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A review of the relationship between chronic periodontitis, obesity and diabetes mellitus

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Abstract

The increasing incidence of chronic periodontitis (CP), obesity and diabetes mellitus (DM) worldwide imposes a rethinking of the interrelation and their pathogenesis. The current review discusses the pathogenesis of diabetes mellitus, obesity and chronic periodontitis with emphasis on the relationship between them.

Keywords: *Chronic periodontitis , obesity and diabetes mellitus*

1. Introduction

The human organism is a unity that is composed by an infinite number of biologic processes so strongly linked that abnormalities in any part of the body and/or its processes may have deep effects in many other body areas[1], for example as in this review, the three highly prevalent diseases: chronic periodontitis, obesity and diabetes mellitus.

2. Chronic periodontitis

Periodontal disease is an entity of localized infections that involve tooth supporting tissues, the structures that make up the periodontium (i.e., gingiva, periodontal ligament, root cementum, and alveolar bone). The designation periodontal disease includes both reversible (gingivitis) and irreversible (periodontitis) processes. In periodontitis, there is destruction of the connective tissue of the tooth attachment apparatus accompanied by apical migration of the apparatus and eventual tooth loss. The first clinical manifestation of periodontal disease is the appearance of periodontal pockets, which offer a favorable niche for bacterial colonization.**[**2**]**

According to the WHO the prevalence of severe chronic periodontitis varies worldwide from 10 to 15% in adult populations whereas complete edentulism (no natural teeth) varies from 10 to 35% among countries depending on national income [3]. The most common forms of periodontal diseases are plaque-induced gingivitis and chronic periodontitis. Gingivitis is defined as an inflammation of

the gingiva induced by bacteria located at the gingival margin. The host response to similar plaque levels varies significantly among patients with gingivitis and bacteria associated with disease progression are also present in health. Gingivitis is reversible upon removal of the etiologic biofilm but when untreated it progresses to chronic periodontitis in certain individuals. Several lines of evidence demonstrated that in some individuals gingivitis never progresses to chronic periodontitis, regardless of periodontal care.[4,5]

Periodontitis is essentially a biofilm induced disease, initiated and progressed by different bacterial species, present in the dental plaque. The periodontopathic bacteria are basically gram-negative in nature and they are present in the depths of periodontal pockets, placed at low oxygen tension. The putative pathogenic bacteria express noxious toxins instrumental for the periodontal destruction.[6]

When bacterial biofilms on the teeth are not disrupted on a regular basis, the emergences of Gram-negative anaerobic bacterial species activate several host processes that will interfere in the extent and severity of the disease.[1]

The most frequently recognized periodontal pathogens belong to three microaerophilic species (*Actinobacillus actinomycetemcomitans, Campylobacter rectus, and Eikenella corrodens*) and seven anaerobic species (*Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, Prevotella intermedia, Fusobacterium nucleatum, Eubacterium, and spirochetes*).[7]

Currently, the consensus regarding pathogenesis of periodontitis has undergone an immense change. According to this concept, periodontitis is not only the result of adverse microbial activity but as an interaction among various other factors like genetics, systemic health, immunity, environmental factors like tobacco and stress. The above mentioned factors play an important role in the modification of host response to the disease process. Thus, sometimes the periodontal disease may exhibit varied expression [6]. Various pro-inflammatory mediators like interleukin (IL)- 1α and IL-1β, IL-6, tumor necrosis factor (TNF)-α, prostaglandin E2 (PGE2), matrix metalloproteinases are expressed in periodontitis, as a result of activation of the host immune-inflammatory mechanisms. Cytokines are liberated by periodontal tissues like fibroblasts, endothelial cells, macrophages, osteoclasts, epithelial cells, neutrophils, monocytes, lymphocytes, and mast cells. Immune cells like neutrophils, monocytes also let out cytokines in inflammatory conditions. This host tissue expressed a large number of factors that may be detrimental to the host tissue itself, amplifying the destructive disease process [8]. The periodontopathogenic flora produce toxins and significant challenge is offered by lipopolysaccharide (LPS), a component of the gram-negative bacterial cell wall. LPS is a potent endotoxin which exacerbates the host inflammatory response. Subjects with periodontitis are reported to present endotoxin activity in the serum [9]. As discussed previously the bacteria are housed in the periodontal pocket. These bacteria, attended with their noxious products can gain a ready access through the ulcerated lining of the periodontal pocket, into the systemic circulation. Studies have identified many systemic biomarkers, exposing the link of periodontitis with systemic conditions and cardiovascular disease [10,11]. Thus, it can be enunciated that periodontitis is a “low

grade infection" capable of developing a "low grade systemic inflammation" with an ability to influence the general systemic health.

