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Risk of Systemic Diseases and Periodontal Disease

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Introduction

Contemporary periodontology is grounded in a detailed understanding of the anatomy and physiology of the tissues that support and surround the teeth. The periodontium, composed of the gingiva, periodontal ligament, cementum, and alveolar bone, forms a dynamic functional unit designed to absorb and distribute occlusal forces, facilitate nutrient exchange, allow controlled tooth mobility, and preserve the integrity of the gingival environment.

Historically, periodontal diseases, particularly periodontitis, were viewed primarily as infectious conditions. However, recent advances in molecular biology and genetics have clarified their multifactorial etiology, where disease progression is influenced by the interplay between genetic predisposition, host immune-inflammatory responses, and environmental factors. Periodontitis is now widely recognized as a probabilistic genetic disorder, in which the mere presence of a susceptible genotype does not ensure disease manifestation—additional external and internal risk factors are required.

This review aims to provide a comprehensive overview of the anatomical structures comprising the tooth attachment apparatus, describe their physiological roles, and contextualize the current understanding of periodontal disease etiology, with emphasis on the biological interactions that drive its initiation and progression.

Anatomy of the Periodontium

Alveolodental Joint (Gomphosis)

The alveolodental joint, or gomphosis, represents the anatomical and functional unit responsible for receiving masticatory loads and transmitting them to the adjacent bone. It is composed of the tooth root(s), the alveolar bone, and the periodontal ligament (PDL), which connects the two.

The periodontium includes the following components:

- Gingiva.
- Periodontal ligament.
- Radicular cementum.
- Alveolar bone.

The alveolar bone consists of the alveolar bone proper (also known as bundle bone) and the alveolar process, which collectively form the bony socket that houses the tooth.

The formation of periodontal tissues is closely tied to tooth development during embryogenesis. Neural crest cells originating from the neural tube migrate into the first branchial arch, giving rise to ectomesenchymal tissue that interacts with the oral epithelium.

These epithelial-mesenchymal interactions drive the formation of the dental lamina and the successive stages of tooth development (bud, cap, and bell stages), ultimately leading to the formation of the tooth and its surrounding support structures.

Specifically:

- The dental organ gives rise to enamel.
- The dental papilla forms the dentin-pulp complex.
- The dental follicle differentiates into the cementum, PDL, and alveolar bone.

This developmental pathway underscores the ectomesenchyme's dominant role in both the morphology and structural composition of the tooth and its attachment apparatus. (Lindhe et al., 2009)

Periodontal anatomy can be analyzed from two perspectives:

- ***Macroscopic***: covering clinical characteristics, visible structures, and their functions.
- ***Microscopic***: including histological composition, epithelial and connective tissues, vascularization, innervation, and biological width.

The Periodontium

The periodontium functions as an integrated unit composed of the gingiva, periodontal ligament, alveolar bone proper, radicular cementum, and the alveolar process. Its principal roles include anchoring the teeth within the alveolar bone and maintaining the integrity of the masticatory mucosa. From an evolutionary standpoint, the periodontium is considered a biologically specialized system comprising both the attachment apparatus and the supporting tissues of the tooth.

Oral Mucosa and Gingiva

The oral mucosa is divided into:

- ***Masticatory mucosa*** (gingiva and hard palate).
- ***Specialized mucosa*** (dorsal surface of the tongue).
- ***Lining mucosa*** (all other oral surfaces).

The gingiva is the portion of masticatory mucosa that covers the alveolar process and surrounds the cervical portion of the tooth. It acquires its final contour and texture upon completion of tooth eruption and is subdivided into:

- ***Free gingiva***: coral pink, firm in consistency, forming the gingival margin and interdental papillae.
- ***Attached gingiva***: extending from the sulcus to the mucogingival junction.

On the buccal and lingual aspects, the free gingiva ends at the gingival sulcus, near the cementoenamel junction (CEJ). Palatal gingiva lacks a mucogingival junction due to its continuity with the hard palate.

The shape of the interdental papilla is influenced by tooth anatomy and contact points: pyramidal in the anterior region and flatter in the posterior. Between buccal and palatal papillae lies the COL, a non-keratinized epithelial depression. (Lindhe et al., 2009)

The width of attached gingiva is variable and generally increases with age due to passive eruption, not migration of the mucogingival junction.

Periodontal Ligament (PDL)

The PDL is a specialized, highly cellular and vascularized connective tissue that surrounds the tooth roots and connects the cemen-

tum to the alveolar bone. Coronally, it continues into the gingival lamina propria and is delineated by the alveolar crest fibers, a subset of the principal fiber groups.

Located between the root and the alveolar bone proper, the PDL occupies a space that is narrowest at mid-root level, averaging 0.25 mm in thickness (range: 0.2-0.4 mm). Its unique structure enables the controlled transmission of occlusal forces and contributes to physiologic tooth mobility. Factors such as PDL thickness, height, and quality significantly influence this mobility. (Lindhe et al., 2009)

PDL fiber groups include:

- ***Circular fibers***: encircle the tooth.
- ***Dentogingival fibers***: extend from the cementum into the gingiva.
- ***Dentoperiosteal fibers***: project apically into the periosteum.
- ***Transseptal fibers***: run between adjacent teeth.1.5 Radicular Cementum.

Cementum is a calcified, avascular tissue that covers the root surface. It shares similarities with bone but lacks innervation, vascularization, and physiological remodeling. It undergoes continuous deposition throughout life and serves as the anchoring medium for PDL fibers. Its composition is roughly 65% inorganic (hydroxyapatite).

