peri-implantitis, endodontic infections, growth and development, expansion of the sinus floor, anatomical preconditions, mechanical overload, thin soft tissues, lack of keratinized mucosa, malpositioning of implants, migration of teeth, lifelong growth, and systemic diseases. There are varying levels of evidence for the different factors. For some there are well-controlled studies, whereas for others there is little to no scientific evidence. More research is needed to better identify the factors possibly leading to hard- and soft-tissue deficiencies at implant and their clinical impact.

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

Peri-implant health, peri-implant mucositis, and peri-implantitis: Case definitions and diagnostic considerations

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Abstract

The objective of this review is to identify case definitions and clinical criteria of peri-implant healthy tissues, peri-implant mucositis, and peri-implantitis. The case definitions were constructed based on a review of the evidence applicable for diagnostic considerations. In summary, the diagnostic definition of peri-implant health is based on the following criteria: 1) absence of peri-implant signs of soft tissue inflammation (redness, swelling, profuse bleeding on probing), and 2) the absence of further additional bone loss following initial healing. The diagnostic definition of peri-implant mucositis is based on following criteria: 1) presence of peri-implant signs of inflammation (redness, swelling, line or drop of bleeding within 30 seconds following probing), combined with 2) no additional bone loss following initial healing. The clinical definition of peri-implantitis is based on following criteria: 1) presence of peri-implant signs of inflammation, 2) radiographic evidence of bone loss following initial healing, and 3) increasing probing depth as compared to probing depth values collected after placement of the prosthetic reconstruction. In the absence of previous radiographs, radiographic bone level ≥3 mm in combination with BOP and probing depths ≥6 mm is indicative of peri-implantitis.

KEYWORDS

diagnosis, peri-implant health, peri-implant mucositis, peri-implantitis

INTRODUCTION

Osseointegrated dental implants have become an increasingly popular modality of treatment for the replacement of absent or lost teeth. Dental implants have high rates of long-term survival (≥10 years) when used to support various types of dental prostheses. However, the long-term success of dental implants is not the same or as high as their survival, as functional implants and their restorations may be subject to mechanical and biological complications.[1]

It is recognized that there are also unusual peri-implant problems (e.g., peri-implant peripheral giant-cell granuloma, pyogenic granuloma, squamous cell carcinoma, metastatic carcinomas, malignant melanoma) or other conditions such as implant fractures that may mimic or share certain clinical features with biofilm-associated peri-implant diseases. With such context in mind, the reader is to be reminded that this manuscript focuses solely on biofilm-induced inflammatory lesions around dental implants.

Biological complications associated with dental implants are mostly inflammatory conditions of the soft tissues and bone surrounding implants and their restorative components, which are induced by the accumulation of bacterial biofilm. Such conditions, which have been named peri-implant mucositis and peri-implantitis, need to be clearly defined and differentiated from a state of peri-implant health, so that the clinician may assign a proper diagnosis and select a proper treatment modality in cases where disease is present.

In a survey of registered specialists in periodontology in Australia and the United Kingdom about the etiology, prevalence, diagnosis and management of peri-implant mucositis and peri-implantitis,

there appears to be no consensus on treatment standards for the management of peri-implant diseases.[2] An American survey that examined the practitioners' understanding of the etiology of peri-implant diseases and the management of peri-implant mucositis and peri-implantitis by periodontists in the United States revealed the absence of a standard therapeutic protocol to treat these conditions and a significant variation in the empirical use of therapeutic modalities that result in moderately effective treatment outcome.[3] Accordingly, there is a need to establish applicable clinical guidelines for the diagnosis of peri-implant mucositis, and peri-implantitis. Additionally, there is a need to develop criteria for peri-implant mucositis and peri-implantitis applicable in not only in for clinical practice but also for clinical and epidemiological research studies.

The objective of this manuscript is to define peri-implant health, peri-implant mucositis and peri-implantitis based on their clinical and radiographic parameters. The case definitions herein described were constructed based on a systematic review of the scientific evidence that currently correlates clinical and radiographic findings with the three diagnostic entities. The scientific evidence for peri-implant health, peri-implant mucositis and peri-implantitis has been summarized in other manuscripts in this volume.[4–6] The case definitions proposed in this paper are intended to apply to situations in which there are reasons to believe that the presence of biofilm on implant surfaces is the main etiological factor associated with the development of peri-implant mucositis and peri-implantitis. It is obvious from previous manuscripts in this volume that there are major patient-specific differences in inflammatory responses to the microbial challenge of bacterial communities that reside on implants and its restorations.[5,6]

PERI-IMPLANT HEALTH

While peri-implant health shares many common clinical features with periodontal health around natural teeth, it is clear that there are major structural differences between the two scenarios, particularly with respect to their relationship with surrounding tissues and biological attachment. The review by Araujo and Lindhe[4] describes the different anatomical and histological characteristics associated with the soft and hard tissues around natural teeth and dental implants and the authors further described how such differences may be responsible for the distinct biological mechanisms involved in host response and tissue homeostasis observed between the two entities.

