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Diabetes Mellitus and Periodontal Disease

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ABSTRACT

Periodontitis is a disease affecting tissue surrounding the tooth structure. Systemic diseases like diabetes mellitus can have an impact on the severity of periodontitis. Diabetes is a chronic disease that develops either when there is insufficient insulin secretion by the pancreas or when the body fails to utilize the insulin it produces. Insulin is a hormone that regulates glucose levels in the blood. A rise in blood glucose levels can lead to manifestations in the oral cavity in the form of inflammation of the gingival tissue, attachment loss and alveolar bone deterioration. There is substantial evidence that diabetes is a risk factor for gingivitis and periodontitis, and the level of glycaemic control appears to be a significant determinant in this relationship.

Keywords: Periodontitis, diabetes mellitus, hyperglycemia

INTRODUCTION

Globally, the incidence of diabetes mellitus (DM) is blowing up to considerably epidemic proportions, at approximately 415 million individuals and is predicted to rise up to 642 million individuals by 2040[1]. The healthcare system is currently faced with a significant challenge by DM as its complications are the main contributors to morbidity and mortality. In 2023, DM will rank as the seventh leading cause of death, as predicted by The World Health Organization [3]. Systemic subclinical inflammation has been hypothesized as the underlying biological mechanisms of its chronic complications, such as microvascular and nerve damage [4], with evidence of a significant correlation between levels of haemoglobin A1c (HbA1c) and risk of complications [5].

Periodontitis is acknowledged as the sixth most common complication for both DM forms though the majority of the studies are related to T2DM[6]. Periodontitis is an infectious disease caused by a chronic inflammatory response to periodontal pathogens in dental biofilm that induces irreparable damage of the tooth-supporting tissues and eventually tooth loss. There is currently consistent and strong evidence of a two directional relationship between T2DM and periodontitis [7–9]. T2DM promotes the risk for the initiation and progression of periodontitis, while periodontal inflammation affects both glycaemic control and the risk to develop chronic T2DM complications [10–12]. A hyperglycaemic state results in a dysregulated inflammatory response, affecting the immunological activity, neutrophil function, and cytokine pattern, contributing to connective-tissue damage [13,14]. On the other hand, the invasion of periodontal pathogens and their metabolic products to the bloodstream generates elevated serum levels of inflammatory mediators that can deteriorate blood glucose control via acute-phase, that is C-reactive protein, and neutrophil oxidative response [15,16].

DM and Periodontal Disease

Diabetes mellitus is a collection of metabolic diseases characterized by hyperglycaemia arising from defects in the secretion of insulin, the action of insulin, or both. Chronic

hyperglycaemia in diabetes can lead to long-term multi-organ damage and failure, particularly the eyes, kidneys, nerves, heart, and blood vessels [17]. The hallmark of diabetes mellitus is the inability of the body to maintain adequate blood glucose levels. The two types of diabetes mellitus, namely type 1 and type 2, both have been demonstrated to have an effect on periodontium. Type 1 Diabetes, otherwise known as Insulin-Dependent Diabetes Mellitus (IDDM), got its name because patients are typically managed with supplemental insulin, as there is there an absolute deficiency of insulin secretion due to decreased number or defectiveness of pancreatic β cells. Contrarily, Type 2 Diabetes, or Non-Insulin-Dependent Diabetes Mellitus (NIDDM), is characterized by insulin resistance, from the dysfunction of insulin receptors which makes the body's cells become less responsive to the effects of insulin.