Functions of cementum include:

- Providing insertion for periodontal fibers.
- Contributing to root surface repair.

Types of cementum:

- ***Acellular extrinsic fiber cementum (AEFC):*** located in coronal and middle thirds of the root; contains Sharpey's fibers.
- ***Cellular mixed stratified cementum (CMSC):*** found in the apical third and furcation areas; contains both extrinsic/intrinsic fibers and cementocytes.
- ***Cellular intrinsic fiber cementum (CIFC):*** involved in repair processes; rich in intrinsic fibers and cementocytes. (Lindhe et al., 2009)

Alveolar Bone

The alveolar process is the part of the maxilla or mandible that forms the socket for tooth insertion. It originates partly from cells of the dental follicle and partly from independent bone-forming cells. Together with the cementum and PDL, it constitutes the tooth attachment apparatus, whose role is to support and redistribute masticatory forces.

Morphophysiology of the Periodontium

The structures of the gingiva, the supporting tissues of the teeth, and their substitutes are studied in dentistry by the specialty of periodontics.

Therefore, it is essential to understand the characteristics of the periodontium—its components, anatomical boundaries, and function—in a state of optimal health, to establish a proper reference point for diagnosis, treatment planning, and prognosis, both in the prevention and management of periodontal diseases.

In 1989, it was recognized that periodontitis had several distinct clinical presentations, with different ages of onset and rates of progression (Caton et al., 1989). Based on these variables, periodontitis was categorized as prepubertal, juvenile (localized and generalized), adult, and rapidly progressive.

At the 1993 Workshop on Periodontitis, it was proposed that the classification should be simplified into two main categories: adult periodontitis and early-onset periodontitis (Proceedings of the 1st European Workshop on Periodontics, 1993. London: Quintessence; 1994).

In 1999, significant changes were introduced in the classification of periodontitis (Lindhe et al., 1999; Lang et al., 1999), which have been in use for the past decades. Periodontitis was reclassified as chronic, aggressive (localized and generalized), necrotizing, and as a manifestation of systemic disease.

Since 1999, substantial new information has emerged from population studies, basic science research, and prospective studies evaluating environmental and systemic risk factors. The analysis of this evidence led to the 2017 World Workshop, where Papapanou et al. proposed a new classification framework for periodontitis.

Staging relies heavily on the severity and complexity of disease management, while grading provides complementary information about the biological features of the disease, including historical progression rates, risk of further progression, expected treatment outcomes, and the risk that the disease or its treatment may negatively impact the patient's overall health (Tonetti et al., 2018; Papapanou et al., 2018).

Staging involves four categories (Stages 1 through 4), determined by several variables, including clinical attachment loss, amount and percentage of bone loss, probing depth, presence and extent of angular bone 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 of progression), and it encompasses factors related to the rate of progression, general health status, and other exposures such as smoking or the degree of metabolic control in diabetes.

Grading allows clinicians to integrate individual patient factors into the diagnosis, which is crucial for comprehensive case management (Caton et al., 2018).

The new classification also includes systemic diseases and conditions that affect the periodontal supporting tissues.

Rare systemic disorders, such as Papillon-Lefèvre syndrome, typically seen in early-onset periodontitis, are grouped under "Periodontitis as a Manifestation of Systemic Disease," and classification should be based on the primary systemic condition (Albandar et al., 2018).

Other conditions such as neoplasms, which are independent of biofilm-induced plaque, should also be classified according to their primary systemic disease and grouped as "Systemic Diseases or Conditions Affecting the Periodontal Supporting Tissues" (Jepsen et al., 2018).

However, common systemic diseases, such as uncontrolled diabetes mellitus, exert variable effects that modify the course of periodontitis. These appear to be part of the multifactorial nature of complex diseases like periodontitis and are now included in the new clinical classification as descriptors during the staging and grading process (Tonetti et al., 2018).

Although common modifiers of periodontitis can substantially influence disease onset, severity, and treatment response, current evidence does not support a unique pathophysiology in patients with both diabetes and periodontitis.

Epidemiology

Not all individuals are equally susceptible to developing periodontitis. These differences in susceptibility are largely determined by risk factors.

The concept of a risk factor has developed in recent years thanks to methodological advances and the creation of comprehensive patient databases containing information on systemic factors, habits, demographics, and dental disease data. These advances were also made possible by increasingly powerful computers and more sophisticated statistical techniques.

The most extensive database, NHANES (National Health and Nutrition Examination Survey), from the United States, provides data such as: nearly 47.2% of individuals over 30 years of age have periodontitis; of these, 8.7% have mild, 30% moderate, and 8.5% severe periodontitis.

Gingivitis and Periodontitis Prevalence

Gingivitis

- Very common across all age groups and populations.
- Present in early childhood.
- Higher prevalence and severity during adolescence, with a tendency to decline thereafter.

Periodontitis

- ***Children***: 0.9-4.5% prevalence in 5-11-year-olds in industrialized countries (primary dentition).
- ***Adolescents***: <1% prevalence in industrialized countries. Up to 10 times higher in certain ethnic groups (Caucasians: 0.1-0.2%; African Americans: 2.6%).
- ***Adults***: Moderate forms of the disease are very common (~40%). Advanced forms affect about 10-15% of the population.
- ***Necrotizing Periodontal Diseases***: In industrialized countries, the prevalence is approximately 0.05%.

Prevalence

Prevalence in the United States

Brown:

- 33% of adults have moderate periodontitis.
- 8% have advanced periodontitis.
- 50% present with gingivitis.