Araujo and Lindhe[4] also concluded that peri-implant health requires the absence of clinical signs of inflammation (i.e. erythema and swelling) including no bleeding on probing. This determination is true to evidence from the periodontal literature that the absence of bleeding on probing is consistent with periodontal health.[4,7] In clinical health, the peri-implant mucosa forms a tight seal around the trans-mucosal component of the implant itself, the abutment or the restoration. The height of the soft tissue around the implant following placement influences the initial probing depth. In general, however, the probing depth associated with peri-implant health should be ≤5.0 mm.[4] It should also be noted that peri-implant tissue health can exist following treatment of peri-implantitis with variable levels of bone support.

It has been proposed that the soft tissue cuff around implants exhibits less resistance to probing than the gingiva at adjacent teeth sites.[8,9] This property of the implant mucosal seal may lead to mechanically induced bleeding on probing on dental implants that are clinically healthy.[9] The clinical relevance of such phenomenon is that the presence of a local bleeding dot may, therefore, represent a traumatic episode rather than a sign of biofilm-induced inflammation. Such trauma-induced bleeding on probing may not only be the result of excessive probing forces, but can also be the consequence of clinical difficulties in aiming the dental probe at the sulcus/pocket around the implant, which can occur because of the implant-restoration spatial relationship and contours. It has been suggested that the absence of a periodontal ligament around implants and the prosthetic design makes assessments of pocket probing depth measurements at dental implants difficult to perform and interpret.[10] Recognizing the above described issue, a modified bleeding index has been proposed using a grading scale of the extent of bleeding at dental implants,[11] where a score of "0" represents healthy conditions, and a score of "1" representing an isolated dot of bleeding.

What clinical and radiographic findings and what clinical examination steps are necessary to detect the presence of peri-implant health?

1. Clinical evaluation of the soft tissue conditions around implants should include registration of oral hygiene in general, with specific focus on the presence of biofilm on implants and their restorations;
2. Dental implants should be visually evaluated and probed routinely and periodically (at least once per year) as part of comprehensive oral exams, similar to natural teeth;
3. Pocket probing on dental implants should be conducted with a light force (approximately 0.25 N); peri-implant pocket depths should in general be ≤5 mm;
4. Bleeding on probing should not occur at implant sites defined as being healthy. Bleeding on probing should be assessed carefully using light forces (0.25 N) to avoid possible effects of trauma caused by the process. It is difficult to differentiate between biofilm-induced peri-implant inflammation and mechanically-induced trauma; bleeding "dots" should be interpreted carefully as this may represent bleeding due to tissue trauma and not bleeding associated with tissue inflammation;
5. Intra-oral radiographic evaluation of changes in bone levels around implants (preferably using a standardized film holder) is necessary to discriminate between health and disease states. A prerequisite for the radiographic evaluation should be an image taken at baseline (supra-structure in place) that clearly allows for identification of an implant reference point and distinct visualization of implant threads, for future reference as well as assessment

of mesial and distal bone levels in relation to such reference points; and

6. Absence of bone loss beyond bone level changes resulting from initial bone remodeling. Alveolar bone remodeling following the first year in function may be dependent on the type and position of the implant, but change (loss) of alveolar bone starting after the implant was placed in function should not exceed 2 mm.[12–14] Changes ≥2 mm at any time point during or after the first year should be considered as pathologic.

Peri-implant health: Case definitions for day-to-day clinical practice

The diagnosis of peri-implant health requires:

1. Visual inspection demonstrating the absence of peri-implant signs of inflammation: pink as opposed to red, no swelling as opposed to swollen tissues, firm as opposed to soft tissue consistency;
2. Lack of profuse (line or drop) bleeding on probing;
3. Probing pocket depths could differ depending on the height of the soft tissue at the implant location. An increase in probing depth over time, however, conflicts with peri-implant health; and
4. Absence of further bone loss following initial healing, which should not be ≥2 mm.

PERI-IMPLANT DISEASES

The scientific literature has provided the evidence to define the diagnosis of peri-implant conditions and diseases, and the reviews by Heitz-Mayfield and Salvi,[5] and Schwarz et al.[6] were used as the basis for the present report. In addition, two recent systematic reviews reporting on the prevalence of peri-implant mucositis and peri-implantitis were also evaluated.[15,16] Through these reports, we identified 33 articles defining clinical and radiographic criteria for the diagnosis of peri-implant mucositis and peri-implantitis (Table 1).

The American Academy of Periodontology has defined peri-implant mucositis as a disease that includes inflammation of the soft tissues surrounding a dental implant, without additional bone loss after the initial bone remodeling that may occur during healing following the surgical placement of the implant.[17] The etiology of peri-implant mucositis is the accumulation of a bacterial biofilm around the implant.[5]

Peri-implantitis has been defined as an inflammatory lesion of the mucosa surrounding an endosseous implant and with progressive loss of supporting peri-implant bone.[6,17–20] It is generally perceived that following implant installation and initial loading, some crestal bone height is lost (between 0.5 and 2 mm) in the healing process.[12,13] Any additional radiographic evidence of bone loss suggests peri-implant disease.

