

# Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations

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## 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.<sup>1</sup> 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<sup>2</sup> and the periodontal attachment loss starts in adolescence. Intrinsic abnormalities of the immune system may predispose these individuals to infections<sup>3</sup>; 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.<sup>4</sup>

In leukocyte adhesion deficiency (LAD) syndromes, neutrophils are confined to blood vessels and are absent from the periodontium.<sup>5</sup> Periodontal tissue loss may be caused by the lack of neutrophil immune surveillance and by the disruption of neutrophil-associated homeostatic mechanisms.<sup>5</sup>

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.<sup>2,6</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup>

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.<sup>2</sup> There is also severe alveolar bone loss that progresses rapidly and leads to premature loss of teeth.<sup>10</sup>

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.	<b>Systemic disorders that have a major impact on the loss of periodontal tissue by influencing periodontal inflammation</b>	
1.1.	<b>Genetic disorders</b>	
1.1.1.	<b>Diseases associated with immunologic disorders</b>	
	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.	<b>Diseases affecting the oral mucosa and gingival tissue</b>	
	Epidermolysis bullosa	
	– Dystrophic epidermolysis bullosa	Q81.2
	– Kindler syndrome	Q81.8
	Plasminogen deficiency	D68.2
1.1.3.	<b>Diseases affecting connective tissues</b>	
	Ehlers-Danlos syndrome (types IV, VIII)	Q79.6
	Angioedema (C1-inhibitor deficiency)	D84.1
	Systemic lupus erythematosus	M32.9
1.1.4.	<b>Metabolic and endocrine disorders</b>	
	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.	<b>Acquired immunodeficiency diseases</b>	
	Acquired neutropenia	D70.9
	HIV infection	B24
1.3.	<b>Inflammatory diseases</b>	
	Epidermolysis bullosa acquisita	L12.3
	Inflammatory bowel disease	K50, K51.9, K52.9
	Arthritis (rheumatoid arthritis, osteoarthritis)	M05, M06, M15-M19
2.	<b>Other systemic disorders that influence the pathogenesis of periodontal diseases</b>	
	Emotional stress and depression	F32.9
	Smoking (nicotine dependence)	F17

(Continues)

**TABLE 1** (Continued)

Classification	Disorders	ICD-10 code
	Medications	
3.	<b>Systemic disorders that can result in loss of periodontal tissue independent of periodontitis</b>	
3.1.	<b>Neoplasms</b>	
	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.	<b>Other disorders that may affect periodontal tissue</b>	
	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.<sup>11</sup>

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.<sup>12</sup> 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.<sup>13,14</sup>

### 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.<sup>15,16</sup> 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.<sup>17</sup> This was supported by the finding of atypical pocket junctional epithelium seen in a histologic examination of periodontal tissue in these patients.<sup>15</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup>

Individuals with plasminogen deficiency may show alveolar bone loss, severe periodontitis, and early loss of teeth.<sup>21,22</sup> 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.<sup>23</sup> 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.<sup>24</sup> Periodontitis also may occur in EDS type IV<sup>25</sup> and, to a lesser extent, in EDS type I.<sup>26</sup> EDS disorders are often caused by mutations in genes encoding fibrillary collagens or enzymes involved in the biosynthesis of these proteins.<sup>27</sup>

