PERIODONTAL DISEASE AND ITS RELATIONSHIP WITH METABOLIC SYNDROME: A DETAILED REVIEW

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Abstract - Periodontal disease is a multifaceted and progressive chronic inflammatory condition that results in the loss of alveolar bone and teeth. It has been linked to numerous systemic diseases, including diabetes mellitus and obesity, many of which belong to the metabolic syndrome cluster. This cluster consists of interconnected systemic disorders such as central obesity, dyslipidemia, insulin resistance, and hypertension, all of which significantly elevate the risk of cardiovascular diseases, diabetes mellitus, and stroke.

This review aims to explore the association between periodontal disease and the components and outcomes of the metabolic syndrome cluster. By examining these correlations, we seek to uncover the underlying mechanisms that connect periodontal disease with systemic conditions within the metabolic syndrome. A

better understanding of these interactions could lead to improved treatment strategies that address the reciprocal influence of managing periodontal disease and systemic diseases in a comprehensive manner.

Keywords: periodontitis, metabolic syndrome, insulin resistance, dyslipidemia, diabetes mellitus, cardiovascular disease, obesity, osteoporosis

INTRODUCTION

Periodontitis is a chronic inflammatory condition marked by dysbiosis and a shift in the subgingival microbiota toward Gram-negative bacteria, resulting in the destruction of tooth-supporting structures through host-mediated mechanisms [1,2]. According to the World Health Organization (WHO), periodontitis is a major risk factor for tooth loss, affecting approximately 40% of individuals over the age of 30 and nearly 60% of those over 65 in the United States [3]. Furthermore, periodontitis has been linked to a range of medical conditions, including diabetes mellitus [4], as well as severe health issues such as cardiovascular diseases and metabolic syndrome [5,6,7]. Key parameters used to diagnose periodontitis include bleeding on probing (BOP), gingival index (GI), plaque index (PI), periodontal pocket depth (PD), and clinical attachment loss (CAL) [1].

Metabolic syndrome, often referred to as "Syndrome X," is a cluster of interconnected conditions, including central obesity, dyslipidemia, insulin resistance, and hypertension [6,8], that collectively increase the risk of cardiovascular diseases and type 2 diabetes mellitus (T2DM) [6]. Additionally, metabolic syndrome has been associated with other conditions such as fatty liver disease [9] and obstructive sleep apnea [10]. Definitions of metabolic syndrome vary among different guidelines, with the most widely used being those from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF).

The NCEP ATP III first established diagnostic criteria for metabolic syndrome in 2001, later updated in 2005 [11,12,13]. According to these criteria, metabolic syndrome is diagnosed when three out of five factors are present: abdominal obesity (waist circumference ≥102 cm for men and ≥88 cm for women), triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides, HDL cholesterol <40 mg/dL (1 mmol/L) for men and <50 mg/dL (1.3 mmol/L) for women or treatment for low HDL cholesterol, blood pressure ≥130/85 mmHg or treatment for hypertension, and fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or treatment for elevated blood glucose.

The IDF guidelines, last updated in 2006, also require three of the following criteria for diagnosis: increased waist circumference based on ethnic-specific cut-points, triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides, HDL cholesterol <40 mg/dL (1.03 mmol/L) for men or <50 mg/dL (1.29 mmol/L) for women or treatment for low HDL, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or treatment for hypertension, and FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes. Compared to the NCEP ATP III criteria, the IDF criteria identify 15–20% more individuals with metabolic syndrome in the U.S. urban population, with 93% overlap between the two definitions [14].

Metabolic syndrome is now recognized as a significant global health concern, with a prevalence of 17–32% in the general population [15]. Inflammation is a key link between periodontitis and systemic diseases associated with metabolic syndrome, such as diabetes [16], cardiovascular diseases [17], and obesity [18].

This review seeks to examine the associations between periodontitis and systemic conditions related to metabolic syndrome, explore how the treatment of one condition impacts the other, and elucidate the pathological mechanisms connecting them. By providing a comprehensive and original perspective, this review aims to enhance understanding of the relationship between periodontitis, individual components of metabolic syndrome, and the syndrome as a whole.