The conversion from an inflammatory process identified as peri-implant mucositis (without evidence of bone loss) to peri-implantitis (with bone loss) remains an enigma. It is, however, generally agreed that both peri-implant mucositis and peri-implantitis have an infectious etiology through the development of biofilm composed of a plethora of bacteria with known pathogenicity.[21–24]

PERI-IMPLANT MUCOSITIS

Case definitions of peri-implant mucositis were identified in 22 out of 33 articles listed in Table 1. Bleeding on probing without any other criteria was identified in three out of 22 articles. Bleeding on probing combined with no radiographic evidence of bone level changes could be identified in seven out of 22 articles as the definition of peri-implant mucositis. Three of these articles accounted for remodeling of the marginal alveolar bone adjacent to the implant as a result of the surgical procedure. The remaining reports also included probing pocket depths and/or bone loss assessments. In addition to bleeding on probing, one study allowed up to 3 mm of bone loss from the implant platform to define peri-implant mucositis.[25]

The diagnosis of peri-implant mucositis should be based on clinical signs of inflammatory disease. In routine clinical examinations, signs of inflammation should be screened for. In addition, radiographic images should be evaluated to exclude bone level changes consistent with the definition of peri-implantitis, as described later in the manuscript.

What clinical and radiographic findings and what clinical examination steps are necessary to detect the presence of peri-implant mucositis?

1. Visually, local swelling, redness, and shininess of the soft tissue surface are classical signs of clinical inflammation. A common symptom reported by patients is soreness;
2. A local dot of bleeding resulting from probing may be the result of a traumatic (probing) injury that should not be considered, in the absence of other inflammatory changes, a definitive criterion to characterize a peri-implant soft tissue lesion;
3. Any bleeding on probing that is combined with visual inflammatory changes of the tissues at the site of probing;
4. Clear evidence of bleeding such as a line of bleeding or drop bleeding should be used as an indication of an inflammatory peri-implant soft tissue lesion;
5. Suppuration upon clinical examination (e.g., application of light pressure to the tissues or following probing); and
6. Intra-oral radiographic evaluation of bone levels around implants should always be included in the presence of clinical signs of inflammation. In addition, a pre-requisite for the evaluation is that a radiograph be taken at baseline (supra-structure in place) and used for future assessment of mesial and distal bone levels in relation to defined references. Accounting for the remodeling

TABLE 1 Criteria used for the case definitions of peri-implantitis and peri-implant mucositis from studies selected in the review

Study	Case definition of peri-implantitis	Case definition of peri-implant mucositis
Fransson et al. (2005)[29]	Bone level change > 3 threads after first year in function	ND
Roos-Jansåker et al. (2006)[31]	Bone level change > 1.8 mm after first year in function + BOP	BOP + PD > 4 mm + no bone loss after first year on function
Ferreira et al. (2006) [32]	PD > 5 mm + BOP and/or suppuration (SUP)	BOP
Gatti et al. (2008)[33]	Bone level change > 2 mm from last radiographic assessment + Pus/ BOP + PD > 5 mm	ND
Maximo et al. (2008)[34]	Bone level change ≥3 threads + BOP and/or SUP + PD ≥5 mm	BOP + absence of radiographic bone loss and no SUP
Koldsland et al. (2010)[35]	Bone level change ≥2 mm from platform + BOP + PD ≥4 mm	BOP + no bone loss from platform
Koldsland et al. (2010)[35]	Bone level change ≥2 mm from platform + BOP + PD ≥6 mm	BOP + no bone loss from platform
Koldsland et al. (2010)[35]	Bone level change ≥3 mm from platform + BOP + PD ≥4 mm	BOP + no bone loss from platform
Koldsland et al. (2010)[35]	Bone level change ≥3 mm from platform + BOP + PD ≥6 mm	BOP + no bone loss from platform
Simonis et al. (2010)[36]	Bone level change > 2.5 mm (or ≥3 threads) from platform + BOP and/or SUP + PD ≥5 mm	ND
Wahlström et al. (2010)[37]	Bone level change > 2 mm after first year in function + BOP and/or SUP + PD ≥4 mm	BOP + PD < 4 mm + no bone loss after first year on function
Zetterqvist et al. (2010)[38]	Bone level change > 5 mm from the platform + BOP/SUP + PD > 5mm	ND
Pjetursson et al. (2012)[39]	Bone level change ≥2 mm after bone remodeling equals marginal bone levels of ≥5 mm below the implant shoulder	Level 1: BOP + PD > 5 mm Level 2: BOP + PD > 6 mm
Mir-Mari et al (2012)[40]	Bone level change > 2 threads from platform + BOP and or suppuration	BOP + bone level change < two threads from platform
Swierkot et al. (2012)[41]	Bone level change > 0.2 mm annually after first year in function, + PD ≥5 mm with or without BOP	BOP + PD > 5 mm + no bone level change
Fardal and Grytten (2013)[42]	Bone level change > 3 threads after bone remodeling + BOP or suppuration	ND
Marrone et al. (2013)[43]	Bone level change > 2 mm from the platform + BOP + PD > 5 mm	BOP + bone level change ≤2 mm from platform. PPD ≤5 mm
Cecchinato et al. (2014)[44]	Progressive bone loss > 0.5 mm +BOP + PD ≥4 mm	BOP
Martens et al. (2014)[45]	Bone level change > 2 mm from the platform + PD > 4 mm	ND
Meijer et al. (2014)[46]	Bone level change ≥2 mm from the platform + BOP	BOP + bone level change < 2 mm from platform
Passoni et al. (2014)[47]	Bone level change > 2 + BOP and/or SUP + PD ≥ 5 mm	BOP + no bone level change
Renvert et al. (2014)[48]	Bone level change ≥2 mm from the platform + PD ≥ 4 mm + BOP and or suppuration	BOP + bone level change < 2 mm from platform
Aguirre-Zorzano et al. (2015)[49]	Bone level change > 1.5 mm after 6 months in function + often associated with suppuration, increased probing depth and bleeding on probing	BOP + no bone loss
Canullo et al. (2015)[50]	Bone level change > 3 mm following implant integration	ND
Daubert et al. (2015)[51]	Bone level change > 2 mm after remodeling + BOP and or SUP + PD ≥4 mm	BOP and/or gingival inflammation + no bone level change after remodeling
Ferreira et al. (2015)[52]	Bone level change > 2 mm after remodeling + BOP and/or + PD ≥4 mm	BOP and no bone loss
Frisch et al. (2015)[53]	Bone level change ≥2 mm after remodeling + BOP +PD ≥5 mm	BOP
Konstantinidis et al. (2015)[54]	Bone level change > 2 mm from the platform (at tissue level implants > 2 mm from the polished collar+ BOP + PD > 4 mm	BOP
Rinke et al. (2015)[55]	Bone level change ≥ 3.5 mm from platform	ND