There is strong evidence that diabetes is a risk factor for gingivitis and periodontitis, and degree of glycemic control appears to be an important determinant of this relationship [43, 44]. With high blood sugar (≥120 mg/dL) an odds ratio (OR) of 2.46 when strict glycemic control appears to be an important determinant of this relationship [18]. Poorly controlled diabetes patients with higher blood sugar (≥120 mg/dL) had an odds ratio (OR) of 2.46 for severe periodontitis [45]. The badly controlled diabetics showed an increase amount of inflammation [20, 21] (See Figure 1 for clinical case of a patient with Type 2 Diabetes Mellitus and severe periodontitis) [22] (See Figure 1 for the hyperglycaemic environment goes to capillary basement membrane thickening, impaired oxygen clinical case of a patient with Type 2 Diabetes Mellitus and severe periodontitis). Impaired neutrophil function destroys the host's protective environment, resulting in thickening of the capillary basement membrane, impaired oxygen diffusion and mechanism, and broken overall immune function against re-infection[22]. Hyperglycemia alters the elimination of waste. Impaired neutrophil function impairs host defense mechanisms and makes fibroblast metabolism not good, inhibits osteoblast cell proliferation, and slows down bone healing. High overall immune function against infection [22]. Hyperglycemia alters fibroblast metabolism; glycemic status also leads to the production and accumulation of advanced glycation end products that inhibit osteoblast cell proliferation and reduce healing. It affects monocytes and macrophages, causing them to release more inflammatory substances leading to the production and accumulation of advanced glycation end products (AGEs). AGEs bind to cytokines such as IL-1β, TNF-α and PGE2 leading to tissue destruction [23,24]. Systemic monocytes and macrophages release more pro-inflammatory cytokines such as IL-1β, the effects of diabetes contributing to periodontal disease through increased inflammation, TNF-α and PGE2, leading to tissue destruction [23,24]. The systemic effects of diabetes influence oxidative stress in the body and decrease repair mechanisms (see Table 1 for a summary of periodontal disease through increased inflammation, oxidative stress, etc.).

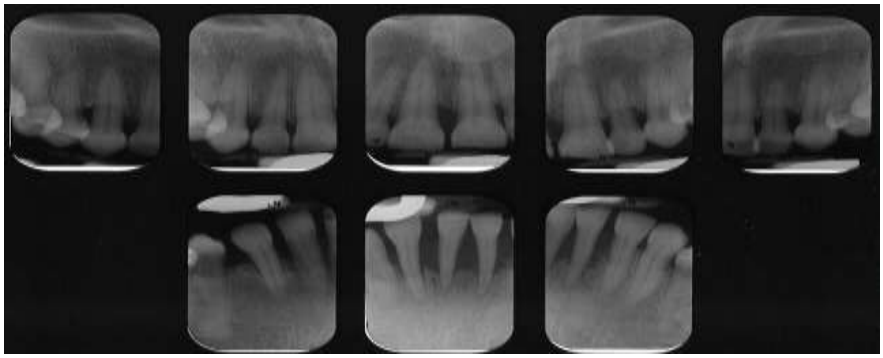

Figure 1. Peri-apical radiographs of patient with Type 2 Diabetes Mellitus. Severe loss of supporting bone is evident. Courtesy of Dr. Brittany Lane.

Table 1. Oral manifestations of Diabetes Mellitus [25]	
a.	Periodontal disease including, gingivitis, varying severity of periodontitis, periodontal abscesses;
b.	Salivary and taste dysfunction
c.	Fungal and bacterial oral infections
d.	Impaired wound healing;
e.	Non-candida oral soft tissue lesions, including fissured tongue, irritation fibroma and traumatic ulcer;
f.	Oral mucosal disease including lichen planus and recurrent aphthous stomatitis;
g.	Neuro-sensory oral disorders including oral dysesthesia or burning mouth syndrome;
h.	Dental caries and tooth loss.

Mechanisms Linking Periodontitis and DM

In this section we will describe the mechanisms underlying the two-directional relationship between periodontitis and DM (Figure 2).