Albandar:

- High prevalence of bleeding and clinical attachment loss < 4 mm.
- Low prevalence of severe periodontitis.

Prevalence in Spain

According to WHO methodology using the Community Periodontal Index (CPI), previously known as CPITN, in three age cohorts:

- ***15 years:***
  - 55% healthy.
  - 30% with calculus.
- ***35-44 years:***
  - 19% healthy.
  - 4.2% with deep periodontal pockets.
- ***65-74 years:***
  - 8.7% healthy.
  - 9% with deep periodontal pockets.

Treatment Needs

- ***15 years:***
  - 50% need oral hygiene instruction.
  - 30% require calculus removal.
- ***35-44 years:***
  - 4.2% require complex periodontal treatment.
- ***65-74 years:***
  - 8.7% require complex periodontal treatment.

Influence of Gender, Socioeconomic Level, and Geographic Area

- ***Gender***: Women show better periodontal health in the 15 and 35-44 age groups.
- ***Socioeconomic and geographic factors***: No significant differences in disease prevalence.
- However, differences are observed in treatment needs:
  - Individuals with higher socioeconomic status require less oral hygiene instruction and fewer prophylaxis/scaling procedures.
  - No differences observed in the need for complex periodontal treatments across socioeconomic levels.

Periodontal Diagnosis and Classification

Clinical periodontal health is defined as the absence of inflammation, which must be present in less than 10% of sites with bleeding on probing (BoP). There must also be no clinical attachment loss or bone loss.

Gingivitis is defined by the presence of inflammation, indicated by BoP in ≥10% of sites, and the absence of detectable clinical attachment loss.

- ***Localized gingivitis***: 10%-30% of sites with BoP.
- ***Generalized gingivitis***: >30% of sites with BoP.

Patients with gingivitis present a clinical picture characterized by:

- Diffuse gingival inflammation.
- Redness.
- Inflammation limited to the gingiva / reversible upon plaque removal.
- Spontaneous bleeding / bleeding on periodontal probing.
- Evolution in episodes of variable duration and intensity.

Risk Factors

Risk factors can be subdivided into genetic, environmental, and acquired categories.

- A risk indicator refers to a factor that may biologically be a causal agent of disease, but whose association has only been demonstrated in cross-sectional studies (it may be reclassified as a risk factor if a prospective association is proven).
- A risk predictor refers to a factor that currently lacks a biological explanation to be a causal agent, but has been associated with disease in cross-sectional or longitudinal studies.
- A risk determinant refers to risk factors that are non-modifiable, such as age or race.

Risk Assessment

Risk assessment is a method of evaluating risks in order to prevent, reduce, or control them.

To define a variable as a risk factor, it must fulfill causality criteria, of which the six most important are:

1. ***Strength of the association*** - measured through relative risk.
2. ***Consistency of the association*** - repeated association in different people, places, circumstances, etc.
3. ***Specificity*** - exclusive relationship.
4. ***Temporal sequence*** - cause precedes effect.
5. ***Dose-response relationship*** - assumes a uniform increase or decrease in effect with the amount of exposure until saturation is reached.
6. ***Biological plausibility*** - depends on the current level of biological understanding.

Risk Factors in Gingivitis

In gingivitis, risk factors are classified as:

- *Predisposing (local) factors*, and
- *Modifying (systemic) factors*. (Murakami et al., 2018; Trombelli et al., 2018)

Local predisposing factors that lead to increased plaque accumulation include:

- Overhanging restorations.
- Subgingival crown margins.
- Xerostomia (dry mouth).

Modifying Risk Factors

Modifying risk factors that alter the immune-inflammatory response include:

- Smoking.
- Hyperglycemia (in diabetic patients).
- Reduced intake of antioxidant micronutrients (e.g., vitamin C).
- Medications, especially those modulating the immune system.
- Elevated levels of steroid sex hormones.
- Hematological disorders (e.g., neutropenia).

There is also an association with other risk factors, especially stress. From early studies on periodontal diseases (e.g., necrotizing gingivitis), stress has been implicated. Increasing evidence links stress, anxiety, and poor coping abilities with chronic periodontitis. A positive correlation exists between stress levels and periodontitis severity—higher stress tends to be associated with more advanced periodontal disease.

Proposed mechanisms by which stress acts as a risk factor for periodontitis include:

- Alteration of the immune response: stress can cause immunosuppression, favoring periodontal breakdown.
- Induction of corticosteroid and catecholamine release.
- Behavioral changes: stress may negatively affect behaviors critical to periodontal health, such as poor oral hygiene, increased smoking, fewer dental visits, and unhealthy eating habits.

In periodontitis, there is loss of periodontal tissue support. This bone loss is commonly evaluated radiographically or through interproximal clinical attachment loss.

A patient with stable periodontitis is defined by the presence of gingival health on a reduced periodontium (BoP in <10% of sites; shallow probing depths of 4 mm or less; and no sites with 4 mm and bleeding on probing).

If, after periodontal treatment, these criteria are met but BoP is >10%, the patient is considered to have stable periodontitis with gingival inflammation.

Sites with persistent probing depths ≥4 mm and BoP are likely unstable and may require additional treatment.

It is important to recognize that patients with successfully treated stable periodontitis remain at increased risk for recurrence, so the presence of gingival inflammation should be addressed appropriately to prevent relapse.

Diagnostic Algorithm (EFP, Trombelli et al., 2020)

The European Federation of Periodontology (EFP) has proposed an algorithm to assist clinicians in the diagnostic process of new patients. It consists of four sequential steps:

1. Identification of a patient suspected to have periodontitis.
2. Confirmation of periodontitis diagnosis.
3. Staging of the periodontitis case.
4. Grading of the periodontitis case.