METHODS

2.1. Search Strategy

An online search for relevant data was conducted using two databases: MEDLINE and Embase. The searches were performed on four separate dates: 31 December 2021, 10 August 2022, 1 March 2023, and 28 July 2023.

2.2. Inclusion Criteria

The review included studies meeting the following criteria:

1. Published in English.
2. Conducted on human subjects.
3. Published between 2010 and 2022.

Additionally, publications without restrictions on age or sex were included. Key relevant studies published before 2010 were also manually added if they were deemed significant to the review's scope.

2.3. Exclusion Criteria

The review excluded studies based on the following criteria:

1. Publications not focusing on the association between periodontal disease and systemic diseases.
2. Studies that did not align with the aims of this review.
3. Studies with fewer than 30 participants.

2.4. Extraction of Publications from Electronic Databases

Using the defined inclusion and exclusion criteria, a structured search strategy was employed. This strategy utilized controlled vocabulary thesaurus terms listed in Appendix A. Table 1 summarizes the publications retrieved from MEDLINE and Embase based on the search terms applied to investigate the associations between periodontal disease and various systemic diseases.

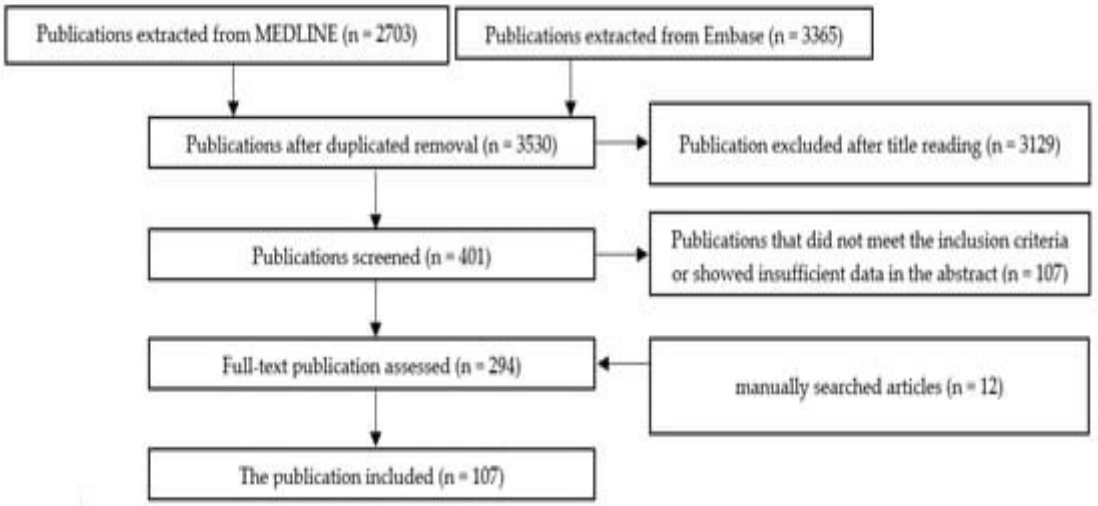
Table 1.

Publications extracted from electronic databases using the search strategy and thesaurus terms.

Systemic Disease	MEDLINE (PubMed)	Embase	Total
Metabolic syndrome	61	334	395
Insulin resistance	110	141	251
Diabetes mellitus	1680	2293	4273
Hyperlipidemia	51	24	75
Obesity	462	640	1002
Hypertension	457	87	544

2.5. Paper Selection Process

The process for selecting papers extracted from the databases is illustrated in Scheme 1. Additionally, detailed selection schemes for each component of the metabolic syndrome cluster are provided in Appendix B. These include Scheme A1 (metabolic syndrome), Scheme A2 (obesity), Scheme A3 (insulin resistance), Scheme A4 (diabetes mellitus), Scheme A5 (hyperlipidemia), and Scheme A6 (hypertension).



Scheme 1. The selection method for publications included in this review.

2.6. Paper Selection Process

The process for selecting papers extracted from the databases is outlined in Scheme 1 and detailed in Appendix B. Following an initial filtering to remove duplicates, a secondary selection was conducted by reviewing article titles. Subsequently, abstracts were analyzed, and a quality assessment of the full articles was performed. Finally, the most relevant articles were selected for inclusion in this review.