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	<ul style="list-style-type: none"> <li>Characteristic physical appearance, variable degree of cognitive impairment, and a range of physical disorders</li> <li>Moderate to severe loss of periodontal attachment and alveolar bone</li> </ul>	<ul style="list-style-type: none"> <li>Karyotype test is positive for trisomy of chromosome 21</li> </ul>
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	<ul style="list-style-type: none"> <li>History of severe recurrent infections with no pus formation</li> <li>Leukocytosis is common</li> <li>Severe gingival inflammation, acute gingival lesions, early-onset and rapidly progressive alveolar bone loss</li> <li>Early loss of the primary and permanent teeth</li> </ul>	<ul style="list-style-type: none"> <li>Flow cytometry shows low CD18 or CD15 expression on neutrophils (&lt; 5% of normal)</li> <li>Genetic testing for mutations in the beta-2 integrin (<i>ITGB2</i>) gene. Testing also shows absence of beta-2 integrin mRNA in leukocytes.</li> </ul>
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	<ul style="list-style-type: none"> <li>Hyperkeratotic lesions affecting multiple organs, particularly the palms, soles of the feet, elbows, and knees</li> <li>Severe gingival inflammation, early-onset and rapidly progressive alveolar bone loss</li> <li>Early loss of the primary and permanent teeth</li> </ul>	<ul style="list-style-type: none"> <li>Genetic testing for mutations of the cathepsin C (<i>CTSC</i>) gene on chromosome 11q14. Also, a laboratory test has recently been developed for early screening for the absence of cathepsin C activity in urine.</li> </ul>
Haim-Munk syndrome	Significant	Case reports, narrative reviews	Not well understood, but compromised neutrophil functions may play a role	<ul style="list-style-type: none"> <li>Palmoplantar hyperkeratotic lesions, arachnodactyly, acro-osteolysis, atrophic changes of the nails, and radiographic deformity of the fingers</li> <li>Severe gingival inflammation soon after eruption of teeth, high rate of attachment loss</li> <li>Early loss of the primary and permanent teeth</li> </ul>	<ul style="list-style-type: none"> <li>Genetic testing for mutations of <i>CTSC</i> (exon 6, 2127A → G)</li> <li>A clinical exam could differentiate this disorder from Papillon-Lefèvre syndrome</li> </ul>
Chediak-Higashi syndrome	Significant	Case reports, narrative reviews	Gene mutations result in impaired function of multiple body cells and systems, particularly the immune system	<ul style="list-style-type: none"> <li>Partial oculocutaneous albinism, varying neurologic problems such as intellectual deficit and dementia, and recurrent pyogenic infections</li> <li>Severe gingival inflammation, early-onset and rapidly progressive alveolar bone loss</li> <li>Early loss of the primary and permanent teeth</li> </ul>	<ul style="list-style-type: none"> <li>Genetic testing for mutations of the Chediak-Higashi syndrome (<i>CHS1</i>)/lysosomal trafficking regulator (<i>LYST</i>) gene</li> <li>Peripheral blood smear demonstrates the classic giant azurophilic granules in neutrophils, eosinophils, and other granulocytes</li> </ul>
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; $\alpha$ -defensins)	<ul style="list-style-type: none"> <li>ANC &lt; 500 cells/<math>\mu</math>L and static</li> <li>Severe and recurrent infections: otitis media, bronchitis, pneumonia, osteomyelitis, cellulitis; fungal infections</li> <li>Severe periodontitis is common</li> <li>Higher risk for tooth loss</li> <li>Oral ulcers</li> </ul>	<ul style="list-style-type: none"> <li>ANC should be determined</li> <li>Reduced plasma levels of hCAP-18 (proprotein of LL-37) determined by ELISA</li> <li>Genetic testing for mutations in the elastase, neutrophil expressed (<i>ELANE</i>) gene</li> <li>A bone marrow test also can assist in diagnosis</li> </ul>