New Periodontal Classification (Papapanou et al., 2018)

The American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) developed a new classification of periodontal diseases in 2018, replacing the 1999 classification.

Periodontal Disease Classification by AAP (2018)
Periodontal health, gingival diseases, and conditions

1. ***Periodontal and gingival health***
    a. Clinical gingival health on an intact periodontium.
    b. Clinical gingival health on a reduced periodontium.
    - Periodontitis patient with stable condition.
    - Non-periodontitis patient.
2. ***Gingivitis induced by dental biofilm***
    a. Associated only with dental biofilm.
    b. Mediated by systemic or local risk factors.
    c. Drug-influenced gingival enlargement.
3. ***Non-dental biofilm-induced gingival diseases***
    a. Genetic/developmental disorders.
    b. Specific infections.
    c. Inflammatory and immune conditions.
    d. Reactive processes.
    e. Neoplasms.
    f. Endocrine, nutritional, and metabolic diseases.
    g. Traumatic lesions.

h. Gingival pigmentation.

Forms of periodontitis

1. ***Necrotizing periodontal diseases***
   a. Necrotizing gingivitis.
   b. Necrotizing periodontitis.
   c. Necrotizing stomatitis.
2. ***Periodontitis as a manifestation of systemic diseases***
   a. The 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.

Periodontitis

a. Staging based on 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***: Severe periodontitis with potential for loss of the dentition.

b. Extension and distribution
   - Localized.
   - Generalized.
   - Molar-incisor pattern.

c. Grading: Based on evidence or risk of rapid progression and anticipated treatment response
   - ***Grade A***: Slow rate of progression.
   - ***Grade B***: Moderate rate of progression.
   - ***Grade C***: Rapid rate of progression.

Periodontal manifestations of systemic diseases and developmental and acquired conditions

1. ***Systemic diseases and conditions affecting the periodontal supporting tissues***
2. ***Other periodontal conditions***
   a. Periodontal abscesses.
   b. Endo-periodontal lesions.
3. ***Mucogingival deformities and conditions around teeth***
   a. Gingival phenotype.
   b. Gingival/soft tissue recession.
   c. Lack of keratinized gingiva.
   d. Reduced vestibular depth.
   e. Aberrant frenum/muscle position.
   f. Gingival excess.
   g. Abnormal color.
   h. Condition of exposed root surface.
4. ***Traumatic occlusal forces***
   a. Primary occlusal trauma.
   b. Secondary occlusal trauma.

c. Orthodontic forces.

5. ***Prosthetic and dental factors that modify or predispose to plaque-induced gingival/periodontal diseases***
   a. Localized factors related to teeth.
   b. Localized factors related to dental prostheses.

Peri-implant diseases and conditions

1. Peri-implant health.
2. Peri-implant mucositis.
3. Peri-implantitis.
4. Peri-implant soft and hard tissue deficiencies.

The corresponding stages and grades of periodontal disease are defined in Tables 1 and 2 according to the 2018 classification system.

	ESTADIO I	***ESTADIO II***	***ESTADIO III***	***ESTADIO IV***
Loss of insertion	1-2mm	3-4mm	> = 5mm	> = 8mm
Bone loss	1/3 coronal (< 15%) of the root	1/3 coronal (15-33%) of the root	1/3 medium	1/3 apical
Lost teeth	No tooth los	No tooth los	Loss of 4 teeth máximum	Loss of 5 or more teeth
Complexity Factors Stage Changes				
Drilling depth			6-7mm bags	Bags 8mm or more
Furcation Involvement			Grade II and III furcation	
Type of bone loss			3mm o >	
				Need for complex rehabilitation due to masticatory dysfunction
				Secondary occlusal trauma (<20 teeth, bite collapse, severe ridge defect)
				LOCALIZED < 30% of teeth GENERALIZED > 30% of teeth INCISIVE-MOLAR PATTERN (affects incisors and first molars, early onset in adolescence)

Table 1: Stages of Periodontal Disease.

GRADOS = EVOLUCION

	LENTO A	***MODERADO B***	***RAPIDO C***
Direct	There is no los	Loss < 2mm in 5 years	Loss > 2mm in 5 years
Hint	0,25	0,25 -1	>1
	Abundant deposit, little destruction	Destruction in accordance with deposit	Destruction greater than expected
Modifiers	Does not smoke	Smokes < 10cg/day	Smokes > 10cg/day
	Blood Glucose N	Diabetic ⬇ Hb/Ac < 7	Diabetic ⬇ Hb/Ac >/= 7

Table 2: Degrees of periodontal disease.

Systemic Diseases Related to Periodontal Disease

Periodontitis can be considered a public health problem because, besides affecting oral health, in the last decade it has been suggested as a risk indicator influencing a variety of systemic diseases such as diabetes mellitus, cardiovascular disease, pneumonia, adverse pregnancy outcomes, chronic obstructive pulmonary disease, and cerebrovascular ischemia, among others. (Scannapieco, 2004)

There is evidence that oral bacterial species can enter the bloodstream and cause bacteremia, which has been demonstrated following daily life activities (tooth brushing, flossing, chewing or biting an apple), although it has been studied more frequently after professional interventions (dental polishing, scaling, dental extraction, surgical extraction of third molars, and periodontal probing). (Sanz et al., 2020)

Alzheimer's Disease

According to World Health Organization (WHO) statistics, Alzheimer's disease is considered the most common form of dementia worldwide, with approximately 50 million people affected. Alzheimer's disease (AD) is conceptualized as a primary neurodegenerative disorder caused by a decrease in acetylcholine, a neurotransmitter that is vital for brain function.

