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PATHOPHYSIOLOGICAL ASPECTS IN THE INTERACTION BETWEEN PERIODONTAL DISEASE AND DIABETES

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Abstract

Diabetes is a systemic disease with a number of major complications that can adversely affect quality of life. The disease is characterized by an increased susceptibility to infection, poor wound healing and increased morbidity and mortality associated with the evolution of the disease. Periodontal disease has been reported as the sixth complication of diabetes, along with neuropathy, nephropathy, retinopathy, and micro and macrovascular damage. Diabetes not only increases the risk and prevalence of periodontal disease, but also increases the progression of periodontal destruction. Both periodontal disease and diabetes have major inflammatory components. Not only is diabetes a risk factor for periodontitis, but periodontitis could also have a negative effect on glycaemic control.

Keywords: *periodontitis, diabetes, inflammation, glycated haemoglobin*

Introduction

Periodontal disease is collectively the most common disease known to mankind. Their classification is complex and takes into account the clinical presentation, age at diagnosis, rate of disease progression, and systemic and local factors that may increase the risk.

Diabetes has been unequivocally confirmed as a major risk factor for periodontitis.[1,2] The risk of periodontitis is about three times higher in people with diabetes compared to non-diabetics.[3]

Diabetes is a systemic disease with a number of major complications that can adversely affect quality of life. The disease is characterized by an increased susceptibility to infection, poor wound healing and increased morbidity and mortality associated with the evolution of the disease.[4]

Periodontal disease has been reported by Loe as the sixth complication of diabetes, along with neuropathy, nephropathy, retinopathy, and micro and macrovascular damage.[5] Diabetes not only increases the risk and prevalence of periodontal disease, but also increases the

progression of periodontal destruction. Both periodontal disease and diabetes have major inflammatory components. Studies have shown the influence of periodontal pathogens on diabetes mellitus.[6] Systemic bacterial and viral infections, such as respiratory viruses or the common flu, lead to increased systemic inflammation, which increases insulin resistance and makes it difficult to control blood sugar levels.[7]

Inflammatory aspects in the relationship between diabetes and periodontitis

Type 1 and 2 diabetes are associated with elevated levels of systemic markers of inflammation.[8] High inflammatory status in diabetes contributes to microvascular and macrovascular complications, and it is clear that hyperglycaemia can lead to activation of pathways that increase inflammation, oxidative stress, and apoptosis.[9] Elevated serum levels of IL-6 and TNF-α have been demonstrated in diabetes and obesity, and serum levels of IL-6 and C-reactive protein (CRP) have been shown to predict the onset of type 2 diabetes. Elevated CRP levels are associated with insulin resistance, type 2 diabetes and the onset of cardiovascular disease.[10] TNF-α and IL-6 are the major inducers of acute phase proteins, including CRP, and both have been shown to affect intracellular insulin signalling that contributes to insulin resistance.[11]

Serum levels of IL-6 and CRP are also elevated in patients with periodontitis. Therefore, systemic inflammation, associated with periodontal disease, can affect diabetes status. Adipokines may also contribute to susceptibility to periodontitis and diabetes, and the proinflammatory properties of leptin may be particularly important in increasing periodontal inflammation in people who are obese and / or have type 2 diabetes.[12]

Diabetes increases inflammation in the periodontal tissues. For example, levels of PGE2 and IL-1β in gingival fluid are higher in patients with type 1 diabetes mellitus and gingivitis or periodontitis, compared to those in non-diabetics with the same severity of periodontal disease. In addition, studies have consistently demonstrated defects in PMN in patients with diabetes, including chemotaxis, phagocytosis, and impaired antimicrobial function.[13] PMNs need energy to function, and these defects may be related to metabolic changes that occur in diabetes. Diabetic patients with severe periodontitis have been shown to have affected PMN chemotaxis compared to people with diabetes and mild periodontitis,[13] as well as defects in PMN apoptosis,[14] which may lead to increased retention of PMN in periodontal tissue, leading to severe tissue destruction through the continuous release of MMPs and reactive oxygen species (ROS). Diabetes prolongs the inflammatory response to *Porphyromonas gingivalis*, with increased production of TNF-α. Periodontal treatment has been shown to reduce serum concentrations of inflammatory mediators, including IL-6, TNF-α, CRP and MMPs, in patients with and without diabetes.[15]

The accumulation of AGE in periodontal tissues is also likely to play a role in stimulating periodontal inflammation in people with diabetes. AGE binding to the receptor (RAGE)

results in increased production of inflammatory mediators, such as IL-1β, TNF-α and IL-6. AGE also stimulates the rupture of PMN,[16] which has the potential to significantly increase local tissue damage in periodontitis. Moreover, AGEs have negative effects on bone metabolism, leading to decreased bone repair and formation and a decrease in extracellular matrix production.

