DIABETES MELLITUS AND PERIODONTITIS: SIGNS OF A BIDIRECTIONAL RELATIONSHIP

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Disclosure: No potential conflict of interest.
Received: 15.05.13 **Accepted:** 30.10.13
Citation: EMJ Diabet. 2013;1:30-36.

ABSTRACT

Periodontitis is a multifactorial, irreversible and cumulative condition, initiated and propagated by bacteria and host factors. The multifactorial nature of periodontitis is related with the complex interactions between microorganisms in the microbial dental plaque and host response mechanisms, as well as environmental factors. Progression of periodontal disease is very much dependent on host response. Diabetes mellitus (DM), a complex metabolic disorder characterised by prolonged hyperglycaemia, has long been recognised as one of the leading causes of morbidity and mortality globally. DM is a complex metabolic syndrome that affects both the quality and length of life with major complications. Periodontal disease and diabetes are highly prevalent chronic diseases and inflammation may play a critical role in their relationship. Prospective clinical studies with larger scale and greater statistical power are required to better clarify the mechanisms of possible effects of chronic periodontitis on diabetes.

Keywords: Diabetes mellitus, periodontal disease, saliva, inflammation, serum.

INTRODUCTION

Periodontal tissues consist of four components: gingiva, periodontal ligament, cementum, and alveolar bone (Figure 1). Periodontal diseases are among the most common chronic infectious and inflammatory diseases in the world. Pathogenesis of periodontal diseases has two major aspects: microorganisms and host response. Interactions between microbial plaque and host immune system play a critical role in the initiation and progression of periodontal diseases. Diabetes mellitus (DM) has long been recognised as one of the leading causes of morbidity and mortality globally.[1] This brief review highlights the evidence for a bidirectional relationship between DM and periodontal disease.

SEARCH STRATEGY

A literature search of the last thirty years was performed using the ISI and PubMed database from 1980 to 30 April 2013, with the following search strategy: ("periodontitis" OR "periodontal disease") AND ("diabetes mellitus") AND ("treatment" OR "interaction" OR "metabolic control") AND ("saliva" OR "gingival crevicular fluid" OR "serum"). The search was limited to the English language. *In vitro* studies on cell cultures, experimental studies on animal models, polymorphism studies, studies particularly investigating possible role of various therapeutic agents such as subantimicrobial-dose doxycycline, anti-inflammatory agents, and studies focused only on smoking were excluded from the present review. Titles and abstracts were screened and the full text of publications was obtained for the selected articles. In addition, the reference lists of review papers were hand searched.

DEFINITIONS OF PERIODONTITIS AND DIABETES MELLITUS

Healthy gingiva has a pink colour and firm consistency with no sign of inflammation (Figure 2). Periodontitis is characterised by gingival inflammation and alveolar bone resorption. Gingival inflammation is visualised by gingival