(Continues)

TABLE 1 (Continued)

Study	Case definition of peri-implantitis	Case definition of peri-implant mucositis
Papantonopoulos et al. (2015)[56]	Bone level change ≥3 mm from platform + BOP and/or SUP +PD ≥5 mm	ND
Trullenque-Eriksson et al. (2015)[25]	Bone level change ≥3 mm from the platform + BOP and/or SUP + PD ≥ 5 mm	BOP + bone level change < 3 mm from platform level
van Velzen et al. (2015)[57]	Bone level change > 1.5 mm after first year in function + BOP	ND
Derks et al. (2016)[1]	Bone loss > 0.5 mm after up to 24 months + BOP/ suppuration. In addition, bone level change > 2 mm + BOP was considered moderate/severe peri-implantitis	BOP + no bone loss
Dalago et al. (2017)[58]	Bone level change > 2 mm from abutment installation + PD > 5 mm + BOP/SUP	ND
Rokn et al. (2017)[59]	Bone level change > 2 mm from platform level + BOP and/or SUP	BOP and/or SUP + bone level change ≤2 mm from platform level
Tenenbaum et al. (2017)[60]	Bone level change > 4.5 mm from platform + BOP + PD ≥5 mm	BOP + no bone level change from platform

BOP = bleeding on probing, PD = probing depth, SUP = suppuration, ND = not defined.

process of alveolar bone during the first year after installation, the change in bone level since the placement of the prosthetic supra-structure should not be > 2.0 mm. Presence of bone loss beyond crestal bone level changes resulting from the intial remodeling process of alveolar bone after implant installation suggests either progressive peri-implant infection, or other local factors such as excess cement and looseness/fracture of implant components.

Peri-implant mucositis: Case definitions for day-to-day clinical practice

The diagnosis of peri-implant mucositis requires:

1. Visual inspection demonstrating the presence of peri-implant signs of inflammation: red as opposed to pink, swollen tissues as opposed to no swelling, soft as opposed to firm tissue consistency;
2. Presence of profuse (line or drop) bleeding and/or suppuration on probing;
3. An increase in probing depths compared to baseline; and
4. Absence of bone loss beyond crestal bone level changes resulting from the intial remodeling.

PERI-IMPLANTITIS

To assign a diagnosis of peri-implantitis, most reports listed in Table 1 (30 out of 33) require bleeding on probing in addition to bone loss. Following the initial healing, additional bone loss 0.5 mm to 5 mm – as assessed from radiographs – was a necessary criterion for the diagnosis of peri-implantitis in 13 reports.