Diabetes can affect periodontitis through the following potential mechanisms: diabetes is characterized by hyperglycaemia, which is associated with elevated levels of FFA, LDL and TRG. In the hyperlipidic status, the production of serum pro-inflammatory cytokines, for example IL-1b and TNF-α, is increased due to an exaggerated inflammatory response to lipopolysaccharides of Gram-negative bacteria (LPS), especially LPS of *P. gingivalis*. Hyperglycaemia can also directly induce the production of pro-inflammatory cytokines by activating the nuclear transcription factor kB (NF-kB).[17,18]

Elevated levels of serum pro-inflammatory cytokines lead to increased levels of pro-inflammatory cytokines in the gingival fluid.[2] Moreover, the release of pro-inflammatory cytokines from host cells into periodontal tissues is induced by AGE / RAGE during the inflammatory response,[19] which leads to the destruction of gingival tissue and supporting bone tissue.

The influence of periodontitis on diabetes

Emphasis was also placed on the "two-way" relationship between diabetes and periodontitis.[20] Not only is diabetes a risk factor for periodontitis, but periodontitis could also have a negative effect on glycaemic control. The first clear evidence to support this hypothesis came from investigations into individuals in the Gila Indian community. Severe periodontitis was initially associated with an increased risk of poor glycaemic control (HbA1c> 9.0%) upon re-evaluation (minimum 2 years), suggesting that severe periodontitis was a risk factor for diabetes, with compromised management.[21] In addition, several studies have reported that the prevalence and severity of non-oral diabetes-related complications, including retinopathy, diabetic neuropathy, proteinuria, and cardiovascular complications, are correlated with the severity of periodontitis.[22]

Moderate and severe periodontitis may predict the development of obvious nephropathy in a "dose-dependent" manner in people with type 2 diabetes.[23] The same researchers also investigated the effect of periodontitis on deaths caused by cardiovascular disease and diabetic nephropathy.

An interesting area of investigation focused on the question of whether periodontitis plays a role in the incidence of diabetes. In a prospective 7-year study of 5,848 non-diabetics aged 30-59 years, the effect of periodontitis on the incidence of diabetes (defined by a fasting plasma concentration> 6.9 mmol / l, equivalent to> 125 mg / dl) was assessed).[24] In unadjusted analysis, moderate (3.5–5.5 mm) and severe (pockets> 5.5 mm) periodontitis were significantly associated with an increased risk of diabetes incidence, but significance was lost after adjustment for sex, smoking,

BMI, triacylglycerol, hypertension, HDL and g-glutamyl transpeptidase.

The impact of periodontitis on changes in glycated haemoglobin (HbA1c) was assessed in a prospective 5-year study of 2,973 non-diabetics.[25] Those participants with the most advanced forms of periodontitis at baseline demonstrated an absolute increase of approximately five times the HbA1c over the 5 years of the study, compared with those who did not have periodontitis at baseline (HbA1c change 0.106% ± 0.03 compared to 0.023 ± 0.02%). This was the first study to report that periodontitis can predict the progression of HbA1c in people without diabetes.

It is important to note that periodontal disease involves a change in oral / dental flora from normal gram-positive anaerobic bacteria (eg, Lactobacillus, Peptostreptococcus, Streptococcus) to predominantly gram-negative anaerobic bacteria. Some of the bacteria believed to be involved in periodontal disease are *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*.[26] The host responds to this change in bacterial flora by developing an inflammatory response, generating such cytokines as tumour necrosis factor (TNF-α) and interleukin 1 (IL-1).

A major concern with periodontal disease is that, in some patients, the immune system does not effectively eliminate the source of inflammation (ie, gram-negative anaerobes). If these bacteria are not eliminated, the patient's immune system is continuously activated and results in a chronic inflammatory process. This chronic inflammation leads to the production of reactive oxygen species, which in turn activate matrix metalloproteinases. [27] These enzymes degrade collagen in the periodontal ligaments, leading to a low attachment of the teeth to the alveolar process and an increase in the depth of the gingival sulcus.