(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	<ul style="list-style-type: none"> <li>ANC &lt; 500 cells/<math>\mu</math>L and occurs every 21 days, lasting 3 to 6 days at a time</li> <li>Recurrent infections, less severe than in congenital neutropenia</li> <li>Increased risk for periodontal attachment loss and oral ulcers</li> </ul>	<ul style="list-style-type: none"> <li>Monitoring of neutrophil count 2 to 3 times per week for 6 weeks</li> <li>Genetic testing for mutations in <i>ELANE</i></li> </ul>
<b>Primary immunodeficiency diseases</b>					
- 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	<ul style="list-style-type: none"> <li>Recurrent, life-threatening bacterial and fungal infections of the skin, airways, lymph nodes, liver, brain, and bones</li> <li>Severity of periodontal involvement is correlated with extent of the immune defect and ranges from gingival inflammation to generalized severe periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>Neutrophil-function testing followed by immunoblot confirmation</li> <li>Genetic testing for mutations in genes encoding for: <i>gp91phox</i>, <i>p47phox</i>, <i>p22phox</i>, <i>p67phox</i>, and <i>p40phox</i></li> </ul>
- Hyperimmunoglobulin E syndromes	Significant for the autosomal recessive form associated with <i>DOCK8</i> mutations; weak for other forms	Case reports, case series, narrative reviews	Mutations in signal transducer and activator of transcription 3 ( <i>STAT3</i> ) gene affect a transcription factor, and mutations in dedicator of cytokinesis 8 ( <i>DOCK8</i> ) gene affect a protein involved in intracellular signaling	<ul style="list-style-type: none"> <li>Recurrent skin abscesses, eczema, pulmonary infections, and other clinical manifestations</li> <li>Some, but not all, cases show severe gingival bleeding and generalized severe periodontitis</li> <li>There is delayed eruption of the permanent teeth</li> </ul>	<ul style="list-style-type: none"> <li>IgE &gt; 1000 IU/mL, a weighted score &gt; 30 of selected clinical/laboratory tests designed by the NIH</li> <li>Genetic testing to confirm mutations of <i>STAT3</i> or <i>DOCK8</i></li> </ul>
- 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	<ul style="list-style-type: none"> <li>Characteristic facial appearance, microcephaly, downward slanting eyes, hypotonia, joint laxity, mental retardation, neutropenia, myopia, and pigmentary retinopathy</li> <li>Increased prevalence and severity of alveolar bone loss</li> </ul>	<ul style="list-style-type: none"> <li>Reduced plasma levels of hCAP-18 (proprotein of the antibacterial peptide LL-37) determined by ELISA</li> </ul>

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
<b>Diseases affecting gingival tissue</b>					
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	<ul style="list-style-type: none"> <li>• Recurrent blister formation of skin and oral cavity that may be localized or generalized</li> <li>• Generalized gingival inflammation and severe loss of keratinized gingiva</li> </ul>	<ul style="list-style-type: none"> <li>• Skin biopsy of an induced blister via immunofluorescence microscopy mapping for basement membrane antigens</li> <li>• Genetic testing for mutations in COL7A1</li> </ul>
- Kindler syndrome	Significant	Case reports, narrative reviews	Mutations in the fermitin family homologue 1 (kindlin-1; <i>FERMT1</i> ) gene can cause lack of integrin activation, affect keratinocyte cell adhesion, and lead to molecular defects in the basement membrane zone	<ul style="list-style-type: none"> <li>• Recurrent blister formation of skin and oral cavity</li> <li>• Photosensitivity</li> <li>• Severe periodontitis and alveolar bone loss that progress rapidly</li> </ul>	<ul style="list-style-type: none"> <li>• Skin biopsy of an induced blister via immunofluorescence microscopy</li> <li>• Genetic testing for mutations in <i>FERMT1</i></li> </ul>
Plasminogen deficiency	Significant	Case reports, narrative review	Not well understood; possible mechanisms involve defective fibrinolysis, fibrin deposition, and abnormal wound healing	<ul style="list-style-type: none"> <li>• Chronic inflammatory disease of the mucous membranes of various organs</li> <li>• Ligneous conjunctivitis is common</li> <li>• Gingiva enlarged and ulcerated, may be covered with white-yellowish membrane, progressive alveolar bone loss and early loss of teeth</li> </ul>	<ul style="list-style-type: none"> <li>• Laboratory tests show decreased plasminogen activity and antigen level</li> <li>• Gingival biopsy shows positive staining for fibrin and negative for amyloid</li> </ul>
<b>Diseases affecting the connective tissues</b>					
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	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Generalized, early-onset severe periodontitis and gingival recession</li> <li>• Early loss of the primary and permanent teeth</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical findings of skin hyperextensibility, atrophic scars, and joint hypermobility</li> <li>• Genetic testing for mutations in collagen type V alpha 1 chain (<i>COL5A1</i>) and collagen type V alpha 2 chain (<i>COL5A2</i>) genes</li> </ul>
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	<ul style="list-style-type: none"> <li>• Serious and potentially life-threatening attacks of subcutaneous and submucosal edemas of upper airways, face, abdomen, and extremities</li> <li>• Localized or generalized severe periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>• Suggestive history and clinical findings</li> <li>• Consideration can be given for checking serum C1 inhibitor or ACE levels based on clinical suspicion</li> </ul>
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	<ul style="list-style-type: none"> <li>• Joint pain and swelling affecting the fingers, hands, wrists, and knees</li> <li>• Skin rash and fatigue</li> <li>• Oral ulcers and increased prevalence of gingival inflammation and periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>• 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</li> </ul>