This review was conducted using the Embase and PubMed research engines and focused on articles published between 2010 and 2022. Key publications identified through manual searches, publications in English, and studies conducted on human subjects were included.

The identification of articles employed a combination of keywords and free terms, including but not limited to:

- "insulin resistance syndrome," "metabolic syndrome," "syndrome X," "insulin sensitivity," "diabetes mellitus," and "diabetes."
- Terms related to lipid disorders, such as "hyperlipidemia," "hyperlipidaemia," "lipemia," and "lipidemias."
- Terms related to obesity, including "abdominal obesity."
- Terms related to hypertension, such as "high blood pressure," "arterial hypertension," "cardiovascular hypertension," and "HTN (hypertension)."

All terms were paired with "periodontitis" or "periodontal disease" to identify studies exploring associations between these systemic conditions and periodontal disease.

RESULTS

3.1. Epidemiological Link Between Metabolic Syndrome and Periodontal Disease

Metabolic syndrome comprises conditions such as abdominal obesity, dyslipidemia, arterial hypertension, insulin resistance, and alterations in lipid metabolism [19]. Hlushchenko et al. reported that individuals aged 25–55 with metabolic syndrome had a 1.2-fold higher prevalence of periodontal disease compared to healthy counterparts [20]. Conversely, Gomes-Filho et al. found that individuals with moderate to severe periodontal disease were twice as likely to have metabolic syndrome compared to those without periodontal disease [21].

Pham et al. further examined this association and observed that 21% of individuals with metabolic syndrome had severe periodontitis, compared to just 6.8% of healthy individuals. Periodontal parameters such as bleeding on probing (BOP), gingival index (GI), plaque index (PI), pocket depth (PD), and clinical attachment loss (CAL) were significantly worse in individuals with metabolic syndrome [22]. The study also highlighted that the severity of periodontal disease correlated with the number of metabolic syndrome components. Participants with zero to two components had better periodontal health than those with three, while those with four to five components exhibited the poorest periodontal parameters [22].

Similar findings were reported in a recent meta-analysis and systematic review, which revealed a dose-response relationship between periodontal disease and metabolic syndrome. The more components of metabolic syndrome an individual had, the stronger the association with periodontal disease [23]. However, a clinical trial showed that while periodontal treatment improved periodontal health in

individuals with metabolic syndrome, it did not lead to significant changes in metabolic parameters such as HbA1c, waist circumference, or CRP levels [24].

3.1.1. Mechanisms Linking Periodontal Disease and Metabolic Syndrome

Inflammatory Mechanisms

One potential mechanism connecting periodontal disease and metabolic syndrome is oxidative stress [25]. Both conditions are inflammatory in nature, with pro-inflammatory cytokines from the gingiva entering the bloodstream and exacerbating oxidative stress. This increased oxidative stress can contribute to insulin resistance and atherosclerosis, both of which are key contributors to metabolic syndrome. The relationship is bidirectional, as inflammation from metabolic syndrome components can heighten oxidative stress in gingival tissues, impairing the periodontium's ability to combat bacterial challenges and increasing susceptibility to periodontal disease [25].

Microbiological Mechanisms

Microbial dysbiosis may also play a role in linking these two diseases. Obesity and type 2 diabetes are known to alter the oral microbiome, leading to microbial imbalances [26]. Individuals with obesity and periodontal disease exhibit significantly different oral microbiome profiles compared to non-obese individuals with periodontal disease. Obese individuals tend to have lower microbial diversity, which may elevate their risk for developing periodontal disease [6].

3.2. Epidemiological Association Between Obesity and Periodontal Disease

Obesity is one of the most prevalent medical conditions of the 21st century. According to a 2022 WHO European regional report, obesity contributes to approximately 1.2 million deaths annually in the European region. The report also highlighted an increase in obesity and overweight prevalence, particularly among children and adolescents, exacerbated by the COVID-19 pandemic [27].

As a core component of metabolic syndrome, obesity is typically measured using waist circumference or body mass index (BMI) (kg/m²). An adult is classified as

overweight with a waist circumference >90 cm for women or >100 cm for men, or a BMI of 25.0–29.9 kg/m². Obesity is defined by a waist circumference >105 cm for women or >110 cm for men, or a BMI ≥30.0 kg/m² [28].