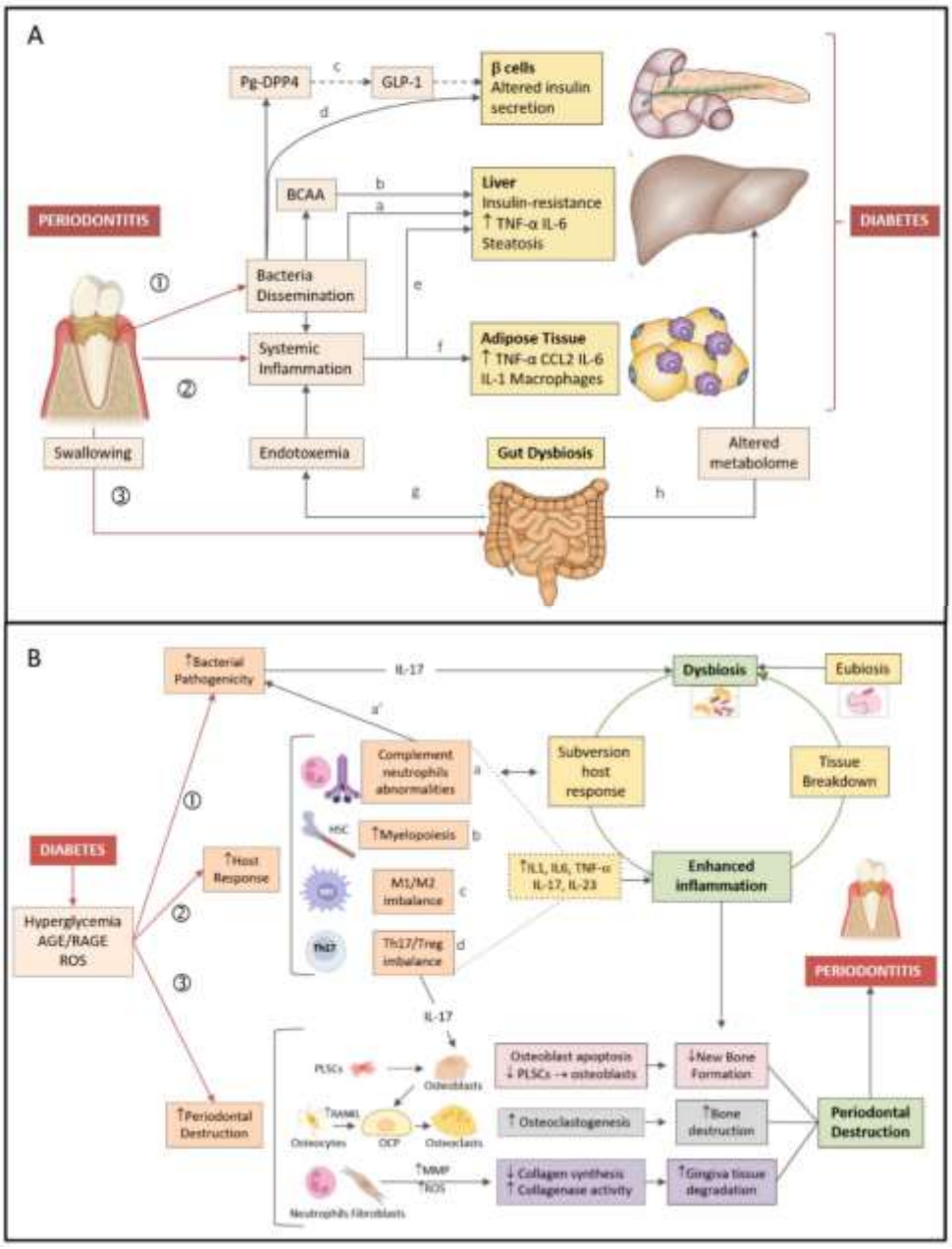

Figure 2. Two-directional relationship between periodontitis and diabetes. (**A**) Periodontitis diabetes direction. Periodontitis is linked to the development/progression of type 2 diabetes by three major mechanisms: (1) Dissemination of periodontal bacteria/metabolic products to the circulation. Bacteria/its products can induce