Chronic periodontitis being a low-grade infection is characterized by infiltration of the inflammatory cells within the periodontal tissues, which act as a source of production for resistin. Lipopolysaccharides produced by periodontal pathogens are shown to induce the resistin gene in macrophages via cascade involving the production of proinflammatory mediators [12]. Pro-inflammatory mediators (PGE2, TNF-α, IL-1, and IL-6) produced during the periodontal pathogenesis in addition to local tissue destruction also exert certain systemic effects [13].

Many conditions can predispose and/or facilitate the occurrence of periodontal diseases (PD) such as smoking**[14]**, genetic influences**[15]**, and obesity [16, 17]. The prevalence of obesity is increasing worldwide. This epidemic is also associated with an increased occurrence of obesity-related diseases like hypertension, cardiovascular disease, metabolic syndrome and diabetes mellitus that are also linked to periodontal diseases[16, 17].

3. Diabetes mellitus

Diabetes mellitus is a chronic, non-communicable disease and also one of the major global public health issues [18]. In 2014, it was estimated that 422 million adults were living with diabetes mellitus worldwide. The global prevalence of diabetes in the adult population has nearly doubled since 1980, rising from 4.7% to 8.5% [19]. Diabetes mellitus is a group of metabolic disorders that leads to hyperglycaemia and is classified into four general categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes and other specific types of diabetes [20].Diabetes mellitus is characterized by frequent episodes of hyperglycemia [21], which initiates chemical and molecular pathways associated with diabetes complications [22].

T1DM is a polygenic autoimmune disease that is characterized by the destruction of insulin-secreting pancreatic beta cells[23].T2DM is a metabolic disorder that is characterized by hyperglycemia and altered lipid metabolism, which is caused by the inability of islet beta-cells of Langerhans to secrete adequate insulin in response to varying degrees of insulin resistance caused by over-nutrition, inactivity or obesity. Metabolic defects that contribute to the development of T2DM include an inability of islet b cells to compensate for high glucose levels that are associated with excess food intake, increased glucagon secretion and reduced incretin response, impaired expansion of subcutaneous adipose tissue, hypoadiponectinaemia, inflammation of adipose tissue, increased endogenous glucose production and the development of peripheral insulin resistance[24]. Chronic increased caloric intake is the primary pathogenic event that drives the development of type 2 diabetes in genetically and epigenetically susceptible individuals.[25,26].

In both types of diabetes mellitus hyperglycemia is directly related to pancreatic dysfunction and ultimately leads to macro- and microvascular complications including atherosclerosis, ischemic heart disease, nephropathy, retinopathy, neuropathy and periodontal disease. Uncontrolled

hyperglycemia is central to development of angiopathy through several biochemical and molecular mechanisms manifested in both intra- and extracellular compartments. The four major pathways through which hyperglycemia alters cellular physiology and extracellular matrix structure are the polyol pathway, the hexosamine pathway, activation of protein kinase c (PKC), and advanced glycation end product (AGE) formation. The first three pathways generally alter cellular function by acting directly on intracellular pathways while AGE directly impact the extracellular matrix quality and indirectly the normal cell function through specific receptors for AGE.[27]