The association between obesity and periodontal disease strengthens as BMI increases [29]. Studies have suggested that weight gain and obesity are potential risk factors for periodontitis [30,31]. A recent meta-analysis reported that individuals who are overweight have a 1.13-fold increased risk of periodontal disease compared to healthy individuals, while obese individuals have a 1.33-fold increased risk [32].

A prospective study conducted in South America found that obese women had a higher clinical attachment loss (CAL) rate and a 1.64-fold increased risk of periodontal disease [33]. Individuals with BMI >30 kg/m² demonstrated worse periodontal parameters (CAL, bleeding on probing [BOP], plaque index [PI], and periodontal pocket depth [PD]) and a higher risk of developing periodontitis across different races, nationalities, and study designs [34].

BMI has also been linked to other components of metabolic syndrome. For instance, Fentoğlu et al. found that BMI correlated positively with hyperlipidemic parameters and negatively with periodontal parameters such as PI, PD, BOP, and CAL [35].

Several studies have identified a notable association between obesity and periodontal disease, particularly in young and middle-aged women with high BMI and waist circumference [36,37]. A meta-analysis confirmed these findings, showing a stronger association between periodontal disease and women aged 18–34 with high BMI and waist circumference. It also noted that European individuals had a higher likelihood of developing periodontal disease compared to other populations [38].

3.2.1. Mechanisms Linking Obesity and Periodontal Disease

Inflammation

A key mechanism connecting obesity and periodontal disease is the role of pro-inflammatory cytokines. In obese individuals, adipocytes and macrophages in fat

tissues produce elevated levels of cytokines such as IL-1β, TNF-α, and IL-6 [39]. These cytokines stimulate the production of C-reactive protein (CRP), inducing an acute inflammatory state [39]. TNF-α, in particular, is significant as it activates osteoclasts, contributing to bone resorption and the progression of periodontitis [18].

Oxidative Stress

Obesity is associated with increased production of reactive oxygen species (ROS), which can chronically activate inflammatory mediators in gingival tissues, including IL-1β, TNF-α, and IL-6. This persistent inflammation leads to alveolar bone destruction, deeper periodontal pockets, and increased clinical attachment loss (CAL) [18]. Interestingly, obesity does not appear to affect the outcomes of nonsurgical periodontal treatments, with obese individuals responding similarly to non-obese individuals [40].

Biochemical Pathways

Obesity may also interfere with osteoblast differentiation. Adipocytes and osteoblasts share a common origin in pluripotent bone marrow stem cells (BMSC). The Wnt/β-catenin signaling pathway, which directs BMSC differentiation into osteoblasts, is inhibited in obesity. Secreted frizzled-related protein 1 (SFRP1), an inhibitor of this pathway, is elevated in mild obesity but decreases in morbid obesity, resulting in increased marrow adiposity and impaired osteogenesis.

Microbiological Factors

Obesity has been shown to alter the composition of the oral microbiota, potentially influencing periodontal health. Studies have identified higher levels of the periodontal pathogen *Tannerella forsythia* (T. forsythia) in the subgingival biofilms of overweight and obese individuals compared to individuals with normal weight. Additionally, obese individuals have elevated levels of *T. forsythia*, *Fusobacterium* spp., and *Porphyromonas gingivalis* (*P. gingivalis*) in their saliva, regardless of periodontal health status. Another study observed that individuals with chronic periodontitis exhibited higher levels of pathogens such as

Aggregatibacter actinomycetemcomitans (*A. actinomycetemcomitans*), *Prevotella intermedia* (*P. intermedia*), *T. forsythia*, and *Fusobacterium* spp.

3.3. Epidemiological Association Between Insulin Resistance and Periodontal Disease

A summary of studies exploring the link between insulin resistance and periodontal disease is provided in Table 4.

Table 4.

Summary of included articles exploring the association between insulin resistance and periodontal disease.