insulin resistance (a) by inhibiting hepatic glycogen synthesis, increasing hepatic gluconeogenesis, and (b) blocking the insulin receptor substrate by the production of branched-chain amino acids (BCAA). (c) Dipeptidyl peptidase-4 (DPP4) produced by P. gingivalis (Pg-DPP4) can decrease glucose-induced insulin production by promoting glucagon-like peptide 1 (GLP-1) degradation (d) P. gingivalis may alter insulin secretion by promoting β cell dedifferentiation. (2) Induction/magnification of systemic inflammation, causing both (e) hepatic and (f) adipose tissue insulin resistance. (3) gut dysbiosis led by swallowed periodontal bacteria, favoring both (g) endotoxemia and (h) changes in the blood metabolome. (**B**) Diabetes periodontitis direction. Pathogenesis of periodontitis is illustrated on the right-hand side of the figure. Dysbiosis, inflammation, and destruction of the periodontium (green boxes) are features unique to periodontitis. Dysbiotic bacteria decrease the efficacy of the host immune response, while fueling inflammation (open green arrow). In turn, inflammation-induced tissue breakdown causes dysbiosis (closed green arrow) closing the vicious cycle. Mechanisms interconnecting diabetes to periodontitis are shown on the left-hand side of the figure. Diabetes favors development/worsening of periodontitis by three major mechanisms. (1) Enhancing periodontal dysbiosis and bacterial pathogenicity via IL-17. (2) Promoting the host response to the bacterial challenge. Diabetes (a) modifies complement and neutrophil function (which also affects susceptibility to infection a'), (b) increases myelopoiesis, heighten (c) the M1/M2 macrophage ratio, (d) the Th17/Treg lymphocyte ratio, thus raising inflammatory cytokines levels (dotted lines) and fueling inflammation. (3) Increasing periodontal destruction. Diabetes decreases new bone formation by promoting apoptosis of bone-forming cells and by reducing periodontal ligament stem cells (PLSCs) proliferation and differentiation in osteoblasts (pink boxes). Diabetes heightens osteoclastogenesis by increasing RANKL release by osteocytes/osteoblasts, causing osteoclast precursor (OCP) differentiation in osteoclasts (grey boxes). Diabetes modifies gingiva tissue degradation by escalating release of metalloproteinases (MMP) and reactive oxygen species (ROS) by neutrophils and fibroblasts (violet boxes) [26].

Oral microbiome in periodontitis and diabetes

In the past, it was thought that a hyperglycemic environment could specifically promote the rapid growth of some pathogenic bacteria in subgingival flora, thus increasing the patients' susceptibility to periodontitis and deterioration of periodontal [27, 28]. Ganesan et al. found that Lactobacillus, Corynebacterium, Pseudomonas in T2D (Figure 3B) increased considerably. However, there is in fact a reduction in the relative abundance of four species of bacteria (Porphyromonas, Treponema, Prevotella and Parvimonas) [29]. Demmer et al. revealed that and Actinomyces, Proteus and Firmicutes in subgingival plaque microbiome were negatively correlated with insulin resistance of T2D[30]. More recent studies revealed that there was no distinction in the effect of T2D on the microflora of subgingival plaque in patients with periodontitis, only a shift in the types of bacteria, like the abundance of "red complex" bacteria, F. nucleatum and Capnocytophaga sputigena (C. sputigena)[31]. C. sputigena, which is a glycolytic bacterium, could digest glucose in gingival crevicular fluid. As a result, the population was higher in patients with T2D and periodontitis. Other research had demonstrated that the primary distinction of periodontal microorganisms between T2D and periodontitis was in the pathogenicity of bacteria at the level of bacteria, or the varying body's response to the flora [32]. Additionally, periodontitis has also been linked with cardiovascular diseases and is regarded as a cardiovascular risk factor [33]. The pathogens associated with periodontitis could promote the emergence of T2D by exacerbating the dyslipidemia, which is the most crucial risk factor in atherosclerosis [34, 35].