4. Obesity

Obesity is a chronic disease[28].The prevalence of obesity is increasing worldwide and is becoming one of the most important health hazards [29], as obesity is highly associated with increased overall morbidity and mortality [30]. Obesity is defined with a body mass index (BMI; body weight in kilogram divided by the square of the height in meters (kg/m2)) of at least 30.0 kg/m2 [31], whereas overweight is defined with a BMI of 25–29.9 kg/m2. Normal weight is characterized by a BMI ranging between 19 to 24.9 kg/m2 [32]. In 2002 WHO reported that over 200 million men and 300 million women were obese[33].Adipose tissue contains usually 5-10 % macrophages, but the adipose tissue of obese patients shows up to 60 % macrophage infiltration. Adipocytes secrete bioactive molecules called adipokines, that can modify or trigger inflammation and fat metabolism locally or systemically as signaling molecules to liver, muscle and endothelium. Therefore, the adipose tissue can be considered as an important metabolically active endocrine organ [32] This explains how obesity acts as a risk factor for several chronic diseases: Hypertension, type 2 diabetes, dyslipidemia, and coronary heart disease are so closely related to obesity that obesity itself is often considered to be a systemic disease. This disease also affects dental health [34]. Accordingly obese persons require attention of physicians and dentists [30].

5. Chronic periodontitis and diabetes mellitus

Chronic periodontitis has been identified as the sixth complication of diabetes alongside retinopathy, nephropathy, neuropathy, macrovascular disease and poor wound healing[35].where individuals with diabetes have a higher prevalence of periodontitis [36–38] and diabetes mellitus can increase the severity of periodontitis [39–41] and the severity of the periodontitis is always greater than individuals without diabetes [36,42].This is due to the following mechanisms: the function of immune cells, including neutrophils, monocytes, and macrophages, is altered in diabetes [43].Neutrophil adherence, chemotaxis, and phagocytosis are often impaired, which may inhibit bacterial killing in the periodontal pocket and significantly increase periodontal destruction[44,45].Although the function of neutrophils is often diminished in diabetes, the monocyte/macrophage cell line may exhibit upregulation in response to bacterial antigens. The

hyperresponsiveness of monocytes/ macrophages results in significantly increased production of proinflammatory cytokines and mediators[46-48].Peripheral blood monocytes from diabetic subjects produce elevated levels of tumor necrosis factor-alpha in response to antigens from *Porphyromonas gingival is* compared to monocytes from non-diabetic control subjects**[**46**]**. also in diabetic patient there is inhibition of osteoblastic cell proliferation and collagen production that result in reduced bone formation and diminished mechanical properties of the newly formed bone[49-52]. Because the periodontal pocket is a site of persistent bacterial wounding, an intact wound-healing response is critical to maintain tissue health. High glucose levels in the gingival crevicular fluid may directly hinder the wound-healing capacity of fibroblasts in the periodontium by inhibiting attachment and spreading of these cells that are critical to wound healing and normal tissue turnover [53].In individuals with sustained hyperglycemia, proteins become irreversibly glycated to form advanced glycation end products (AGEs) [54].These stable carbohydrate-containing proteins have multiple effects on cell-to-cell and cell-to-matrix interactions and are commonly thought to be a major link between the various diabetic complications. The formation of AGEs also occurs in the periodontium, and higher levels of periodontal AGE accumulation are found in those with diabetes than in non-diabetic subjects[55]. AGEs often form on collagen, increasing collagen cross-linking and resulting in the formation of highly stable collagen macromolecules. These molecules accumulate in tissues due to their resistance to normal enzymatic degradation and tissue turnover [54]. Changes in collagen synthesis, maturation, and homeostatic turnover are common in diabetes. These changes can contribute to the pathogenesis of periodontal diseases and to alterations in wound healing because collagen is the major structural protein in the periodontium. Human gingival fibroblasts produce decreased amounts of collagen and glycosaminoglycans in high-glucose environments[56]. There is additional evidence emerging that decreases in matrix-producing cells critical to maintaining the periodontium, including fibroblasts and osteoblasts, occur due to an increased rate of apoptosis in a hyperglycemic state in response to *Porphyromonas gingivalis* infection [57-59]. The structural changes that characterize diabetic angiopathy include abnormal growth and impaired regeneration of vessels. The changes seen in the microvasculature of the retina, glomerulus, and other end organs in people with diabetic complications also occur in the periodontium[60].

periodontitis may be a risk factor for worsening glycemic control among patients with diabetes. Periodontitis may initiate or propagate insulin resistance in a manner similar to that of obesity, by enhancing activation of the overall systemic immune response initiated by cytokines[61,62].

