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Association between periodontitis and metabolic syndrome: A review

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ABSTRACT

Periodontitis and metabolic syndrome (MetS) are concerning issues affecting well-being and are prevalent. The MetS comprises a conglomerate of numerous physical conditions that occur concurrently, as well as intensifying the likelihood of heart disease and type 2 diabetes mellitus (T2DM). Periodontitis is a microbial oral condition that causes the loss of tooth attachment and can proceed to edentulism if left untreated. Epidemiologic, experimental, and interventional studies have documented that periodontitis could have a consequence on systemic health and share a common pathway with several chronic noncommunicable diseases, namely DM, cardiovascular disease, and MetS. Current data suggest that periodontitis may promote the onset or acceleration of MetS. The overall oxidative load and overactive inflammatory repercussions could be responsible for this interaction. As a result, it is crucial to comprehend the current condition of the association as well as the prospective contribution of periodontitis to MetS. The findings of published studies that provide consistent data on the varied outcomes of periodontitis on MetS are encapsulated in this review. Systematic reviews, meta-analyses, original studies, and review articles were appraised in synthesizing this review, using PubMed and Google Scholar search engines.

Introduction

Periodontitis is a complex multifactorial inflammatory illness presented by dysbiotic plaque biofilms that results in persistent non-resolving and damaging inflammatory responses leading to periodontal attachment and bone loss. It has multifaceted pathophysiology involving microbial, environmental, and host factors (1). Metabolic syndrome (MetS) a burdensome disorder possessed by a range of clinical physical issues and metabolic abnormalities could maximize mortality, through cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (2). MetS, diabetes mellitus (DM), and CVD have been linked to periodontitis. Furthermore, there is evidence that Mets and DM can affect the oral microbiome. The relationship between periodontitis and Mets is considered to be connected by systemic inflammation and insulin resistance, and they may impact one another (3). This review elaborates on the link between periodontitis and MetS, and its association with each of its components.

We conducted a literature search using PubMed and Google Scholar search engines using the keywords “oxidative stress”, “cardiovascular disease”, “type 2 diabetes mellitus”, “metabolic syndrome”, “periodontitis”, “obesity”, and “dyslipidemia”. Systematic reviews, meta-analyses, original studies, and current reviews describing the interaction between periodontitis and MetS were appraised in synthesizing this review.

Metabolic syndrome and its definition

In 1988, Reaven (4) coined the term MetS, also cited as syndrome X or insulin resistance syndrome. MetS is recognized as a multifactorial illness with a cluster of interconnected sociodemographic and biochemical traits, as well as immunological and vascular abnormalities. Its risk profile underpins the gradual development of ailments such as CVD and T2DM (5). 20-25% of the global adult population is estimated to be inflicted with MetS (6).

The definition of MetS has been propounded by several health federations, which deviate vaguely, but chiefly centering on overweight (notably central adiposity), deranged lipid proportions, elevated blood pressure (BP), and glycemic level (7). The International Diabetes Federation reconceptualized the specification for MetS, as an attempt to avoid the perplexity of several definitions. As per its guidelines, to diagnose MetS, an individual must possess central obesity (measured as waist circumference, with different values depending on ethnicity) along with any two among the three components (Table 1) (8).

Etiopathogenesis of metabolic syndrome

The etiology of MetS is diverse, including several interacting mechanisms, genetic variants, and environmental variables. A crucial role is witnessed in a sedentary lifestyle, and obesity, besides genetic and epigenetic variables in promoting the disorder (9). Insulin resistance is the most widely supported and unifying concept for interpreting the pathophysiology of MetS, although the molecular link between insulin resistance and the majority of the MetS components is not fully known (8). Major mechanisms leading to MetS are provoked by visceral adiposity, conferred by surplus calorie intake (10).

The elements accounted for the initiation and advancement of MetS to CVD and T2DM chiefly comprise diminished insulin sensitivity, longstanding inflammation, and neurohormonal activation (11). Adipose tissue releases pro-inflammatory cytokines, which may be involved in insulin resistance, lipolysis, and the creation of pro-thrombotic substances by the liver. Thus, the chronic inflammatory state induced by the obese adipose tissue via aberrant adipokine synthesis leads to endothelial dysfunction (12). The inflammatory milieu created by MetS causes endothelial dysfunction, paving the way for the heightened plausibility of CVD and T2DM (13). Of late, the dysbiotic gut microbial community has gained recognition in the genesis of MetS. Thus, the endotoxins released by bacteria in serum, inflammatory vulnerability, and unstable gut microbial community mainly comprise the primary features in the development of MetS (14).