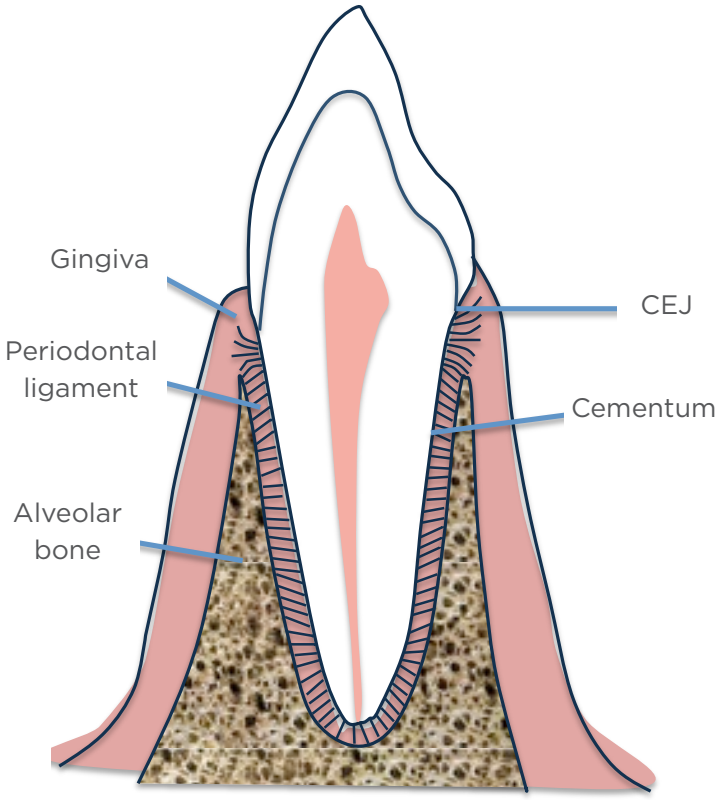

Figure 1. Diagram of healthy periodontal tissues namely; gingiva, periodontal ligament, cementum, and alveolar bone.
The cementoenamel junction (CEJ) is at the base of the sulcus, the periodontal ligament fibres are all intact lying between cementum on the root surface and the alveolar bone. Thus, there is no attachment loss and no pocket when probed with a periodontal probe. Pocket depth (PD) is the distance between the free gingival margin and the base of the sulcus/pocket in millimetres. Clinical attachment level (CAL) on the other hand shows the distance from the CEJ to the base of the sulcus/pocket.

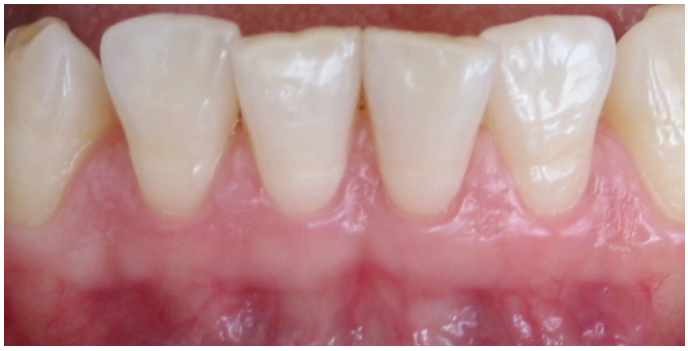

Figure 2. Clinical picture of healthy teeth and periodontium.
Inflammation-free gingiva is characterised by a coral-pink colour, there is no sign of oedema or bleeding and the gingiva is tightly surrounding the tooth.

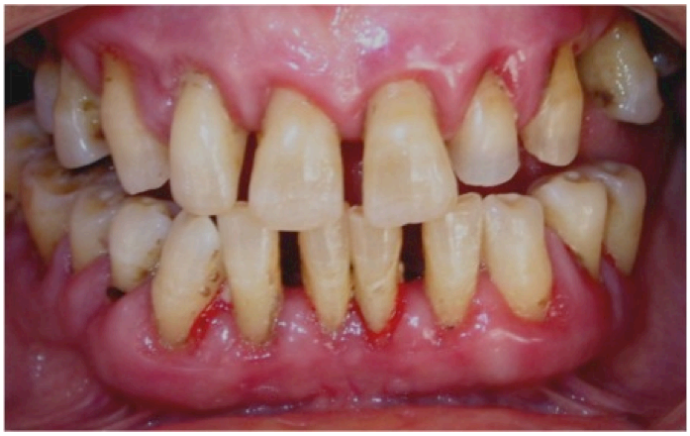

Figure 3. Clinical picture of a case of severe chronic periodontitis with type 2 diabetes mellitus.
Note the pronounced gingival inflammation, bleeding, and swelling, but also gingival recession. There is visible plaque accumulation at the necks of the teeth and calculus deposits are also easily detectable. The upper anterior teeth had migrated due to severe periodontal destruction and lost their contacts with each other.

reddening, oedema, and bleeding on probing (BOP) with a periodontal probe (Figure 3). Alveolar bone resorption can be detected radiographically and also clinically by measuring the probing depth and clinical attachment level (CAL) in millimetres by a periodontal probe. The World Health Organization reported that severe chronic periodontitis leading to tooth loss was found in 5-15% of most populations worldwide. Periodontitis is a chronic local oral infection regarded as triggering not only a local but also a systemic immuno-inflammatory response.[2] More than 500 different bacterial species are able to colonise the oral biofilm and up to 150 different species of bacteria are possible in any individual's subgingival plaque. Systemic diseases and conditions may affect the onset and course of periodontal disease or vice versa.