A bidirectional relationship has been established between diabetes and periodontitis, where in one can influence the other [63]. Chronic subclinical inflammation has been shown to decrease the insulin sensitivity. Levels of resistin are found to be increased in periodontitis, and resistin plays an important role in inducing insulin resistance, thus increasing the risk for type II diabetes [64].

Periodontitis is also associated with an increased risk for diabetic complications. 82% of diabetic patients with periodontitis experienced one or more major cardiovascular, cerebrovascular or

peripheral vascular events[65]. Another study examined the effect of periodontal disease on mortality in more than 600 subjects with type 2 diabetes. After accounting for other known risk factors, the death rate from ischemic heart disease was 2.3 times higher in people with severe periodontitis than in patients without periodontitis or with only mild periodontitis, while the death rate from diabetic nephropathy was 8.5 times higher in those with severe periodontitis[66].
Periodontal treatment can adversely affect on glycemic control in diabetics where Periodontal treatment that reduces periodontal inflammation may help to restore insulin sensitivity, thereby improving glycemic control[38,62]. Studies of patients with both diabetes and periodontitis have shown that nonsurgical periodontal therapy with adjunctive local delivery of minocycline reduced circulating levels of TNF-α. The reduction in serum levels of TNF-α was closely related with, a significant decrease in mean HbA1c values (from 8% to 7.1%)[67].

6. Chronic periodontitis and diabetes mellitus

Obesity is a possible risk factor for periodontitis [68]. One study identified obesity even as the second strongest risk factor for periodontitis preceded only by smoking [69]. The first report on the relationship between obesity and periodontal disease appeared in 1977. Perlstein and co-workers found greater alveolar bone resorption in obese than in non-obese rats. Under healthy oral conditions, obesity itself did not promote periodontal damage, but in the presence of bacterial plaque accumulation periodontal inflammation was more severe in obese than in non obese animals. [70]
In another study the researchers found that an increased prevalence odds ratio for obesity among subjects with periodontal disease and in clinical practice, a higher prevalence of periodontal disease should be expected among obese adults. [71].
Maintaining good oral health is also fundamental for obese individuals. Dental practitioners should educate their obese patients about the risk of periodontal disease and reinforce the importance of proper oral hygiene.[72]
A recent systematic review including a meta-analysis concluded that obese and overweight/obese individuals together are 1.8 times and 2.3 times more likely to suffer from periodontitis independent of traditional risk factors in comparison with normal-weight control individuals, respectively[73].
Obesity has been shown to be associated with adverse post-surgical outcomes such as infectious complications and compromised healing[74, 75]. The hypothesis of altered immune response and wound healing associated with obesity raises the question of a possible modifying effect of obesity on periodontal therapy clinical response .
The biological mechanism by which obesity predisposes to periodontitis is not fully understood[68]. Compared to individuals with normal weight individuals with obesity have higher levels of circulating tumor necrosis factor-α and interleukin-6 (IL-6), which are also secreted from adipose tissue and are involved in the pathophysiology of both obesity and periodontitis. Not surprisingly, serum levels of these cytokines decrease with loss of weight [76].
Adipocytokines are bioactive mediators released from the adipose tissues including adipocytes and other cells present within fat tissues. These include several novel and highly active molecules released abundantly by adipocytes like leptin, resistin, adiponectin, and visfatin, as well as some