Without accounting for the initial (remodeling-associated) bone loss, the remaining articles identified bone loss using the implant platform level as reference. Bone loss requirements varied between 1.8 to 4.5 mm to diagnose the implant as having peri-implantitis. Different cut-off levels for probing pocket depth around implants were also required in 20 of the articles to define a diagnosis of peri-implantitis. It is clear from the data summarized in Table 1 that there is a large variation in the requirements to define a case as having either peri-implant mucositis or peri-implantitis. Such variation in the application of individual clinical judgement is confirmed by Ramanauskaite et al.[26] who concluded that there is currently no single uniform definition of peri-implantitis, or parameters that could be used to define peri-implant disease entities.

Understanding the wide heterogeneity in defining peri-implantitis, the most uniform consensus in characterizing peri-implantitis is as follows; 1) peri–implantitis lesions present with the same clinical signs of inflammation as peri-implant mucositis and 2) the distinctive difference between a diagnosis of peri-implant mucositis and peri-implantitis is the presence of bone loss in peri-implantitis, as identified from dental radiographs.[6]

During the last 10 to 15 years, there has been a general agreement that following the first year in function, bone loss around dental implants ≥2 mm represents peri-implantitis.[14,27,28] Recent data suggest that the pattern of bone loss in general is not linear.[1,29] Typically, the development of peri-implantitis appears within the first few years after which the implant is in function. This suggests that it is important to carefully monitor changes that may occur around dental implants in the early post-restorative phase, with focus on bleeding on probing/suppuration and in combination with radiographic evidence of bone loss. From the clinical perspective, it is important to

recognize that there is no predictable model or algorithm to predict the progression of peri-implantitis based on diagnostic methodologies currently available in daily practice.

Furthermore, experiences from the knowledge about the progression of periodontitis can only be extrapolated to peri-implantitis with extreme care. For decades, it has been recognized that the progression of periodontitis is unpredictable, as lesions alternate phases of dormancy and bursts of disease activity, which may be slow or rapid.[30] Based on this knowledge and in attempting to extrapolate it to peri-implantitis, any bone loss greater than the measurement error (≥2 times its standard deviation) or approximately 2 mm is indicative of peri-implantitis.[28]

What clinical and radiographic findings and what clinical examination steps are necessary to detect the presence of peri-implantitis?

1. The visual inspection with assessment of the presence of classical signs and symptoms of inflammation, i.e. redness, swelling, pain, and bleeding on probing (characteristics of the latter, described for peri-implant mucositis, also apply to the diagnosis of peri-implantitis);
2. The differential diagnosis between peri-implant mucositis and peri-implantitis is based on evidence that alveolar bone loss following initial healing and bone remodeling has occurred and requires a radiographic evaluation of the bone level around dental implants over time. This is in addition to the presence of inflammatory changes and bleeding on probing on a given site;
3. Presence of bone loss beyond crestal bone level changes resulting from the intial remodeling in conjunction with BOP after the implant has been placed in function should be considered as a marker for peri-implantitis; and
4. Radiographs should be taken based on clinical judgement after findings. Standardized radiographs should be taken and compared to reference radiographs when the implant(s) was placed in function.

Peri-implantitis: Case definitions for day-to-day clinical practice

The diagnosis of peri-implantitis requires:

1. Evidence of visual inflammatory changes in the peri-implant soft tissues combined with bleeding on probing and/or suppuration;
2. Increasing probing pocket depths as compared to measurements obtained at placement of the supra-structure; and
3. Progressive bone loss in relation to the radiographic bone level assessment at 1 year following the delivery of the implant-supported prosthetics reconstruction; and
4. In the absence of initial radiographs and probing depths, radiographic evidence of bone level ≥3 mm and/or probing depths ≥6 mm in conjunction with profuse bleeding represents peri-implantitis.

For day to day clinical practice it may be valuable to assess the yearly rate of bone loss. This can be calculated if it is known when the implant was placed in function.

CRITERIA TO BE USED IN EPIDEMIOLOGIC (SURVEILLANCE) STUDIES

The same criteria used to define peri-implant health and peri-implant mucositis in day-to-day practice should be applied in epidemiological studies. In epidemiological studies, radiographic and clinical information from the time point when the supra-structure was placed may not be available. Under such circumstances a distance from the implant platform to bone contact ≥3 mm, and in conjunction with bleeding on probing would be required for the diagnosis of peri-implantitis.

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2017 WORLD WORKSHOP

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Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions

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Abstract

A classification for peri-implant diseases and conditions was presented. Focused questions on the characteristics of peri-implant health, peri-implant mucositis, peri-implantitis, and soft- and hard-tissue deficiencies were addressed.

Peri-implant health is characterized by the absence of erythema, bleeding on probing, swelling, and suppuration. It is not possible to define a range of probing depths compatible with health; Peri-implant health can exist around implants with reduced bone support.

The main clinical characteristic of peri-implant mucositis is bleeding on gentle probing. Erythema, swelling, and/or suppuration may also be present. An increase in probing depth is often observed in the presence of peri-implant mucositis due to swelling or decrease in probing resistance. There is strong evidence from animal and human experimental studies that plaque is the etiological factor for peri-implant mucositis.

Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone. Peri-implantitis sites exhibit clinical signs of inflammation, bleeding on probing, and/or suppuration, increased probing depths and/or recession of the mucosal margin in addition to radiographic bone loss.

The evidence is equivocal regarding the effect of keratinized mucosa on the long-term health of the peri-implant tissue. It appears, however, that keratinized mucosa may have advantages regarding patient comfort and ease of plaque removal.

Case definitions in day-to-day clinical practice and in epidemiological or disease-surveillance studies for peri-implant health, peri-implant mucositis, and peri-implantitis were introduced. The proposed case definitions should be viewed within the context that there is no generic implant and that there are numerous implant designs with different surface characteristics, surgical and loading protocols. It is recommended that the clinician obtain baseline radiographic and probing measurements following the completion of the implant-supported prosthesis.

KEYWORDS
case definition, dental implant, hard tissue deficiencies, peri-implant mucositis, peri-implant tissues, peri-implantitis, soft tissue deficiencies

The objective of Workgroup 4 was to present a classification on peri-implant diseases and conditions. Five position papers describing the characteristics of peri-implant health,[1] peri-implant mucositis,[2] peri-implantitis,[3] soft and hard tissue deficiencies[4] and case definitions and diagnostic considerations[5] were prepared prior to the workshop.

In preparing this consensus report regarding the criteria for peri-implant health and disease it was recognized that there are a number of somewhat unusual peri-implant problems (e.g., implant fractures) and other conditions that may mimic or share certain clinical features with biofilm-associated peri-implant diseases. The following assumptions have been made: 1) complete medical-dental histories have been obtained including details on implant-supported reconstructions; and 2) an appropriate differential diagnostic analysis has been performed.

The following questions and case definitions are intended to apply to situations in which the clinician has reasons to believe that biofilms on implant surfaces are the main etiological exposures associated with the development of peri-implant mucositis and peri-implantitis. It is important to emphasize that there are major patient-specific differences in inflammatory responses to the microbial challenge of bacterial communities that reside on implants. In addition, it has been assumed that the implants were properly placed and subsequently integrated with soft and hard tissues.

PERI-IMPLANT HEALTH

1. *What are the clinical characteristics of a healthy peri-implant site?*
   In health, the peri-implant site is characterized by absence of erythema, bleeding on probing, swelling and suppuration.
2. *What are the main clinical differences between healthy peri-implant and periodontal tissues?*
   In health, there are no visual differences between peri-implant and periodontal tissues. However, the probing depths are usually greater at implant versus tooth sites. The papillae at the interproximal sites of an implant may be shorter than the papillae at interproximal tooth sites.
3. *What clinical methods and instruments should be used to detect the presence or absence of inflammation at an implant site?*
   The clinical methods to detect the presence of inflammation should include visual inspection, probing with a periodontal probe, and digital palpation.
4. *Why is it important to probe peri-implant tissues during a complete oral examination?*
   It is necessary to probe peri-implant tissues to assess the presence of bleeding on probing, and to monitor probing depth changes and mucosal margin migration. This assessment may alert the clinician to the need for therapeutic intervention. There is evidence that probing of the peri-implant tissue using a light probing force is a safe and important component of a complete oral examination.
5. *What peri-implant probing depths are compatible with peri-implant health?*
   It is not possible to define a range of probing depths compatible with health; of more importance are the clinical signs of inflammation.
6. *Can peri-implant health exist around implants with reduced bone support?*
   Yes, peri-implant tissue health can exist around implants with reduced bone support.
7. *What are the histological characteristics of a healthy peri-implant site?*
   The histological characteristics of a healthy peri-implant site are derived mainly from animal studies. The healthy peri-implant mucosa averages 3 to 4 mm in height and is covered by either a keratinized (masticatory mucosa) or non-keratinized epithelium (lining mucosa). The portion of the peri-implant mucosa that is facing the implant/abutment contains a "coronal" portion that is lined by a sulcular epithelium and a thin junctional epithelium, and a more "apical" segment in which the connective tissue is in direct contact with the implant surface. The connective tissue lateral to the sulcular epithelium harbors a small infiltrate of inflammatory cells. Most of the intrabony part of the implant is in contact with mineralized bone, while the remaining portion faces bone marrow, vascular structures, or fibrous tissue.
8. *What are the main histological differences between healthy peri-implant and periodontal tissues?*

   Compared to the periodontium, the peri-implant tissues do not have cementum and periodontal ligament. The peri-implant epithelium is often longer and in the connective tissue zone there are no inserting fibers into the implant surface. The peri-implant tissues are less vascularized in the zone between the bone crest and the junctional epithelium when compared to the connective tissue zone of the periodontium.