DM is a complex metabolic syndrome that affects both the quality and length of life with major complications, which is caused by either a deficiency in insulin production or an impaired utilisation of insulin. Type 1 DM is caused by progressive autoimmune destruction of pancreatic insulin-producing ß cells. Type 2 DM describes a metabolic disorder of multiple aetiology,

characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1]

EPIDEMIOLOGY

Clinical and epidemiological studies have reported higher prevalence and increased severity of periodontitis in diabetic patients.[3-5] It was reported that type 2 DM patients are 2.8 times more likely to have periodontitis,[6] and 4.2 times more likely to have significant alveolar bone loss[7] than systemically healthy individuals. Indeed, periodontal disease has been proposed to be the sixth complication of DM[8] with evidence showing a correlation between poorer glycaemic control and worsening periodontal health.[9,10] Higher gingivitis index and gingival recession in diabetic patients compared to the systemically healthy controls were reported.[11] Higher gingival index and attachment loss were also associated with HbA1c levels in diabetic patients.[12] HbA1c correlated positively with percentage of sites that bleed on probing and sites exhibiting probing depths ≥5 mm.[13] The best predictor for severe periodontal disease in subjects with type 2 DM has been reported to be smoking followed by HbA1c level.[14] Diabetic patients commonly present with xerostomia[15] and lower salivary flow rates compared to the systemically healthy controls. Thus, there is substantial information supporting a close association between DM and periodontitis.[16]

INTERSECTIONS IN PATHOGENIC MECHANISMS

Diabetes-associated susceptibility traits for periodontitis include neutrophil dysfunction, abnormal cross-linking and glycosylation of collagen, defective secretion of growth factors, cytokines and subsequent impaired healing. Reactive oxygen species have a role in periodontal diseases as well as diabetes. Prolonged inflammation, such as periodontitis, is a source of reactive oxygen species and can compromise the antioxidant capacity of serum and tissues.[17] Significantly higher salivary glutathione peroxidase and reductase activities with lower mean glutathione level was reported in DM patients.[18] Oxidative stress burden was increased in serum and saliva resulting in different redox state of DM patients from that of normoglycaemic control subjects.[19] Reduced salivary glutathione concentrations were noted in type 1 DM patients as a sign for careful follow-up of these patients in regards to periodontal disease.[20] Moreover, gene expression of antioxidant enzymes in gingival tissue was up-regulated in the poorly-controlled diabetic group with periodontitis.[21]

DM-induced changes in immune cell function also up-regulate proinflammatory cytokines from monocytes/polymorphonuclear leukocytes and down-regulate growth factors. This creates a predisposition to chronic inflammation, progressive tissue breakdown, and diminished tissue repair capacity. DM patients have elevated levels of advanced glycation end-products (AGEs) in their gingival tissues that may be associated with a state of enhanced oxidant stress, a potential mechanism for accelerated tissue injury.[22] AGEs can interact with specific receptors on cells, such as macrophages, impairing chemotactic and phagocytic function of polymorphonuclear leukocytes and stimulating the production of matrix metalloproteinases and IL-1ß.[23] Monocytes from DM patients produce significantly greater amounts of IL-1ß, and prostaglandin E2 (PGE2) than non-diabetic controls.[24,25] These proinflammatory cytokines may partially explain the increased severity of periodontitis in diabetic patients.

The level of metabolic control has a central role in the intersection of periodontitis and DM. Decreased metabolic control in type 2 DM resulted in increased serum triglycerides, and all clinical periodontal measurements and gingival crevicular fluid (GCF) levels of IL-1ß showed a trend to increase as diabetic control diminished.[26] Type 1 DM patients with periodontitis exhibited significantly higher GCF levels of IL-1ß and PGE2.[25] Elevated GCF IL-1ß was associated with poor glycaemic control in type 2 diabetic patients with untreated periodontitis.[27,28]

On the other hand, adipokines, like leptin, resistin and adiponectin, highly activate cells releasing TNF-α and IL-6.[29] This, in turn, stimulates greater hepatic C-reactive protein (CRP) synthesis which may also increase insulin resistance.[30,31] Inflammatory and infectious stimuli such as lipopolysaccharides and cytokines increase leptin levels in the acute phase.[32] Adiponectin plays a significant role in regulating glycaemia, lipidemia, endothelial dysfunction, and proinflammatory mechanisms.[33] Low serum concentrations of

adiponectin have been reported to be linked with decreased insulin sensitivity.[34] A low plasma adiponectin concentration is associated with a decrease in whole body insulin sensitivity in humans.[35]