Over the past 15 years, studies have linked periodontal disease and its pathogen, specifically *Porphyromonas gingivalis*, as a causal factor and risk for developing this type of dementia. (Ilievski et al., 2018; Poole et al., 2015; Wu et al., 2017)

Various observational and in vitro studies show the possible relationship between *Porphyromonas gingivalis* and its toxic by-products such as lipopolysaccharides (LPS) and gingipains as potential risk factors and causal agents in the pathogenesis of Alzheimer's disease. (Vaca et al., 2021)

According to Wu et al. (2017), the presence of *P. gingivalis* DNA and its associated gingipains and lipopolysaccharides related to periodontal disease could present a risk factor for brain cell function. Considering Alzheimer's pathogenesis, it is established that *P. gingivalis* LPS triggers a cascade reaction, as it can induce beta-amyloid protein, and gingipains induce Tau protein, showing that *P. gingivalis* can produce both proteins causing Alzheimer's disease.

Porphyromonas gingivalis due to its cytotoxic products, LPS and gingipains RgpB and Kgp, provoke inflammation throughout brain tissue that incites the production of amyloid precursor protein (APP), leading to increased AB42, an abnormal peptide that forms extracellular amyloid plaques. Simultaneously, Tau protein inside neurons is altered, generating neurofibrillary tangles—both risk

factors and histological features of Alzheimer's disease. (Vaca et al., 2021)

Butyric acid, a virulence factor of pathogenic periodontal bacteria, can stimulate oxidative stress in the blood and lead to a systemic inflammatory response, further stimulating oxidative stress and endoplasmic reticulum stress in the brain, and inducing calcium signaling and cell death signaling in several brain regions such as the cerebellum and hippocampus. (Cueno et al., 2018)

A 2012 study by Sparks et al. showed that in the years prior to cognitive decline, subjects had elevated antibodies related to anti-periodontal pathogens in their serum, suggesting periodontitis may induce the onset of Alzheimer's disease. However, some studies suggest that for people with dementia under 70 years, periodontal pathogens may not trigger Alzheimer's disease. (Laugisch et al., 2018)

In patients with Alzheimer's, periodontitis can be more severe due to difficulties in routine oral hygiene measures, further feeding the previously described process, as inflammation is the basis of both Alzheimer's disease and periodontal disease. (Armstrong, 2019).

Diabetes

Currently, diabetes (Figure 2) is classified as an emerging epidemic, arousing great interest in the scientific community due to its evolution and scope, thus being the subject of many scientific studies. Many studies have been developed to establish a correlation between diabetes and periodontal disease. It has been shown that diabetes is a risk factor for periodontal disease and that diabetic patients develop more accelerated and severe periodontitis. There is also evidence that periodontal disease influences the endocrine metabolic state of diabetics, so diabetic patients treated for periodontal disease achieve better metabolic stability, remaining compensated for longer.

Globally, over the past 30 years, the number of people with diabetes mellitus has quadrupled and is the ninth leading cause of death. It affects about 1 in 11 individuals. Between 10% and 20% of diabetics have Type I, and the remaining 80-90% have Type II, which is the most common. (Navya et al., 2021; Zheng et al., 2017)

Diabetes mellitus is a chronic, systemic, and multifactorial pathology characterized by persistently elevated blood glucose levels, which can cause numerous complications. The pancreas produces an anabolic hormone called insulin. When there is a deficiency of this hormone, glucose is not properly transported to cells and adipose tissues, causing hyperglycemia (significantly increased blood sugar). (Navya et al., 2021)

Diagnosis includes a fasting blood glucose level ≥126 mg/dl on two or more tests. Also, a random blood glucose ≥200 mg/dl in the presence of hyperglycemia symptoms. Additionally, when fasting glucose is ≥110 mg/dl but <126 mg/dl, it is called impaired fasting glucose, and these patients are termed prediabetics. (Zheng et al., 2017)

Glycated hemoglobin (HbA1c) is used to measure the percentage of hemoglobin molecules bound to glucose. HbA1c is higher the greater the average blood glucose concentration over the previous 2-3 months. The HbA1c test is a blood test used to diagnose diabetes when average glucose levels are elevated.

According to the American Diabetes Association, diabetes is classified into four main groups depending on pathogenesis: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes (GDM), and specific types of diabetes due to other causes.

Fowler (2011) and Kosiborod et al. (2018) report that persistent hyperglycemia in T1DM and T2DM is significantly associated with the development of micro- and macrovascular complications such as retinopathy with potential vision loss, nephropathy leading to renal failure, peripheral neuropathy, coronary heart disease, cerebrovascular disease, and peripheral arterial disease with higher risk of diabetic foot and amputation.

Gestational diabetes mellitus (GDM) is associated with an increased risk of adverse pregnancy outcomes (Johns et al., 2018) and a high probability of developing T2DM later (Bellamy et al., 2009).

Although there are no specific oral lesions associated with diabetes, hyperglycemia can cause oral manifestations such as burning sensation of the oral mucosa, xerostomia, caries, and periodontal disease (gingivitis and periodontitis), which leads to premature tooth loss. (Verhulst et al., 2019).

Type 1 diabetes can be diagnosed at any age but is more frequent between 5-7 years and adolescence. It is one of the most common chronic conditions in childhood and involves insulin dependence.