more classical cytokines released possibly by inflammatory cells infiltrating fat, like TNF-α, IL-6and IL-1 [77].
Adiponectin is a product of adipocytes and its levels decrease in obese subjects. Adiponectin has several beneficial effects like anti inflammatory, vasoprotective and antidiabetic effects. These protective effects occur due to suppression of tumor necrosis factor-α, interleukin-6 and along with induction of interleukin-1 receptor antagonist. Iwayama et al showed that adiponectin has potent beneficial function to maintain the homeostasis of periodontal health, improve periodontal lesion and contribute wound healing and periodontal regeneration [78].
Resistin belongs to secretory protein family called as resistin like molecules, which is characterized by a highly conserved cysteine rich C- terminal. Resistin has been named since it is believed to convey the resistance to insulin. Resistin may not originate directly from adipocytes but may originate from inflammatory cells infiltrating the fat tissue. Release of resistin appears to be stimulated by inflammation, LPS, IL-6, hyperglycemia, growth and gonadal hormones. While released within the fat tissue, resistin acts on adipocytes leading to insulin resistance. Levels of resistin increase with increasing obesity which is a major contributing factor for the development of type 2 diabetes mellitus, and periodontitis. Two studies showed the positive association of periodontal disease with gingival crevicular fluid resistin levels [13,79].
There are three mechanisms for the role of oral bacteria in the development of obesity as suggested by Goodson et al. First, oral bacteria may increase metabolic efficiency, as suggested by infectobesity proponents. The second hypothesis is that oral bacteria could increase weight gain by increasing appetite. The third hypothesis is that oral bacteria redirect energy metabolism by facilitating insulin resistance through increasing levels of TNF-α. Using any of these mechanisms, even a small excess in caloric consumption with no change in diet or exercise could result in unacceptable weight gain. Periodontal disease may contribute to the development of obesity and the role of the oral microbiota in obesity has been gaining more attention. [80] Obesity is also associated with increased counts and proportions of certain periodontal pathogens, including *Tannerella forsythia and Selenomonas noxia* [81].

7. Obesity and type 2 diabetes

Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency[82]. Type 2 DM results from interaction between genetic, environmental and behavioral risk factors[83,84].Type 2 DM is due primarily to lifestyle factors and genetics[85]. A number of lifestyle factors are known to be important to the development of type 2 DM. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol[86]. Obesity has been found to contribute to approximately 55% of cases of type 2 DM[87].
Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure[88,89].

A strong relationship between obesity and the onset of diabetes has been reported in a number of studies. Research has shown that people carrying more weight particularly around the tummy are more insulin resistant [90-93] and may struggle to achieve good diabetes control.[94-96]
Pathogenesis of obesity appears to play a central role in the dysregulation of cellular mechanism that accounts for insulin resistance, which is the state of reduced responsiveness of liver, muscle and adipose tissue to insulin in type 2 diabetes. The stored fat is required for survival during nutritionally deprived states, however during state of prolonged abundance of food, excessive fat storage results in obesity.[97,98]This excessive storage of fat that creates obesity eventually leads to the release of elevated levels of fatty acids (FFAs) from enhanced lipolysis. The release of these FFAs then induces lipotoxicity, as lipids and their metabolites create oxidant stress to the endoplasmic reticulum and mitochondria. This affects adipose as well as non-adipose tissues resulting in insulin-receptor dysfunction. The consequence is an insulin-resistant state which then creates hyperglycemia with compensated hepatic gluconeogenesis.[99-101] Insulin resistance is a key factor for type 2 diabetes. FFAs also decrease utilization of insulin-stimulated muscle glucose, contributing further to hyperglycemia. Lipotoxicity from excessive FFAs also decreases secretion of pancreatic β-cell insulin, which eventually results in β-cell exhaustion. Moreover, excess adipocytes release inflammatory adipokines [TNF-α, IL-6, complement C3, leptin and macrophage migration inhibitory factor (MIF)], which, along with free fatty acids, provide the pathophysiologic basis for comorbid conditions associated with obesity such as insulin resistance and type 2 diabetes. Along with fatty-acid lipotoxicity, visceral adipokines also contribute to the adipokine inflammatory injury that leads to pancreatic β-cell dysfunction, which, in turn, decreases insulin synthesis and secretion.[102,103] Adipocytes also stimulate fat-associated macrophages that also secrete monocyte chemoattractant protein 1 (MCP-1), macrophage migration inhibiting factor (MMIF), and resistin, all of which decrease insulin sensitivity (i.e. enhance insulin resistance).[104,105]

8. Conclusions

Chronic periodontitis, obesity and diabetes mellitus are important chronic health problems and are closely associated. Obesity is associated with an increased prevalence of periodontitis and diabetes mellitus. Diabetes mellitus associated with an increased prevalence of chronic periodontitis and chronic periodontitis is considered as a risk factor for diabetes mellitus and obesity.

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