At the same time, periodontitis patients with T2D (PD&T2D) have also been extensively studied on the subgingival dominant flora, and findings revealed that Gemella, Streptococcus, Leptotrichia, Veillonella, TM7 and Terrahemophilus were specific; Fusobacterium, Peptostreptococcus, Filifactor shared with PD; and Parvimonas shared with PD and T2D (Figure 3C). Some studies had also reported a large increase in the absolute abundance of C. sputigena [36], and other studies indicated the presence of a distinct dominant bacteria[30, 35]. Despite the widespread use of microbial sequencing technologies, there was still no consensus on the precise changes in oral bacteria caused by diabetes. Some factors to consider affecting these results are the duration of

hyperglycemia, diet, oral hygiene, drugs and other confounding factors, as well as the limitations of sequencing methods which could also lead to deviation [37]. Some researchers proposed three potential pathways for diabetes to impact periodontal flora:

1. diabetes patients' increased salivary glucose levels would encourage the growth of some bacterial species;
2. diabetes would cause oral dehydration and a decreased microbial diversity;
3. oral acidification and disrupt oral microbiota might be a result from hyperglycemia [38].

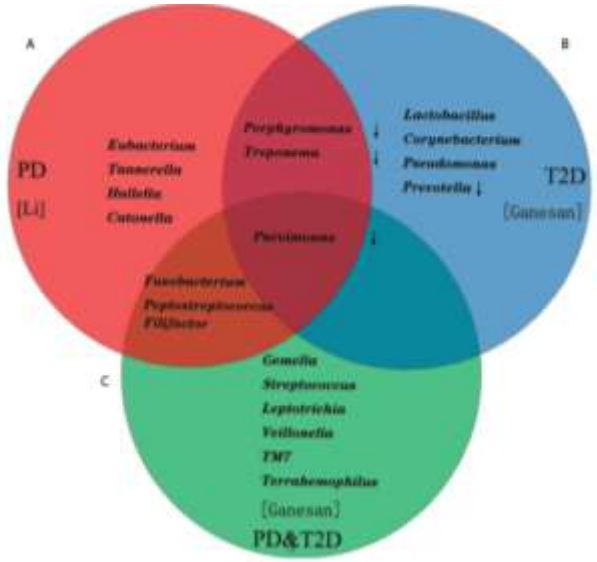

Figure 3. The composition of the top 10 bacterial genera by relative abundance in patients with T2D and periodontitis. (A) periodontitis was closely related to the tannerella, catonella, eubacterium, parvimonas, hallella, and so on. (B) significant increase is shown in the lactobacillus, Corynebacterium, pseudomonas in T2D. (C) those shared with PD are the fusobacterium, peptospreptococcus, filifactor, whereas parvimonas shared with PD and T2D

Viruses in periodontitis and type-2 diabetes mellitus

A few recent investigations had reported the virus infection in T2D and periodontitis. In type 2 diabetic subjects with poor glycemic control, EBV was more frequently found in shallow periodontal pockets [39]. Another cross-sectional study with a total of 120 patients had shown that EBV-1 was more prevalent in those with poor glycemic status patients, and the highest levels of EBV-1 were seen in periodontitis with T2D [40]. Furthermore, it was hypothesized that the increase of microRNA-146a and microRNA-155 in the oral cavity induced by T2D and periodontitis upregulates the expression of ACE2, the essential SARS-CoV-2 entry receptors, which modulates the host's antiviral response. This might suggest that patients with T2D and periodontitis were more likely to get an infection [41].

In conclusion, viral infection played an integral role in the development of T2D and periodontitis, particularly in the former. When the two diseases were present at the same time, there was a higher chance for a viral infection to occur. The potential role of viruses should be fully taken into account in the process of diagnosing and treating related diseases, and when necessary, the combined treatment of bacterial and viral infections would be a novel idea for the management of periodontitis and T2D [42].

Management

The following is the recommended treatment approach for diabetic patients according to the consensus report of the joint European Federation of Periodontology and the American Academy of Periodontolog[43].