Type 2 diabetes is significantly promoted by sedentary lifestyle and unhealthy diet. These individuals are non-insulin-dependent.

A systematic review by Graziani et al. (2018) shows evidence that periodontitis adversely affects glycemic control and worsens complications in both T1DM and T2DM.

Most literature explores the relationship between T2DM and periodontal disease due to the higher prevalence of T2DM, while evidence on T1DM is scarce.

Insulin treatment mitigates the impact of hyperglycemia (since it regulates it) and seems to stimulate osteoblast activity.

It is important to note that periodontal treatment can reduce glycated hemoglobin in the short term, which can increase insulin sensitivity and therefore improve the overall state of the diabetic patient, potentially having systemic effects improving diabetes-related complications.

Given the increased prevalence of diabetes, dental health professionals can play an important role in managing periodontitis in diabetic patients, especially in identifying undiagnosed diabetes or prediabetes.

Mechanisms of Influence

Mechanisms by Which Diabetes Influences Periodontitis

1. Hyperactivated inflammatory response due to increased inflammatory mediators.
2. Vascular system alterations modifying the capacity for periodontal tissue repair. Diabetic patients have increased fibroblast apoptosis, which interferes with tissue repair, influencing periodontitis severity.
3. Immune system alterations. Diabetic patients show altered neutrophil function, including adhesion, phagocytosis, and chemotaxis. Neutrophil apoptosis is also altered, increasing their numbers in periodontal tissues and causing greater tissue destruction.

Mechanisms by Which Periodontitis Influences Diabetes

Periodontitis increases levels of proinflammatory and prothrombotic mediators in serum. Systemic inflammation associated with the local inflammatory response caused by periodontal microbiota may provoke insulin resistance.

Clinical Situations to Consider:

- ***Prediabetes***: 30% of the adult population has prediabetes, defined as high risk of diabetes (elevated HbA1c or fasting glucose but below diabetes diagnostic values).

  Studies show increased periodontitis in prediabetics, with a probability of 27-53% of undiagnosed prediabetes or diabetes among periodontitis patients. Prediabetics have a 71.3% prevalence of periodontitis versus 75.6% in diabetics. Odds ratio (OR) for hyperglycemia is 2.46.

- ***Gestational Diabetes***: Women with gestational diabetes have a higher risk of periodontitis, with a prevalence of 30.5% versus 4.8% in non-diabetics. OR is 2.6.

  Based on the evidence, a paradigm emerges highlighting the importance of including periodontal treatments in systemic disease management. Multidisciplinary evaluation by physicians and dentists is important due to the established correlation between diseases. As health professionals, we must alert for these pathological conditions, improve quality of life, establish early diagnosis, and promote prevention and health promotion.

Cardiovascular Diseases

In recent years, it has been proposed that the close relationship between periodontitis and chronic non-communicable diseases is due to an exacerbated inflammatory response presenting an altered immune response. Among chronic non-communicable diseases, various studies have indicated that periodontitis could be a risk factor for ischemic cardiovascular disease. Ischemic cardiovascular disease is reported as an entity responsible for a large number of deaths and disabilities worldwide.

Several mechanisms supporting this hypothesis have been described, such as: direct effect of oral bacteria inducing platelet activation and aggregation, pro-inflammatory mediators produced in periodontitis, increased plasma levels of C-reactive protein, and tissue damage caused by invasion of oral pathogens into the arterial endothelium.

Tooth loss is the long-term consequence of periodontitis, due to destruction of the tooth's attachment tissues, and its progression is closely related to partial or total tooth loss.

Greater attachment loss in patients with periodontitis indicates more severe destruction of periodontal tissues and therefore also points to greater severity of this disease. Periodontal pathogens evade the host immune defense mechanisms, reach, and colonize atherosclerotic plaques and thrombosis through the bloodstream. Atherosclerotic plaques, aneurysm walls, and thrombotic tissues of the aneurysm can harbor various periodontal pathogenic bacteria such as *Porphyromonas gingivalis*, *Treponema denticola*, *Actinomyces*, *Fusobacterium*, and *Prevotella intermedia*. (Kannosh et al., 2018)

Oral infections such as periodontitis increase the risk of arteriosclerotic diseases; both diseases share inflammatory markers such as C-reactive protein, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), fibrinogen, and LDL cholesterol (due to secretion of interleukin-1).

Atherosclerosis

Periodontal pathogenic bacteria can also adhere to the vascular lining, cross it, produce antibodies that mediate damage, impair vascular endothelial function, and promote the appearance and progression of atherosclerosis.

Vascular endothelial cells invaded by *Porphyromonas gingivalis* via bacterial fimbriae upregulate nitric oxide synthase expression to stimulate endothelial cells to release large amounts of nitric oxide, damaging endothelial cells and promoting atherosclerosis.

The virulence factors of periodontal pathogenic bacteria may also promote atherosclerosis development, such as the arginine gingipain protease of *Porphyromonas gingivalis*, which can induce platelet aggregation, selectively hydrolyze the main component of high-density lipoprotein carrying apolipoprotein B-100, and cause lipid peroxidation of lipoproteins, accelerating the atherosclerosis process. (Liljestrand et al., 2017).

Abdominal Aortic Aneurysms

Periodontal pathogens are also closely related to abdominal aortic aneurysms. *Porphyromonas gingivalis* can invade arterial endothelial cells, enter the aneurysm wall and thrombus, promote the formation of neutrophil extracellular traps in thrombi, increase the

thrombus volume in the aneurysm lumen, and accelerate its progression. *Porphyromonas gingivalis* lipopolysaccharide (LPS) can also activate the TLR/NF-κB signaling pathway, aggravate the inflammatory response within the aneurysm wall, and accelerate the course of abdominal aortic aneurysm. (Salhi et al., 2019)

Pneumonias

Pneumonia is a major cause of morbidity and mortality in patients of all ages, especially the elderly and immunocompromised.