PERI-IMPLANT MUCOSITIS

1. *What are the clinical characteristics of peri-implant mucositis?*
   The main clinical characteristic of peri-implant mucositis is bleeding on gentle probing. Erythema, swelling and/or suppuration may also be present.
2. *Does peri-implant mucositis exist in the absence of clinical signs of inflammation?*
   Clinical signs of inflammation are necessary for a diagnosis of peri-implant mucositis.
3. *How does probing depth relate to the detection of peri-implant mucositis?*
   An increase in probing depth is often observed in the presence of peri-implant mucositis due to swelling or decrease in probing resistance.
4. *What is the evidence for plaque as the main etiological factor for peri-implant mucositis?*
   There is strong evidence from animal and human experimental studies that plaque is the etiological factor for peri-implant mucositis.
5. *Does non–plaque-induced peri-implant mucositis exist?*
   There is limited evidence for non–plaque-induced peri-implant mucositis.
6. *Can peri-implant mucositis resolve?*
   There is evidence from experimental human studies that peri-implant mucositis can resolve. Resolution of the clinical signs of inflammation may take more than 3 weeks following reinstitution of plaque/biofilm control.
7. *What are the environmental and patient-specific risk indicators for peri-implant mucositis?*
   The major etiological factor is plaque accumulation. Host response to the bacterial challenge may vary between patients. Smoking, diabetes mellitus, and radiation therapy may modify the condition.
8. *What are the histological characteristics of peri-implant mucositis?*
   Peri-implant mucositis is characterized by a well-defined inflammatory lesion lateral to the junctional/pocket epithelium with an infiltrate rich in vascular structures, plasma cells, and lymphocytes. The inflammatory infiltrate does not extend "apical" of the junctional/pocket epithelium into the supracrestal connective tissue zone.

PERI-IMPLANTITIS

1. *What is peri-implantitis?*
   Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone.
2. *What is the evidence for plaque/biofilm as a principal etiological factor for peri-implantitis?*
   There is evidence from observational studies that patients exhibiting poor plaque control and not attending regular maintenance therapy are at higher risk of developing peri-implantitis. Studies on treatment of peri-implantitis reveal that anti-infective treatment strategies are successful in decreasing soft tissue inflammation and in suppressing disease progression.
3. *What are the clinical characteristics of peri-implantitis?*
   Peri-implantitis sites exhibit clinical signs of inflammation, bleeding on probing and/or suppuration, increased probing depths and/or recession of the mucosal margin in addition to radiographic bone loss compared to previous examinations. At sites presenting with peri-implantitis, probing depth is correlated with bone loss and is, hence, an indicator for the severity of disease. It is important to recognize that rate of progression of bone loss may vary between patients.
4. *What are the histological characteristics of peri-implantitis?*
   Peri-implantitis lesions extend apical of the junctional/pocket epithelium and contain large numbers and densities of plasma cells, macrophages and neutrophils. In addition, peri-implantitis lesions are larger than those at peri-implant mucositis sites.
5. *Are there any specific microbiological and immunological characteristics of peri-implantitis?*
   No specific or unique bacteria or proinflammatory cytokines have been identified.
6. *What is the evidence for peri-implant mucositis being the precursor of peri-implantitis?*
   Peri-implant mucositis is assumed to precede peri-implantitis. Data indicate that patients diagnosed with peri-implant mucositis may develop peri-implantitis, especially in the absence of regular maintenance care. However, the features or conditions characterizing the progression from peri-implant mucositis to peri-implantitis in susceptible patients have not been identified.
7. *What is known about the onset and progression pattern of peri-implantitis?*
   The onset of peri-implantitis may occur early during follow-up as indicated by radiographic data. Peri-implantitis, in the absence of treatment, seems to progress in a non-linear and accelerating pattern. Data suggest that the progression of peri-implantitis appears to be faster than that observed in periodontitis.
8. *What are the major risk indicators for peri-implantitis?*
   There is strong evidence that there is an increased risk of developing peri-implantitis in patients who have a history of severe periodontitis, poor plaque control, and no regular maintenance care after implant therapy. Data identifying smoking and diabetes as potential risk indicators for peri-implantitis are inconclusive.
   Implants that have been placed under less than ideal circumstances are often encountered in day-to-day practice. As a result, there may be an increased prevalence of peri-implantitis associated with these situations.
   There is some limited evidence linking peri-implantitis to factors such as post-restorative presence of submucosal cement and positioning of implants that does not facilitate oral hygiene and maintenance. The role of peri-implant keratinized mucosa, occlusal overload, titanium particles, bone compression necrosis, overheating, micromotion and biocorrosion as risk indicators for peri-implantitis remains to be determined.
   There is a high priority to conduct studies that are designed to develop diagnostic, preventive, and intervention strategies for the management of these peri-implant issues.
9. *Does progressive crestal bone loss around implants occur in the absence of soft tissue inflammation?*
   Observational studies have indicated that crestal bone level changes at implants are typically associated with clinical signs of inflammation. However, there are situations in which peri-implant bone loss may occur due to iatrogenic factors, including malpositioning of the implant or surgical trauma.