1. Inform diabetic patients that there is a bidirectional relationship between periodontal disease and diabetes;
2. Inform these patients that they should get a comprehensive oral exam that includes a complete periodontal exam;
3. Provide education on oral health to the patients;

4. Address children and adolescents with diabetes should undergo annual oral screenings;
5. Address that diabetic patients are more susceptible to oral fungal infections and have impaired wound healing.

Periodontal Disease and Lipid Profile

Two mechanisms have been proposed to explain the link between periodontitis and atherosclerosis: either directly by the periodontal pathogens or indirectly by bacterial components or inflammatory mediators. A third mechanism that might potentially support the association is the connection between periodontitis and the lipid profile. Atherosclerosis, which is considered to be one of the main causes of CVD, is characterized as the progressive accumulation of lipids, macrophages, calcium, fibrotic tissue and other components in the coronary artery wall [44]. Recently, it is thought that an immunologic mechanism is considered instead to be responsible for its development [45]. Previous research has demonstrated that certain bacterial infections may increase plasma concentrations of very-low-density lipoprotein and small dense LDL levels in humans [46,47]. Gingipain from P. gingivalis caused a selective proteolysis of apoB-100, a main component of LDL particles, and crucial for the binding of LDL to cell surface receptors, which is a critical step for the promotion of atherosclerosis [48]. Furthermore, gingipain has also shown to alter vascular LDL/VLDL and HDL through proteolytic effects to an atherogenic state (mainly lipid peroxidation). This evidence supports the idea that lipoproteins is a key link between periodontal disease and the emergence of atherosclerosis [49]. LDL manifests itself differently between particles depending on the size and density. These subclasses exhibit variations in surface lipid content and conformational changes in apoB-100, with increased exposure on the particle surface [50]. An LDL subclass known as small, dense low-density lipoproteins were found to be highly atherogenic and have little affinity for the apoB/E receptor of hepatocytes, slowing down their blood clearance. They also have a strong affinity for vascular glycosaminoglycans, which prolongs their contact with the vascular artery wall. They are taken up more easily by arterial tissue and also exhibit a greater oxidative and glycation susceptibility [51]. Small, dense LDLs have recently been found to play a significant role in atherosclerosis, which may be predictive of various cardiometabolic states, and interact with a number of traditional cardiovascular markers [52]. Moreover, elevated levels of this LDL subclass have been seen in patients with periodontitis [53]. A recent systematic review has been published investigating serum lipid levels (total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol) in subjects with and without periodontitis. The vast variation and lack of agreement in the diagnosis and case definition of periodontitis, which was also confirmed by the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, led them to the conclusion that studies cannot provide consistent information. Significant flaws were identified in this workshop (lack of clear pathobiology distinction between categories, diagnostic imprecision, and implementation difficulties) and a new framework for a new case definition and classification of periodontitis is proposed in order to improve the methodology of assessment and the data quality for future studies [54]. The authors conducted a meta-analysis with meta-regression of 19 studies, with a total of 2104 participants. The analysis was conducted by sorting the papers into those with secure diagnosis of periodontitis and those with an insecure diagnosis. They came to the conclusion that periodontitis was fundamentally linked with a decline of HDL-cholesterol and an increase in LDL, cholesterol and triglycerides. They claim that periodontal inflammation may negatively impact serum lipid regulation, as well as contributing to the incidence of CVD. Since dyslipidemia is linked to a condition of

systemic inflammation, lipid dysregulation would also increase the susceptibility to periodontitis [55]. This implies a possible two-directional relationship between dyslipidemia and periodontitis (Fig. 3) [56].