Function and activation of endothelial cells are also impaired in DM.[36] Adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, play key roles in leukocyte adhesion to arterial endothelial cells.[37] Serum concentrations of soluble ICAM-1 (sICAM-1) and other adhesion molecules were increased in DM patients.[38,39] Periodontitis patients have higher serum sICAM-1 levels than periodontally-healthy individuals.[40] Elevated serum levels of TNF-α, IL-6, CRP, leptin, sICAM-1, and decreased adiponectin levels in diabetic patients with periodontitis may eventually act to aggravate insulin resistance and deteriorate glycaemic control.

PERIODONTAL TREATMENT AND DIABETES

Effects of periodontal treatment on clinical periodontal parameters, systemic mediators, and glycaemic control were evaluated in well or poorly-controlled type 2 diabetic as well as systemically healthy periodontitis patients.[35] The poorly-controlled diabetic group exhibited significantly decreased HbA1c levels 3 months after completion of non-surgical periodontal treatment. Increased adiponectin levels may at least partially explain the significant improvement in glycaemic control by non-surgical periodontal treatment in the DM group.[35] These findings corroborate the previous studies demonstrating significant improvements in HbA1c levels and clinical periodontal parameters following non-surgical periodontal treatment.[41-46] Almost no change in the HbA1c percentage in the well-controlled diabetics with non-surgical periodontal treatment in contrast to the significant improvement in the poorly-controlled diabetics have been reported.[47] This may be regarded as further proof of the beneficial effects of periodontal treatment in the glycaemic control of type 2 DM. While their current medical therapies are efficient in the well-controlled diabetics, the 1.5% improvement in glycaemic control of the poorly-controlled diabetics with periodontal treatment may correspond to significant improvement in general health.[47] It may be suggested that the deeper the baseline peritoneal dialysis (PD) is, the longer follow-up period is required for proper periodontal healing as well as significant decrease in HbA1c level. The risk of diabetic complications were strongly associated with previous hyperglycaemia in type 2 diabetics and any reduction in HbA1c is likely to reduce the risk of complications.[48] Therefore, periodontal treatment may be regarded as a means of reducing HbA1c levels, eventually helping the overall management of diabetic patients.[49]

In a study reporting better HbA1c levels in people with better tooth brushing self-efficacy, it was suggested that motivation and instruction on better oral hygiene is important in diabetic patients especially those with poor metabolic control.[50] The importance of prevention of oral diseases for a better systemic health was also emphasised recently.[51] Poorly-controlled diabetics have been reported to exhibit significant reductions in PD, peritonitis incidence (PI), and BOP following mechanical periodontal treatment.[41,42,52-55] Higher PI and BOP levels have been reported in poorly-controlled diabetics, 1 and 3 months after periodontal treatment compared to baseline.[53,54] Poor glycaemic control was suggested to have contributed to higher BOP scores in the poorly controlled group. It is likely that microvascular changes due to prolonged hyperglycaemia create a tendency for bleeding in these patients despite the similar plaque scores with the well-controlled group.

Increased serum levels of proinflammatory cytokines like TNF-α, IL-6, CRP, and sICAM-1 may play a role in insulin resistance and deteriorate glycaemic control in diabetic patients. Such an increase in serum levels of inflammatory cytokines may be one of the mechanisms by which infection by Gram-negative bacteria promotes atherosclerosis in diabetic patients.[56] Intervention trials suggest that periodontal therapy, which decreases the intraoral bacterial bioburden and reduces periodontal inflammation, can have a significant impact on systemic inflammatory status. Reports suggest that periodontal therapy is associated with improved glycaemic control in many patients with both diabetes and periodontal diseases.[57] TNF-α, IL-6, CRP, and sICAM-I concentrations tended to decrease in the poorly-controlled diabetics following periodontal treatment.[35] These decreases may at least partially explain the significant improvement in HbA1c level. Recently, the

possibility of a direct relationship between the severity of periodontitis and diabetic complications has been discussed in a workshop and it was concluded that moderate-to-severe periodontitis is associated with increased risk for macroalbuminuria, end-stage renal disease, calcification of atherosclerotic plaques, carotid intima-media thickness and cardio-renal mortality.[58]