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.<sup>28,29</sup>

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.<sup>30</sup> An increase in the prevalence of gingivitis and periodontitis has been reported.<sup>30</sup> 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.<sup>31</sup>

#### 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.<sup>2</sup>

The oral manifestations of Gaucher disease (GD) are often detected during routine dental radiographic examinations.<sup>32</sup> 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.<sup>33</sup>

In individuals with hypophosphatasia (HPP) the dentin is not affected, although both the acellular and cellular cementum may be absent, hypocalcified, or dysplastic.<sup>34</sup> These defects in root cementum result in compromised periodontal attachment and reduction in alveolar bone height.<sup>35</sup> 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.<sup>36,37</sup> 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.<sup>38</sup> 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.<sup>39</sup>

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.<sup>40</sup> Individuals with Hajdu-Cheney syndrome develop osteoporosis and commonly present with severe periodontitis and premature loss of teeth.<sup>41</sup>

## 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.<sup>42</sup> More recent data have confirmed a significant association between chronic hyperglycemia and a high prevalence of severe periodontitis.<sup>43,44</sup> 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.<sup>45-47</sup> 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.<sup>48</sup> Furthermore, in many diabetic patients DM is undiagnosed, and the prevalence of these individuals is increasing.<sup>49</sup> 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.<sup>50</sup>

Chronic hyperglycemia has direct and indirect detrimental effects on multiple organs and is implicated in the development and progression of diabetic micro- and macroangiopathy.<sup>51,52</sup> It may exert long-lasting detrimental effects on the cardiovascular system and other organs.<sup>53</sup> 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.<sup>54</sup>

The pathogenic mechanisms responsible for the effects of hyperglycemia on periodontitis have been extensively reviewed in the literature.<sup>55-58</sup> 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.<sup>55</sup> 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.<sup>56</sup> 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.<sup>59</sup> Blocking of RAGE using soluble receptors for AGE subsequently was shown to reverse these effects independently of the level of hyperglycemia.<sup>60</sup>