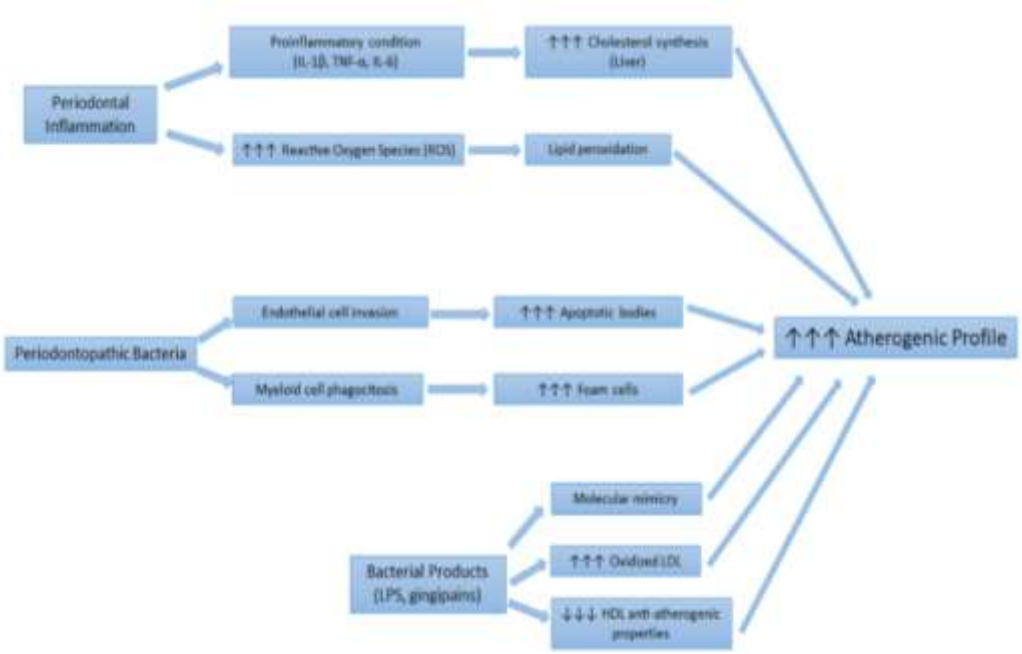

Figure. 4. Diagram of the correlation between periodontitis and atherosclerosis

Obesity, Metabolic Syndromes, and Diabetes Mellitus

Obesity, characterized by an excessive buildup of body fat, is a chronic disease that has been associated with a number of diseases, including hypertension, coronary heart disease, type 2 diabetes and cancer [57]. Additionally, obesity can have a negative impact on periodontal health [58]. The mechanism underlying this relationship are thought to be caused by the adipose tissue's increasing production of proinflammatory cytokines [59]. Metabolic syndrome (a clustering of metabolic conditions), on the other hand, is associated with a higher risk of type 2 diabetes and cardiovascular disease. The criteria for defining metabolic syndrome include the following: central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension and elevated fasting plasma glucose levels. Individuals exhibiting of at least three of the symptoms would confirm a diagnosis of metabolic syndrome [60]. Globally, the prevalence of metabolic syndrome varies in a range from less than 10% to more than 40% [61]. According to a cross-sectional analysis, patients with moderate or severe periodontitis are more likely to have metabolic syndrome compared to subjects with no or mild periodontitis [62]. Furthermore, a cohort study showed that long-term metabolic syndrome exposure is associated with deep probing depths and alveolar bone loss [63]. Oxidative stress might be a bidirectional link between periodontitis and metabolic syndrome, with reduced insulin sensitivity, decreased antioxidant capacity and increased oxidative damage involved in the interaction [64].

CONCLUSION

Severe periodontitis is strongly correlated with poor glycemic control, lipid metabolism, obesity and metabolic syndrome. An integral component of the diabetes visit should include a periodontal examination, as proposed by the recent joint guidelines from the European Federation of Periodontology and the International Diabetes Federation. As part of the overall management of the disease, thorough interview by a physician is crucial to recognize the symptoms of periodontitis, and

the patient should be referred and encouraged to receive periodontal treatment. In this context, the dental profession may play a significant role in diagnosis, as the condition may be first identified by the dental practitioner, and also be a part in the treatment of the metabolic syndrome.

Declaration by Authors

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