Periodontitis and metabolic syndrome-a common link

The two chronic inflammatory conditions, periodontitis and MetS, are considered to be linked by inflammation. The regionally liberated inflammatory cytokines in the periodontium in response to virulent pathogens or lipopolysaccharides (LPS) could gain access to the systemic circulation, thereby precipitating MetS (15). Diminished insulin sensitivity is generated as a consequence of oxidative stress provoked by the inflammatory status. Oxidative stress induces insulin resistance by altering the intracellular signaling pathway, which paves the way for MetS through elevated BP, deranged lipid profile, and CVD. This suppresses the antioxidant capability in periodontal tissues either by MetS in-toto or by its contributing elements, which disturb the immune response to the microbial assault, thereby inducing periodontal infection (16). Diverse factors of the host immune system exert an impact on periodontitis and MetS. Risk factors include genetic and environmental factors such as older age, smoking, and lifestyle, which are synergistic between the two conditions (17). Poor periodontal conditions with higher prevalence, severity and extension were exhibited among the individuals diagnosed with MetS, highlighting their interrelationship (18).

The results from a case-control study by Gomes-Filho et al. (19) in 2020 concluded that individuals with moderate or severe periodontitis were twice as likely as those without periodontitis to have MetS, with an increased risk among individuals with severe periodontitis. The salivary microbiome of periodontally compromised individuals with MetS expressed an altered microbial composition compared with healthy individuals (3). The samples retrieved from dental implants from individuals with MetS had significantly higher levels of periodontal pathogens, strengthening the systemic impact of MetS (20). The results from an interventional study reflected that C-reactive protein levels were lowered in MetS individuals following periodontal therapy, signifying that a reduction in periodontal inflammation could decrease systemic inflammation and CVD risk (21). In a

Table 1. Components of the metabolic syndrome (8)

Components	Diagnostic values
Abdominal obesity	Measured as waist circumference, with different values depending on gender and ethnicity
Increased triglycerides	≥150 mg/dL or specific treatment for this abnormality
Decreased HDL cholesterol	<40 mg/dL in males; <50 mg/dL in females or specific treatment for this abnormality
High blood pressure	Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension
Increased fasting plasma glucose	≥100 mg/dL or previously diagnosed type 2 diabetes

HDL: High-density lipoprotein, BP: Blood pressure

randomized clinical trial among the Japanese population, dental interventions such as periodontal therapy combined with dietary and exercise guidance showed better waist circumference and anthropometric measurements, thereby lowering the risk of MetS (22).

Obesity and periodontitis

Obesity, a cumbersome multifactorial chronic condition, is interpreted as an atypical exorbitant accumulation of fat that presents health distress, with its prevalence accelerating globally (23). The level of abdominal obesity is reported as waist circumference or waist-hip ratio values, as it is deemed superior to the body mass index (24). The 2017 periodontal diseases classification states a critical alliance of obesity with loss of periodontal tissues and a heightened chance of periodontitis, suggesting a comorbidity effect between the two conditions (25). The complex subgingival biofilm in periodontitis, through interaction with host cells, releases proinflammatory cytokines and reactive oxygen species (ROS) accompanied by their raised levels in serum (26). Pro-inflammatory adipokines namely visfatin, leptin, and resistin, are elaborated by chronically inflamed periodontal tissues similar to adipocytes, highlighting the critical role of excessive adipose tissue in the etiopathogenesis of periodontitis. An increase in serum pro-inflammatory cytokines with diminished anti-inflammatory adipokines such as adiponectin, a characteristic feature of obesity, is involved in periodontitis conditions (27). A cohort study in 2022 concluded that individuals with obesity showed a higher proportion of progression of periodontitis with several common risk factors shared by the two conditions (28). Strong evidence points to hyperinsulinemia as a significant precursor to the metabolic disorders linked with obesity (29). Insulin resistance could get augmented under periodontitis conditions, which is evident by the results obtained from a clinical trial conducted in rat models (30). Hyperinsulinemia, evolved from increased insulin secretion augments the absorption of glucose and fat accumulation, thereby manifesting obesity (31).

Insulin resistance or hyperglycemia and periodontitis

DM has a bidirectional and causal link with periodontitis. Better glycemic control has been suggested to minimize the risk and severity of periodontitis. Furthermore, periodontal inflammation resolution can enhance metabolic regulation (32). Subgingival bacteria in periodontitis could penetrate the host tissues or their products, such as LPS that enter the systemic circulation, which is counteracted by an acute-phase protein burst and elevated levels of pro-inflammatory mediators, resulting in insulin resistance (33).