**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	<ul style="list-style-type: none"> <li>Hypoglycemia, hepatosplenomegaly, seizures, myeloid dysfunctions, neutropenia, and recurrent bacterial infections</li> <li>Severe periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>Genetic testing for mutations in the glucose 6-phosphatase, catalytic subunit (G6PC) gene and solute carrier family 37 member 4 (SLC37A4) gene encoding G6PT</li> </ul>
Gaucher disease	Moderate	Case reports	Deficiency of the enzyme glucocerebrosidase causes formation of Gaucher cells, which infiltrate into organs of the reticuloendothelial system	<ul style="list-style-type: none"> <li>Anemia, neutropenia, spontaneous bleeding, hepatosplenomegaly, and defective bone remodeling and osteopenia</li> <li>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</li> <li>Generalized severe alveolar bone loss may be present</li> </ul>	<ul style="list-style-type: none"> <li>Glucocerebrosidase enzyme assay to assess enzyme activity in peripheral leukocytes</li> <li>Genetic testing for mutations in the gene encoding glucocerebrosidase (GCD)</li> </ul>
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.	<ul style="list-style-type: none"> <li>Mild form: foot pain, stress fracture of the metatarsals</li> <li>Severe form: skeletal deformities, short stature, waddling gait, bone pain, high risk for bone fractures</li> <li>Defective cementum, alveolar bone loss, and premature loss of teeth</li> </ul>	<ul style="list-style-type: none"> <li>Evaluation of comprehensive metabolic panel to assess for low alkaline phosphatase in the serum</li> <li>Genetic testing for mutations in ALPL</li> </ul>
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	<ul style="list-style-type: none"> <li>Short stature and leg deformities</li> <li>Endodontic involvement and spontaneous periapical infections not due to tooth decay or trauma</li> <li>Alveolar bone loss, which may be severe</li> <li>Increased prevalence of periodontitis</li> <li>Premature loss of teeth</li> </ul>	<ul style="list-style-type: none"> <li>The following 4 conditions must be present: increased serum alkaline phosphatase, normal serum parathyroid hormone, normal serum calcium, and decreased serum phosphate levels</li> </ul>
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	<ul style="list-style-type: none"> <li>Short stature, small face, acro-osteolysis (resorption of the distal phalanx on X-ray), hearing loss, and osteoporosis</li> <li>Severe periodontitis and premature loss of teeth</li> </ul>	<ul style="list-style-type: none"> <li>Clinical diagnosis</li> <li>Genetic testing can detect the truncating mutation in the terminal exon of NOTCH2</li> </ul>
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)	<ul style="list-style-type: none"> <li>Decrease in bone mineral density and weakening of bone microarchitecture, leading to a high risk for bone fracture</li> <li>Higher prevalence and severity of radiographic alveolar bone loss</li> <li>No clear association with periodontitis (probing depth or clinical attachment loss)</li> </ul>	<ul style="list-style-type: none"> <li>Clinical diagnosis</li> </ul>

(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	<ul style="list-style-type: none"> <li>Chronic status of elevated blood glucose level</li> <li>Increased prevalence and severity of attachment loss</li> </ul>	<ul style="list-style-type: none"> <li>Fasting plasma glucose level</li> <li>HBA1c test</li> </ul>
Obesity	Significant	Animal models, surveys, case-control study, systematic reviews	Possible mechanisms include an impaired immune response and increased production of proinflammatory cytokines	<ul style="list-style-type: none"> <li>BMI <math>\geq 30</math></li> <li>Increased risk for periodontitis, periodontal progression, and loss of periodontal attachment</li> </ul>	<ul style="list-style-type: none"> <li>Clinical diagnosis</li> </ul>

AGE, advanced glycation end product; BMI, body mass index; G6PT, glucose-6-phosphate dehydrogenase; HbA<sub>1c</sub>, 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.<sup>61</sup> 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<sub>1c</sub>  $\geq 6.5\%$ .<sup>62</sup> 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.<sup>63</sup>

## 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.<sup>64</sup>

Dysfunction of processes in adipose tissue compartments may trigger various metabolic disorders, including obesity, metabolic syndrome, lipodystrophy, and cachexia.<sup>65</sup> Studies show that cross-talk between T cells and adipose tissue shapes the inflammatory environment in obesity-associated metabolic diseases.<sup>66</sup> Likewise, obesity-induced changes to macrophages and adipocytes may lead to chronic inflammation and insulin resistance.<sup>67</sup> 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.<sup>68</sup> 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.<sup>69</sup> Other effects on the immune response include decreased phagocytic activity and impaired antigen presentation.<sup>67</sup>

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.<sup>70,71</sup> 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,<sup>72</sup> and the risk may be higher among women who are obese compared with men who are obese.<sup>73</sup> 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.<sup>74</sup>

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.<sup>75,76</sup> The increased production by adipose tissue of various humoral factors (adipokines) and proinflammatory cytokines may contribute to the pathogenesis of periodontitis.<sup>77</sup> Obesity also may abate the innate immune response in the periodontium, for example via attenuation of macrophage infiltration and activation.<sup>78</sup> This may explain the higher occurrence of spontaneous<sup>79</sup> and ligature-induced<sup>80</sup> 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.<sup>81</sup> 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.<sup>82</sup> 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.<sup>83</sup> 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.<sup>84</sup> Studies show greater attachment loss and higher prevalence and severity of periodontitis in adults with IBD than in controls.<sup>85</sup> 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.<sup>86</sup>