Authors	Methods	Study Population	Etiology	Main Outcomes
Gurav et al.	Review	Epidemiological, in vivo, and in vitro publication	Pro-inflammatory mediators: TNF-α, Il-6, prostaglandins E2, and oxidative stress	Pro-inflammatory cytokines are associated with the connection between periodontal disease and insulin resistance.
Roberts et al.	Review	Epidemiological publication	Metabolic syndrome components	Insulin resistance is a significant component in the metabolic syndrome cluster. Insulin resistance and diabetes may improve by doing aerobic activity.
Benguigui et al.	Cross-sectional study	1625 subjects between the ages 35 and 74	Metabolic syndrome components	Insulin resistance is associated with periodontal disease and especially with moderate and severe periodontitis.
Demmer et al.	Retrospective, multicenter study	3616 participants, mean age (±SD) 43 ± 17 years, who received a	C-reactive protein, insulin resistance diagnosis	Periodontal infection was associated with insulin resistance.

Authors	Methods	Study Population	Etiology	Main Outcomes
		periodontal examination and fasting blood draw		
Altay et al.	Retrospective, single-center study	22 dyslipidemic patients with obesity and 24 healthy individuals without obesity with generalized chronic periodontitis	Pro-inflammatory mediators: TNF-α, IL-6, and CRP	Periodontal treatment lowers the levels of circulating pro-inflammatory cytokines and may be associated with a decrease in insulin resistance in obese patients.
Abou-Raya et al.	Retrospective, single-center study	185 patients: 96 women and 89 men, mean age of 53.5 (7.3)	Pro-inflammatory mediators: TNF-α, IL-6, CRP, and ICAM-1	Periodontal therapy appears to have an impact on diabetic and prediabetic patients. Periodontal therapy reduced systemic inflammation and improved glycemic control in T2DM patients.
Marchetti et al.	Review	Epidemiological, in vivo, and in vitro publication	Pro-inflammatory mediators and oral bacteria	Oxidative stress is associated with the connection between periodontal disease and components of the metabolic syndrome.
Bhat et al.	Retrospective, single-center study	Pancreatic β cell line MIN6	*P. Gingivalis*	*P. Gingivalis* stimulates insulin secretion by the pancreatic cell line.

Insulin resistance is a metabolic condition often considered a precursor to diabetes. It is characterized by a reduced responsiveness of tissues to normal insulin levels, leading to elevated blood glucose levels. One of the diagnostic criteria for metabolic syndrome includes fasting plasma glucose (FPG) levels ≥100 mg/dL (5.6 mmol/L), a diagnosis of diabetes mellitus, or treatment for elevated blood glucose

[11]. Insulin resistance has also been linked to other components of metabolic syndrome, such as central obesity and dyslipidemia.

Research has established a connection between insulin resistance and periodontal disease. Individuals with a history of insulin resistance exhibit significantly higher rates of moderate to severe periodontal disease compared to healthy individuals. Furthermore, the severity of periodontal disease correlates with insulin resistance. A study using the homeostasis model assessment of insulin resistance (HOMA-IR) found that for every 1 mm increase in periodontal probing depth, the HOMA-IR score increased by 1.04.

3.3.1. Mechanisms Linking Insulin Resistance and Periodontal Disease

Inflammation is considered a key mechanism linking insulin resistance and periodontal disease [51]. Insulin resistance is a chronic low-grade inflammatory condition associated with increased levels of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α [40]. Reactive oxygen species (ROS) are another inflammatory mediator implicated in the connection between these conditions.

Beyond inflammation, bacterial interactions may also contribute to the link. An in vitro study demonstrated that *Porphyromonas gingivalis* (*P. gingivalis*), a key periodontal pathogen, can stimulate insulin secretion in pancreatic cell lines, suggesting a microbial influence on insulin regulation.

The connection between insulin resistance and periodontal disease is believed to be bidirectional. Periodontal disease, being a chronic inflammatory condition, releases pro-inflammatory cytokines from the gingiva into systemic circulation. These cytokines can exacerbate existing insulin resistance and potentially contribute to its progression into diabetes mellitus.

Despite the recognized link, there is a significant lack of high-quality studies investigating the relationship between insulin resistance and periodontal disease. This gap may be attributed to the greater focus on diabetes mellitus, a well-established consequence of insulin resistance and a major systemic condition

associated with periodontal disease. Additionally, identifying individuals in the prediabetic stage remains challenging, as most patients are studied or treated after a diabetes mellitus diagnosis.