HARD- AND SOFT-TISSUE DEFICIENCIES

1. *What are the main factors associated with hard- and soft-tissue deficiencies at potential implant sites?*
   The healing process following tooth loss leads to diminished dimensions of the alveolar process/ridge representing hard- and soft-tissue deficiencies. Larger deficiencies may occur at sites exposed to the following factors: loss of periodontal support, endodontic infections, longitudinal root fractures, thin buccal bone plates, buccal/lingual tooth position in relation to the arch, extraction with additional trauma to the tissues, injury, pneumatization of the maxillary sinus, medications, and systemic diseases reducing the amount of naturally formed bone, agenesis of teeth, pressure from soft-tissue supported removable prosthesis, and combinations.
2. *What factors are associated with recession of the peri-implant mucosa?*
   The principal factors for recession of the peri-implant mucosa are malpositioning of implants, lack of buccal bone, thin soft tissue, lack of keratinized tissue, status of attachment of the adjacent teeth and surgical trauma.
3. *Does the presence/absence of keratinized mucosa play a role in the long-term maintenance of peri-implant health?*
   The evidence is equivocal regarding the effect of keratinized mucosa on the long-term health of the peri-implant tissue. It appears, however, that keratinized mucosa may have advantages regarding patient comfort and ease of plaque removal.

4. *What is the role of the peri-implant bone in giving form to the peri-implant soft tissues?*

   The papilla height between implants and teeth is affected by the level of the periodontal tissues on the teeth adjacent to the implants. The height of the papilla between implants is determined by the bone crest between the implants. Results are equivocal whether the buccal bone plate is necessary for supporting the buccal soft tissue of the implant in the long-term.

CASE DEFINITIONS AND DIAGNOSTIC CONSIDERATIONS

The following case definitions and characteristics of peri-implant health, peri-implant mucositis, and peri-implantitis should be viewed within context of several potential confounding factors.

It is known that there is no generic implant and that there are numerous implant designs with different surface characteristics, surgical and loading protocols. The degree of physiological remodeling after implant placement may vary and will determine the crestal level of bone expected in peri-implant health. The amount of remodeling will also be influenced by a number of local and systemic factors. Clinicians should be aware that extensive peri-implant bone loss may also be reflective of the development of peri-implantitis during the remodeling phase.

It is recommended that the clinician obtain baseline radiographic and probing measurements following the completion of the implant-supported prosthesis. An additional radiograph after a loading period should be taken to establish a bone level reference following physiological remodeling. If the patient presents for the first time with an implant-supported prosthesis the clinician should try to obtain clinical records and previous radiographs in order to assess changes in bone levels.

How do we define a case of peri-implant health in day-to-day clinical practice and teaching situations?

Diagnosis of peri-implant health requires:

- Absence of clinical signs of inflammation.
- Absence of bleeding and/or suppuration on gentle probing.
- No increase in probing depth compared to previous examinations.
- Absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling.

It should be noted that probing depths depend on the height of the soft tissue at the location of the implant. Furthermore, peri-implant tissue health can exist around implants with variable levels of bone support.

How do we define a case of peri-implant mucositis in day-to-day clinical practice and teaching situations?

Diagnosis of peri-implant mucositis requires:

- Presence of bleeding and/or suppuration on gentle probing with or without increased probing depth compared to previous examinations.
- Absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling.

It should be noted that visual signs of inflammation can vary and that peri-implant mucositis can exist around implants with variable levels of bone support.

How do we define a case of peri-implantitis in day-to-day clinical practice and teaching situations?

Diagnosis of peri-implantitis requires:

- Presence of bleeding and/or suppuration on gentle probing.
- Increased probing depth compared to previous examinations.
- Presence of bone loss beyond crestal bone level changes resulting from initial bone remodeling.

In the absence of previous examination data diagnosis of peri-implantitis can be based on the combination of:

- Presence of bleeding and/or suppuration on gentle probing.
- Probing depths of ≥6 mm.
- Bone levels ≥3 mm apical of the most coronal portion of the intraosseous part of the implant.

It should be noted that visual signs of inflammation can vary and that recession of the mucosal margin should be considered in the probing depth evaluation.

How do we define a case of peri-implant health and peri-implant mucositis in epidemiological or disease surveillance studies?

The same criteria used to define peri-implant health and peri-implant mucositis in day-to-day practice should be applied in epidemiological studies.

How do we define a case of peri-implantitis in epidemiological or disease surveillance studies?

Diagnosis of peri-implantitis requires:

- Presence of bleeding and/or suppuration on gentle probing.
- Increased probing depth compared to previous examinations.
- Presence of bone loss beyond crestal bone level changes resulting from initial bone remodeling. Epidemiological studies need to take into account the error of measurements in relation to assessments of bone level changes. Bone loss should be reported using thresholds exceeding the measurement error (mean 0.5 mm).

Epidemiological studies should ideally include previous examinations performed after the first year of loading. In the absence of previous radiographic examinations, bone levels ≥3 mm apical of the most coronal portion of the intra-osseous part of the implant together with bleeding on probing are consistent with the diagnosis of peri-implantitis.

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FIGURE 1 Participants of Workgroup 4