Microorganisms can infect the lower respiratory tract by inhalation of infectious aerosols, spreading infection to contiguous and extrapulmonary sites.

The oral cavity, especially saliva along with dental plaque associated with periodontal patients, appears to be a logical source for pathogens to accumulate and spread to the lower respiratory tract. Several oral pathogens have been implicated in pulmonary infections, including *Aggregatibacter actinomycetemcomitans*, *Actinomyces israelii*, *Capnocytophaga spp*., *Chlamydia pneumoniae*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Fusobacterium necrophorum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Streptococcus constellatus*. (Hajishengallis et al., 2008)

Heo et al., in 2011, demonstrated in intensive care units that respiratory pathogens isolated from dental plaque and bronchoalveolar lavage fluid of the same patients were genetically identical, reinforcing the idea that dental plaque may serve as a reservoir for respiratory pathogens.

Individuals with periodontitis are three times more likely to develop nosocomial pneumonia compared to patients without periodontal disease. In 2016, Porto et al. concluded that the oral environment, even without teeth, presents favorable conditions for accumulation of pathogenic bacteria.

Fusobacterium is a potential lung pathogen and should be considered when investigating respiratory complications. Conversely, *Chlamydia pneumoniae* is well studied as a respiratory pathogen and has been associated with asthma, bronchitis, and chronic obstructive pulmonary disease.

The plaque biofilm on the tooth surface is a reservoir for respiratory tract infection pathogens; inflammatory cytokines from periodontal tissue can enter the respiratory tract, damage the respiratory epithelium, and promote colonization by respiratory pathogens. Proteases, virulence factors of periodontal pathogens, can also enter the respiratory tract, preventing respiratory mucosa from clearing pathogens adhered to mucous membranes and promoting respiratory pathogen adhesion and colonization. (Bansal et al., 2013)

Porphyromonas gingivalis gingipains can exacerbate the host immune response, causing excessive inflammation, bronchopneumonia, lung abscesses, bleeding, and even necrosis. (Benedyk et al., 2016) Studies show that *Porphyromonas gingivalis* content in the oral cavity of chronic obstructive pulmonary disease patients increases and correlates inversely with the forced expiratory volume in 1 second (FEV1%), suggesting that increased *Porphyromonas gingivalis* content in the oral cavity may impair lung function. (Tan et al., 2019) Besides Porphyromonas gingivalis, *Prevotella intermedia* and *Actinomyces* can also cause pneumonia and lung abscesses. (Scannapieco et al., 1996)

Pregnancy

During pregnancy, specific oral problems may appear, such as inflammation, bleeding, and increased periodontal probing depth, which decrease significantly after childbirth. Lipopolysaccharides from anaerobic bacteria provoke release of inflammatory cytokines such as IL-1, IL-6, PGE2, and tumor necrosis factor alpha, due to increased vascular activity caused by elevated estrogen and progesterone levels during pregnancy. Therefore, the fewer bacteria present in the oral cavity, the less gingival inflammation is found in patients.

Increased levels of pro-inflammatory cytokines (PGE2) and cells in the fetoplacental space can lead to premature rupture of membranes and consequently induce preterm births.

Good professional care along with proper oral hygiene can reduce the prevalence of low birth weight premature infants (LBWPI) in women suffering from periodontitis. These expectant mothers also tend to have a higher risk of preeclampsia.

Increased production of female hormones during pregnancy contributes to gingivitis and periodontitis development due to increased vascular permeability and tissue edema.

As pregnancy progresses, periodontal disease tends to worsen, depending also on the number of previous pregnancies and patient age, making basic periodontal treatment and oral hygiene education necessary.

Gingival alterations in pregnant women usually appear from the second month of gestation, peaking around the eighth month. Studies show that the molar gingiva had the highest inflammation values; however, the greatest increase was seen in the anterior region. Interproximal areas are the most frequent sites of gingival inflammation both during pregnancy and after delivery.

There is a relationship between concentrations of sex hormones and subgingival microflora in saliva during pregnancy. Around 300 species colonize the oral cavity as a result of the significant hormonal changes caused by pregnancy. Sex hormones are considered modifying factors that may influence the pathogenesis of periodontal disease.

During pregnancy, progesterone secretion is 10 times higher and estrogen secretion 30 times higher due to continuous hormone production. Increased progesterone leads to increased vascular permeability, crevicular fluid, gingival edema, and prostaglandin production, resulting in gingival inflammation. (Lindhe et al., 2019)

Between the 3rd and 5th months of pregnancy, the number of bleeding sites in the mouth increases dramatically, leading to higher levels of *P. intermedia* and *P. gingivalis*. Increased gestational hormones alter keratinization of the epithelium and connective tissue matrix. These epithelial and vascular permeability changes may cause an exaggerated response to dental plaque.

High levels of gestational hormones may also suppress immune response to plaque. (Tilakaratne et al., 2000)

Periodontal Treatment (Sanz et al., 2022)

Treatment sequence for periodontitis in stages I, II, and III

Once diagnosed and depending on the stage of the disease, patient treatment should be gradual and incremental, including different interventions at each step.