3.4. Epidemiological Association Between Diabetes Mellitus and Periodontal Disease

Diabetes mellitus (DM) is a metabolic disorder classified into the following categories based on etiology:

- **Type 1 Diabetes Mellitus (T1DM)**
- **Type 2 Diabetes Mellitus (T2DM)** – the most common form, accounting for 90% of cases.
- **Gestational Diabetes Mellitus (GDM)**

DM is a significant risk factor for periodontal disease. Research by Demmer et al. found that individuals with diabetes are approximately three times more likely to develop periodontal disease than those without diabetes.

T1DM and Periodontal Disease

Although less prevalent than T2DM, a clear association exists between T1DM and periodontal disease. T1DM typically affects young, otherwise healthy individuals and is associated with higher rates of dental plaque and chronic gingivitis, which can progress to periodontitis at an earlier age. Adolescents with T1DM have a prevalence of periodontal disease five times higher than their non-diabetic peers, with more severe and rapid periodontal breakdown. Children with T1DM are four times more likely to develop periodontal disease and show a higher incidence of gingivitis compared to healthy children.

Poor metabolic control further exacerbates periodontal conditions. Severe periodontal disease was more prevalent in poorly controlled diabetic patients than in well-controlled patients and non-diabetic individuals (26% vs. 20% vs. 5%). Clinical attachment loss (CAL) was nearly twice as high in adults with diabetes compared to healthy individuals (4.3 mm vs. 2.3 mm) and worsened with poor glycemic control.

However, the effectiveness of periodontal therapy in improving glycemic control in T1DM remains inconclusive. A review revealed that while most studies found no significant improvement, one study showed positive results, highlighting the need for high-quality, long-term research.

T2DM and Periodontal Disease

The link between T2DM and periodontal disease is well established. Studies have consistently shown that individuals with T2DM are two to three times more likely to develop periodontal disease than healthy individuals. Additionally, they tend to exhibit greater periodontal loss, higher CAL, and deeper pockets.

3.4.1. Mechanisms Linking Diabetes Mellitus and Periodontal Disease

Oxidative Stress

DM creates a chronic hyperglycemic state, exacerbating oxidative stress through pathways such as the polyol pathway, hexosamine pathway, and activation of protein kinase C (PKC). Insulin resistance associated with diabetes further increases ROS production, pro-inflammatory cytokines, and systemic inflammation while reducing adiponectin levels.

Inflammation

The inflammatory response plays a crucial role in the relationship between DM and periodontal disease. Pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-18, contribute to systemic inflammation, promoting bone loss and periodontal breakdown. Poor glycemic control, indicated by elevated hemoglobin A1C (HbA1c), is strongly associated with an increased risk of periodontal disease.

Inflammation also activates metalloproteinases (MMPs), which, along with ROS, degrade collagen and contribute to periodontal attachment loss. DM further increases the RANKL/OPG ratio, promoting osteoclast activation and leading to alveolar bone loss and deeper periodontal pockets.

Interestingly, nonsurgical periodontal treatment has been shown to benefit glycemic control. Studies indicate a reduction in HbA1c levels (3–4 mmol/mol or 0.3–0.4%) after 3–4 months of periodontal therapy, with continued improvement

over time. Additionally, periodontal treatment has shown benefits in prediabetic individuals and diabetic smokers, improving metabolic parameters such as HbA1c and fasting plasma glucose, as well as inflammatory markers like CRP.

Microbiological Factors

DM alters the oral microbiome, reducing its biological and phylogenetic diversity compared to healthy individuals. Diabetic patients also show less subgingival microbiome diversity but higher levels of periodontal pathogens.

Research has shown that while the periodontium may appear healthy, diabetic patients are predisposed to periodontal disease due to elevated numbers of pathogens, particularly those from the red complex, such as *Porphyromonas gingivalis*. Additionally, diabetic patients with periodontal disease harbor pathogens that form connections with others (orange complex), accelerating periodontal disease progression.

This microbial dysbiosis, combined with systemic inflammation and oxidative stress, underscores the bidirectional relationship between DM and periodontal disease. While periodontal disease worsens glycemic control, improved periodontal health can positively influence diabetes management.