Through the excessive formation of advanced glycation end products (AGEs), DM/hyperglycemia could pave the way for developing periodontitis. Upon binding with receptors for AGEs, periodontal inflammation and destruction are upregulated by the liberation of active inflammatory molecules. Alveolar bone loss can occur due to collagen cross-linking, impaired periodontal tissue renewal, and apoptosis in osteoblastic cells (34). Microbial invasion and enhanced inflammatory processes are amplified by aberrated immune/inflammatory systems such as compromised chemotaxis and phagocytosis of neutrophils and hyperactive macrophages (35).

An ample number of studies have underpinned the interconnection between hyperglycemia and periodontitis. A systematic review by Chopra et al. (36) in 2022 concluded that escalated level of AGEs was evident in blood, salivary secretions, crevicular fluid, and gingival tissues as a consequence of periodontal tissue inflammation. The authors also emphasized that AGE levels were influenced more by the combined effect of DM and periodontitis. Another systematic review and meta-analysis confirmed such a bidirectional relationship, concluding a 34% higher risk of periodontitis in T2DM, whereas the incidence of T2DM increased by 53% in severe periodontitis (37). The study by Mirzaei et al. (38) in 2021 depicted a positive correlation between hyperglycemia and periodontitis, and the management of hyperglycemia could be considered a preventive strategy for periodontitis.

Dyslipidemia and periodontitis

Dyslipidemia is typically defined by elevated blood levels of cholesterol, triglycerides, or both, as well as elevated levels of associated lipoprotein species, with reduced concentration of high-density lipoprotein cholesterol. It constitutes an established independent marker of CVD risk (39). The shared risk elements, genetic predisposition, and overall inflammatory load could act as the possible facets responsible for the interconnection between the two disorders. In response to periodontal microbiota, the host responds with higher levels of numerous common inflammatory mediators in the inflamed periodontal tissues, thus establishing an inflammatory environment (40).

The LPS released by Porphyromonas gingivalis, a key pathogen in periodontal disease due to its proteolytic enzymes, namely gingipains that degrades host proteins, can alter macrophage gene expression, resulting in foam cell development and overexpression of genes encoding cholesterol synthesis that elicit structural changes in circulating lipoproteins via the emission of ROS, which appear to be a risk factor for atherosclerosis (41).

A Japanese study concluded that high triglyceride in conjunction with enhanced lipolysis produced by infection due to endotoxins could be a mechanism by which periodontal disease might promote atherosclerotic change. The authors claimed that visceral adipose tissues, even in individuals without obesity, play a key role in mediating this harmful effect (42). The results of a meta-analysis conducted in 2017,

showed that individuals with periodontitis exhibited a greater probability of elevated blood triglyceride or total cholesterol levels compared with individuals without periodontitis (43).

Hypertension and periodontitis

High BP and periodontitis are widespread conditions with a profound impact on the complications of CVD. Various risk constituents, including demographic status namely age, sex, race, and confounding factors such as smoking, and overweight, DM, are distributed between the two abnormalities (44). Inflammation and oxidative stress initiated by periodontitis may promote functional and anatomic vascular disruptions over a period, leading to arterial stiffness, increased vascular resistance, and volume overload, with an eventual elevation in BP (45). Hypertension is speculated to be a low-grade inflammatory illness entailing the stimulation of the adaptive immune system (46).

T-cells exert a significant role in the onset of hypertension. Activated T-cells cluster in the perivascular region and express cytokines (tissue necrosis factor-α, interleukin-6, 17), encouraging the onset of hypertension (47). An interventional study in 2019 reported that rigorous periodontal therapy was attributed to a fall in the proportion of activated T-cell subsets (48). Significantly greater arterial BP values, as well as a higher tendency to hypertension, have been reported in patients with periodontitis (49). Overlapping inflammatory processes and endothelial dysfunction have been hypothesized as the foundation for the substantial impact of hypertension on individuals with periodontal disease, according to a study result (50).

Conclusion

Most current evidence-based literature indicates that periodontitis can be linked to various systemic diseases, including MetS, through several shared mechanisms to each of its components, thereby contributing a potential role in the emergence of T2DM and CVD. Oxidative stress is a common thread between them, which puts an individual under chronic systemic inflammation. Systemic inflammation may lead to the development of components of MetS in individuals with periodontitis, which ultimately heightens the risk of T2DM and CVD. Most of the pathways in the development of MetS appear driven by abdominal adiposity. In addition, dyslipidemia, hyperglycemia, and hypertension are the potential contributors, which are linked to periodontitis. Furthermore, there is evidence suggesting that periodontal intervention could subside the degree of serum inflammatory molecules, thereby contributing to the reduction in the severity of systemic disorders such as MetS.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.A.K., N.S., A.R.B., Design: B.A.K., N.S., Data Collection or Processing: A.R.B., S.S., Literature Search: B.A.K., N.S., S.S., Writing: B.A.K., N.S.

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