A key prerequisite for treatment is informing the patient of the diagnosis and treatment alternatives, including benefits/risks and the option of no treatment. Therefore, all treatments should be personalized, including possible modifications of the treatment plan depending on changes in general health, clinical findings, and patient preferences.

First Step: Behavior Change and Supragingival Biofilm Control

Objective: Motivate the patient to successfully eliminate supragingival dental biofilm and control risk factors.

Main interventions:

- Control of supragingival dental biofilm.
- Education and motivation to improve oral hygiene (Oral Hygiene Instructions, OHI).
- Complementary therapies for gingival inflammation.
- Professional mechanical plaque removal (PMPR), including removal of plaque/biofilm and supragingival calculus, as well as

retention factors that hinder oral hygiene.

- Control of risk factors, including behavioral health interventions to eliminate or reduce recognized risk factors for the onset and progression of periodontitis (smoking cessation, better metabolic control of diabetes, possibly physical exercise, dietary counseling, and weight loss).

Frequent reevaluation to:

- Continue motivating and ensuring compliance, or explore alternative approaches if issues arise.
- Develop and modify skills for biofilm removal according to needs.
- Allow appropriate response to the following treatment steps.

Second Step: Cause-Directed Therapy

Objective: Control (reduce/eliminate) subgingival biofilm and calculus (subgingival instrumentation). This step applies to teeth with periodontal support loss and/or pocket formation.

Additional possible interventions:

- Use of adjunctive physical or chemical agents.
- Use of host response modulators (local or systemic).
- Use of adjunctive local subgingival antimicrobials.
- Use of adjunctive systemic antimicrobials.

Reevaluation:

Evaluate individual response after periodontal tissues have healed.

If final treatment goals are not met [no pockets >4 mm with bleeding on probing or no deep pockets (≥6 mm)], consider the third step.

If successful, patients enter a supportive periodontal care (SPC) program.

Third Step: Treatment of Sites Not Responding to Second Phase

Objective: Treat teeth/sites not adequately responding to step two (pockets >4 mm with bleeding or pockets ≥6 mm), to improve access for instrumentation or to perform regenerative or resective surgery in complex lesions (intraosseous lesions and furcation defects).

Interventions may include:

- Repetition of subgingival instrumentation with or without adjunctive therapies.
- Periodontal flap surgery.
- Resective periodontal surgery.
- Regenerative periodontal surgery.

Notes:

- Surgical interventions require additional patient consent.
- Specific evaluation of risk factors and medical contraindications is needed.
- Reevaluation of individual response after this step.

- Ideally, final treatment goals are reached and patient is integrated into maintenance care, though not all goals may be fully met in stage III periodontitis.

Periodontal Maintenance

Objective: Maintain periodontal stability in all treated periodontitis patients.

Interventions

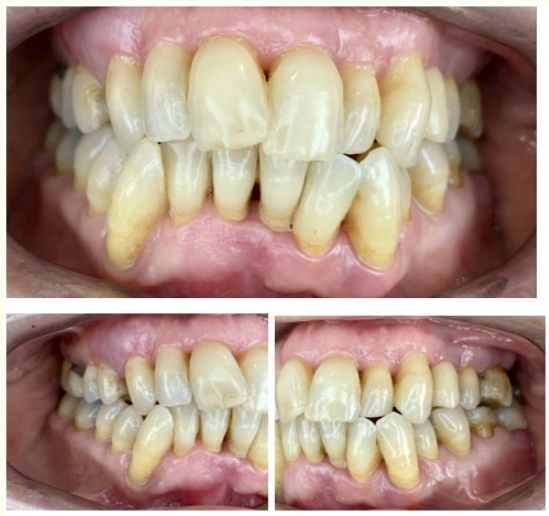
- Combination of preventive and therapeutic actions defined in earlier phases, based on patient's gingival and periodontal status.
- Performed at regular intervals, personalized to the patient's needs.
- During maintenance visits, new treatment may be necessary if disease recurrence is detected, requiring re-diagnosis and treatment planning.
- Compliance with oral hygiene instructions and healthy lifestyle are integral parts of maintenance.

Additional Note

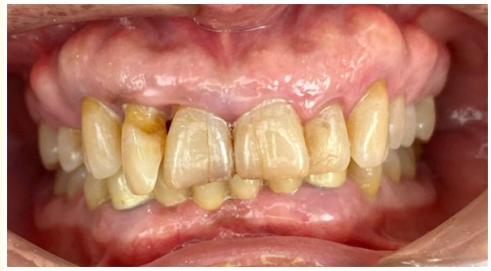
Extraction of teeth may be considered at any treatment phase if the prognosis is deemed hopeless.

These recommendations are from the European Federation of Periodontology (EFP) S3 level clinical practice guideline for Treatment of Periodontitis Stages I-III.

Pictures



Case 1



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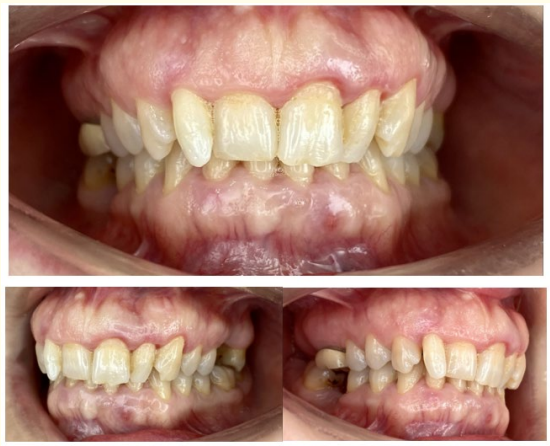

Case 3

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