Moreover, the participants with the most severe periodontitis at baseline exhibited approximately 5-fold greater increase in HbA1c levels over 5 years, and the authors suggested that severe periodontitis predicts the progression of DM.[59]

Non-diabetic patients had more healthy sextants and diabetic patients showed a higher variability in salivary-IgA levels as compared with non-diabetic patients.[60] Serum levels of high-sensitivity CRP, TNF-α, IL-6, fasting plasma glucose, HbA1c, fasting insulin decreased and adiponectin increased 3 months after periodontal treatment in type 2 DM patients and periodontal treatment may improve glycaemic control, lipid profile, reduce serum inflammatory cytokine levels, and increase serum adiponectin levels in poorly controlled type 2 DM patients.[61] Levels of high-sensitivity CRP and stem cell factor in serum and GCF were reported to be increased in patients with periodontitis and DM.[62]

SPECIFIC MOLECULES IN THE INTERACTION

The strongest relationship was found between the intensity of periodontal pathology markers and the activity of β-glucuronidase of neutrophilic leukocytes in patients with type 1 DM and periodontitis.[63] It was speculated that if periodontal impairment is severe, DM possibly causes a faster destruction of periodontal tissues, increasing the risk of periodontitis.

Diabetic patients exhibited significantly higher mean salivary levels of alkaline and acid phosphatase, osteopontin, and osteocalcin than healthy controls.[64] Substance P, a potent proinflammatory neuropeptide present in sensory neurons, is important in initiating and sustaining inflammation. Serum substance P levels were higher in the poorly-controlled diabetic group than in well-controlled patients; within the poorly-controlled group, patients with severe attachment levels had the highest circulating substance P levels.[65]

Lipid peroxidation (LPO) evaluated by malondialdehyde in plasma and GCF is increased in diabetes and may be related to modulation of inflammatory response. Significant correlations between LPO markers and periodontal parameters suggest a direct relationship between these two entities.[66]

Plasma adrenomedullin level is elevated in pathophysiological conditions such as arterial hypertension, acute coronary syndrome, renal diseases, DM and periodontal diseases. Type 2 DM patients with/without periodontitis had significantly higher periodontal clinical indices than the non-diabetic control groups. Chronic periodontitis and type 2 DM group had significantly higher total adrenomedullin level.[67]

Human β-defensins (hBD-1 and hBD-3) have strong antibacterial action against various microorganisms, especially periodontal pathogens. Patients with type 2 DM and chronic periodontitis had worse clinical periodontal parameters, they also had significantly higher GCF levels of total hBD-1 and hBD-3 than systemically healthy patients with periodontal disease.[68]

Toll-like receptor (TLR) 2, 3, 4, and 9 levels in gingival tissue were higher in individuals with diabetes, possibly due to an exacerbated inflammatory reaction.[69] Levels of osteoclastogenesis-related factors (soluble receptor activator of nuclear factor-kappa B ligand [sRANKL] and osteoprotegerin [OPG]) have been evaluated in GCF from poorly or well-controlled type 2 diabetes and chronic periodontitis before and after periodontal therapy. Levels of sRANKL and RANKL/OPG ratios were higher in poorly-controlled group at baseline and after therapy.[70]

Visfatin, a human pre-B cell colony-enhancing factor is secreted by the adipocytes of the body that induces the production of IL-1β, TNF-α, and IL-6 during infection and inflammation. The mean visfatin concentration was increased in both serum and GCF in type 2 DM patients with chronic periodontitis.[71]

CONCLUSION

In conclusion, it is uncertain which of the hypothesised mechanisms or combinations of mechanisms is directly responsible for the detrimental effects of diabetes on periodontal

health or vice versa. Prospective clinical studies with a larger scale are required to better clarify the mechanisms of possible interactions between these two entities. It is quite clear that especially poorly-controlled DM increases the risk for periodontitis, whereas there is ever-increasing evidence which shows adverse effects of periodontal disease on DM onset and progression. Existing evidence suggests that improvement of patients' awareness on oral health should be an integral part of the routine prevention and treatment protocol of DM. This can be best achieved by a closer collaboration between dentists and physicians and referral to a dentist is highly suggested after diagnosis of DM.

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