DISCUSSION

Periodontal disease is a widespread condition affecting a large proportion of the adult population globally [3]. It is a multifactorial disease strongly associated with various systemic conditions, particularly the metabolic syndrome cluster. This cluster includes obesity, hyperlipidemia, insulin resistance, and hypertension [6]. The etiology of both periodontal disease and metabolic syndrome is complex, involving multiple factors. The primary link between them is thought to be their shared inflammatory nature, characterized by elevated levels of inflammatory cytokines and systemic oxidative stress [25].

As highlighted in this review, insulin resistance is associated with an increase in pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, along with elevated

levels of reactive oxygen species (ROS). Similarly, in type 2 diabetes mellitus (T2DM), elevated levels of TNF-α, IL-1β, IL-6, and IL-18 are associated with higher glycated hemoglobin (HbA1C) levels, which increase the risk of periodontal disease. Additionally, inflammation triggers the activation of matrix metalloproteinases (MMPs), which, together with ROS, lead to periodontal tissue breakdown. T2DM also disrupts the RANKL/OPG balance, promoting osteoclastogenesis and alveolar bone loss.

A study demonstrated that a high-fat diet induces osteoclastogenesis, increases RANKL levels, and leads to alveolar bone loss, further driven by pro-inflammatory cytokines such as IL-6, MCSF, and MCP-1. Obese individuals also exhibit elevated levels of IL-1β, TNF-α, and IL-6, which stimulate C-reactive protein production, triggering acute inflammation [39]. Increased ROS in obese individuals further exacerbates the inflammatory state, contributing to periodontal tissue destruction [18].

In addition to inflammatory pathways, bacterial mechanisms also appear to play a role in the association. For instance, *Porphyromonas gingivalis* (*P. gingivalis*) has been shown to stimulate insulin secretion in pancreatic cell lines [54]. Reduced oral microbiome diversity, along with an increased prevalence of periodontal pathogens, has been observed in T2DM patients. Individuals with low HDL cholesterol and high LDL cholesterol have elevated serum antibody levels against periodontal pathogens such as *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*). Similarly, obese individuals have been found to harbor higher levels of *Tannerella forsythia* (*T. forsythia*) in subgingival biofilms and increased levels of other periodontal pathogens.

Periodontal pathogens are also implicated in chronic endothelial inflammation, potentially leading to vasospasm and thrombosis. Inflammatory cytokines from periodontal tissues may exacerbate this process by stimulating endothelial cells to produce vasoconstrictors, promote leukocyte aggregation, and contribute to thrombosis formation.

In summary, the mechanisms linking periodontal disease to metabolic syndrome components share common pathways: an increased inflammatory burden driven by cytokines (notably IL-1β, IL-6, and TNF-α), elevated systemic oxidative stress, and the proliferation of Gram-negative bacteria. These factors collectively intensify the inflammatory state, activate bone-resorbing agents, and exacerbate both periodontal disease and the metabolic syndrome cluster components.

This review highlights the interconnected relationship between periodontal disease and the components of metabolic syndrome. Each component influences the others, creating a cycle that elevates the risk for periodontal disease. Given this bidirectional relationship, we propose that managing metabolic syndrome or its components should include periodontal examinations. Conversely, periodontal treatment in patients with diagnosed metabolic syndrome components should also involve screening for other systemic conditions, particularly within the metabolic syndrome cluster. Adopting an integrated approach to treatment may improve outcomes for both periodontal and systemic health.

CONCLUSIONS

Periodontal disease is strongly and positively associated with metabolic syndrome. The underlying mechanisms linking these conditions involve increased levels of pro-inflammatory mediators, such as various cytokines, reactive oxygen species (ROS), and elevated C-reactive protein (CRP), as well as the persistent infiltration of periodontal pathogens into the bloodstream.

Given the significant influence of periodontal health on the development and progression of metabolic syndrome and its individual components, periodontal evaluation should be integrated into the management and treatment strategies for metabolic syndrome.

Future research should address existing gaps by conducting multicenter, longitudinal studies across diverse ethnic populations. These studies should explore the relationship between periodontal disease and each component of metabolic

syndrome, as well as the impact of periodontal treatment on the syndrome as a whole. This will provide a more comprehensive understanding of their association and inform improved clinical approaches.

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