Periodontal pockets are areas where bacteria can potentiate proliferation, leading to worsening infections and / or inflammation. Oxygen pressure (PO2) in the periodontal pockets is low, favouring the growth of anaerobic bacteria. For the most part, these bacteria do not invade periodontal tissue because the PO2 of the tissue is much higher than in pockets. However, in some patients, such as smokers who have vasoconstriction and decreased PO2 in tissues, bacterial invasion of periodontal tissue may occur.[27]

Chronic periodontal disease also has the potential to worsen insulin resistance and worsen glycaemic control, while periodontal treatment decreases inflammation and may contribute to decreased insulin resistance.[28] A study by Sastrowijoto et al. [29] demonstrated higher concentrations of periodontal pathogens in patients with poor metabolic control. The risk of periodontal disease may be higher in patients with diabetes who have poor glycaemic control than in patients with well-controlled diabetes.[30] Studies have provided evidence of the impact of periodontal infection control on improved glycaemic control,[31] evidenced by decreased insulin demand and decreased HbA1c levels. [32]

There is a strong two-dimensional relationship between

periodontal disease and diabetes. Not only are populations and patients with uncontrolled diabetes more likely to develop periodontal disease, but even the presence of active periodontal disease can worsen glycaemic control. Effective periodontal therapy combined with systemic antibiotics appears to have a dual effect for diabetic patients, reducing periodontal infection and improving glycaemic status. Professional dentists should also monitor the patient's glycaemic control to provide optimal dental care.[33]

Numerous years of research have established a number of mechanisms by which diabetes can influence periodontitis. Many of these mechanisms share the same common features as those involved in the classic complications of diabetes, such as retinopathy, nephropathy, neuropathy, macrovascular disease, and changes in wound healing. Because periodontal disease is an infectious disease, research initially focused on possible differences in subgingival microbial flora in patients with and without diabetes. Although some recent studies have reported higher proportions of certain bacteria in the subgingival sulcus in patients with diabetes, later studies involving cultures showed little difference between diseased periodontal sites in subjects with diabetes as well as those in subjects. who did not have diabetes. Because the pathogens associated with periodontitis do not appear to differ much in people with and without diabetes, researchers have focused on potential differences in the immune response of bacteria in people with diabetes and healthy people.[34]

The function of the cells involved in this response, including neutrophils, monocytes, and macrophages, is altered in several people with diabetes. Adhesion, chemotaxis, and phagocytosis of neutrophils is often different. These cells are the first line of defence for the host, and inhibiting their function can prevent the destruction of bacteria in the periodontal sulcus, thus increasing periodontal destruction. Other immunoinflammatory responses are usually in people with diabetes. For example, macrophages and monocytes are often responsible for increasing the production of proinflammatory cytokines and mediators such as tumour necrosis factor (TNF-) in response to periodontal pathogens, which can accelerate the destruction of host tissue. High levels of TNF-are found. in the blood and gingival crevicular fluid, suggesting both local and systemic responses of these immune cells. Glycaemic control may be a determining factor in this response.

The relationship between diabetes and periodontal disease becomes a two-way relationship.[34] Both diabetes and periodontal disease can stimulate the chronic release of proinflammatory cytokines that have a detrimental effect on periodontal tissues.[15] Chronic systemic increase in proinflammatory cytokines caused by periodontal disease may even predispose individuals to the development of type 2 diabetes.[35] A model was presented by Pucher,[36] in which periodontal pathogens can cause an increase in proinflammatory cytokines that mediate an increase in insulin resistance, resulting in an increase in blood sugar. After periodontal therapy, this process can be reversed. Extensive studies have shown

that effective blood glucose control can prevent or delay the onset of complications, despite the duration of the disease.[37]

Conclusions

Periodontal disease is a definite complication in patients with diabetes. Diabetes is associated with an increased risk of developing periodontal inflammatory diseases and blood sugar control is a determining factor in this relationship. It also seems that, in turn, the diabetic status can be negatively influenced by the presence of the inflammatory load in periodontal disease. Moreover, appropriate periodontal treatment has been shown to improve glycaemic control.

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