## 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	<ul style="list-style-type: none"> <li>ANC &lt; 1500 cells/<math>\mu</math>L (mild), &lt; 1000 cells/<math>\mu</math>L (moderate), or &lt; 500 cells/<math>\mu</math>L (severe)</li> <li>Increased risk for infections correlated with severity of neutropenia</li> <li>Increased risk for periodontitis correlated with the severity of neutropenia</li> </ul>	<ul style="list-style-type: none"> <li>Determine ANC</li> </ul>
HIV infection	Weak	Surveys, case-control study, narrative reviews	Deficiency of the immune system due to infection with the HIV virus	<ul style="list-style-type: none"> <li>The CDC and Council of State and Territorial Epidemiologists recommend a revised case definition of HIV infection</li> <li>Increased risk for infections, Kaposi sarcoma</li> <li>Oral candidiasis, oral hairy leukoplakia, severe aphthous ulcers</li> <li>Increased risk for necrotizing periodontal diseases</li> </ul>	<ul style="list-style-type: none"> <li>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.</li> </ul>

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	<ul style="list-style-type: none"> <li>Mechanobullous type: characterized by blisters, mild mucosal involvement, and healing with dense scars primarily at trauma-prone areas</li> <li>Inflammatory form: present as a generalized vesiculobullous eruption primarily on the trunk and flexural areas</li> <li>Recurrent blister formation of oral cavity that may be localized or generalized</li> <li>Generalized gingival inflammation and severe alveolar bone loss that may be localized or generalized</li> </ul>	<ul style="list-style-type: none"> <li>Detailed history and clinical evaluation for skin lesions, followed by direct immunofluorescence microscopy of perilesional skin and immunofluorescence on basement membrane zone-split skin</li> </ul>
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	<ul style="list-style-type: none"> <li>Abdominal pain, fever, diarrhea, and weight loss</li> <li>Colonoscopy showing polypoid mucosal changes, ulcerations, and inflammatory changes</li> <li>Increased prevalence and severity of periodontitis and loss of periodontal attachment and alveolar bone</li> </ul>	<ul style="list-style-type: none"> <li>History, colonoscopy, and intestinal biopsy</li> </ul>
Arthritis	Significant	Animal models, systematic review	Rheumatoid arthritis is an autoimmune disease; osteoarthritis is due to gradual deterioration of cartilage	<ul style="list-style-type: none"> <li>Joint pain, swelling, stiffness, redness, and limited motion</li> <li>Increased risk for loss of periodontal attachment and alveolar bone</li> </ul>	<ul style="list-style-type: none"> <li>Clinical history and physical examination for arthritis</li> </ul>

**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	<ul style="list-style-type: none"> <li>Changes in behavior, mood, and physiological markers</li> <li>Risk factor for ulcerative periodontal disease; association with alveolar bone loss in animal models</li> </ul>	<ul style="list-style-type: none"> <li>There is no specific test to diagnose stress</li> <li>Diagnosis of depression may include a physical exam and psychological evaluation</li> </ul>
Hypertension	Inconclusive	Surveys	Undetermined	<ul style="list-style-type: none"> <li>Chronic status of high blood pressure</li> <li>Most studies reported no significant association with periodontitis or attachment loss</li> </ul>	<ul style="list-style-type: none"> <li>Physical exam</li> </ul>

experimentally induced stress significantly increases periodontal destruction in rats, whereas interventions to modulate the hypothalamic-pituitary-adrenal axis reverse this effect.<sup>87</sup> 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.
<b>For malignancies</b>			
Anticancer chemotherapy	Increase	Case-control	93
VEGF inhibitors (bevacizumab)	Increase	Case report	94,95
TKIs (sunitinib, pazopanib)	Increase	Case report	96
<b>Anti-inflammatory agents</b>			
NSAIDs	Decrease	Case-control study; case series	Reviewed in <sup>97</sup>
Anti-TNF therapies	Decrease	Case-control	98
<b>Miscellaneous</b>			
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	<ul style="list-style-type: none"> <li>Localized swelling or ulceration of the gingiva, typically in the mandibular molar region</li> <li>Other features similar to localized periodontitis</li> <li>Regional lymphadenopathy</li> <li>Risk for late-stage metastases</li> </ul>	<ul style="list-style-type: none"> <li>Biopsy</li> </ul>
- Odontogenic tumors	Moderate	Case reports	Neoplasm of odontogenic epithelium	<ul style="list-style-type: none"> <li>Early lesion: mandibular or maxillary localized swelling and tooth displacement</li> <li>Late features: similar to localized periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>Biopsy</li> </ul>
- Other primary neoplasms of periodontal tissue	Moderate	Case reports	Malignant neoplasm	<ul style="list-style-type: none"> <li>Osteolytic expanding lesion in the jaw</li> </ul>	<ul style="list-style-type: none"> <li>Biopsy</li> </ul>
Secondary metastatic neoplasms of periodontal tissue	Moderate	Case reports	Malignant neoplasm	<ul style="list-style-type: none"> <li>Osteolytic expanding lesion(s) in jaws</li> <li>Presence of primary lesion elsewhere in the body; location of primary neoplasm varies according to the type of neoplasm</li> </ul>	<ul style="list-style-type: none"> <li>Biopsy</li> <li>Systemic examination to rule out primary lesion</li> </ul>

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.<sup>88</sup> In addition, loss of the lamina dura and widening of the periodontal ligament may be common findings.<sup>89</sup> Other diseases that may cause alveolar bone loss include systemic sclerosis (scleroderma)<sup>90</sup> and vanishing bone disease.<sup>91,92</sup>

## 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	<ul style="list-style-type: none"> <li>Respiratory and renal impairment</li> <li>Characteristic fiery red hyperplastic gingivitis</li> <li>Alveolar bone loss</li> </ul>	<ul style="list-style-type: none"> <li>Clinical appearance</li> <li>Biopsy</li> </ul>
Langerhans cell histiocytosis	Moderate	Case series and case reports	Due to proliferation of cells with characteristics similar to bone marrow-derived Langerhans cells	<ul style="list-style-type: none"> <li>Wide spectrum of clinical presentations, including solitary chronic bone lesions, diabetes insipidus, and proptosis</li> <li>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</li> </ul>	<ul style="list-style-type: none"> <li>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</li> </ul>
Giant cell granuloma	Moderate	Case series	Reactive proliferation	<ul style="list-style-type: none"> <li>Peripheral GCG: expanding epulis-like gingival swelling, occasional loss of periodontal supporting tissue</li> <li>Central GCG: loss of deep periodontal supporting tissue, which may expand toward marginal periodontal tissue</li> <li>No systemic features</li> </ul>	<ul style="list-style-type: none"> <li>Biopsy</li> </ul>
Hyperparathyroidism	Moderate	Case series	Primary: benign adenoma of parathyroid glands; secondary: result of hypercalcemia; tertiary: parathyroid hypertrophy following secondary type	<ul style="list-style-type: none"> <li>Weakness, kidney stones, excessive urination, abdominal pain, bone and joint pain</li> <li>Widening of the PDL and single or multiple osteolytic lesions (brown tumors) in the jaw that may mimic bone loss due to periodontal disease</li> </ul>	<ul style="list-style-type: none"> <li>Test shows elevated serum PTH</li> <li>Biopsy</li> </ul>
Systemic sclerosis (scleroderma)	Moderate	Case reports	Autoimmune disease of the connective tissues	<ul style="list-style-type: none"> <li>Many different systemic presentations</li> <li>Widening of the PDL and higher prevalence of periodontitis</li> </ul>	<ul style="list-style-type: none"> <li>Physical exam</li> <li>Raynaud phenomenon</li> <li>Autoantibody screening</li> </ul>
Vanishing bone disease	Moderate	Case reports	Unknown	<ul style="list-style-type: none"> <li>Progressive destruction of one or multiple bones</li> <li>Progressive loss of the mandibular alveolar bone and increased mobility of teeth</li> </ul>	<ul style="list-style-type: none"> <li>Clinical and radiographic exams</li> <li>Biopsy</li> </ul>

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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