THE RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND DIABETES MELLITUS

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Abstract

Periodontitis is a common complication in patients with diabetes. Their classification is complex and it is based on the clinical presentation, rate of disease progression, age at diagnosis and local and systemic factors that may multiply the risk. The two major stages of periodontal diseases are gingivitis and periodontitis. The relationship between these two diseases appears bidirectional insofar that the existence of one disease tends to promote the other and that the meticulous management of either may help the treatment of the other. Treatment of periodontitis using a association of mechanical therapy, scaling and root planning, plus systemic tetracycline antibiotics has been demonstrated to have important reductions in HbA1c values. Therefore, for a better control of diabetes we suggest that periodontal patients with diabetes should be consulted and treated by a periodontist.

key words: periodontal diseases, diabetes, HbA1c, glycemic control

Periodontal diseases are the most common diseases known to humanity. Their classification is complex and it is based on the clinical presentation, rate of disease progression, age at diagnosis and local and systemic factors that may multiply the risk. The two major stages of periodontal diseases are gingivitis and periodontitis. In the early stage of gingivitis the inflammation is located to the gingiva, it is reversible and can usually be treated with good oral hygiene. The second stage involves the extension of inflammation and results in tissue destruction and alveolar bone resorption; stage called periodontitis. In periodontitis tissue destruction results in disruption of the collagen fibres of the periodontal ligament, which may form a periodontal pocket between the gingiva and the tooth. ‘Pocketing’ is not identified on simple visual inspection, and in evaluation it is
essential to use a periodontal probe. Periodontitis is a slowly progressing disease but destruction of the tissue that occurs is in a great measure irreversible. This condition is typically asymptomatic in the early stages; usually it is not painful and many patients are unaware until the condition has progressed enough to determine tooth mobility. Advanced periodontitis is characterised by gingival erythema and oedema, gingival bleeding, gingival recession, tooth mobility, drifting of teeth, suppurative from periodontal pockets and tooth loss [1]. The examination of the available data have proved that diabetes is an important risk factor for periodontitis and gingivitis, and that the level of glycemic control is an important determinant in this relationship [2].

**Periodontal disease and bacterial infection**

Periodontal infection is a complication that can be responsible of damaging systemic physiology in diabetic patients. Periodontitis may be more than a confined oral infection, the consequences have been assumed to be far-reaching. Chronic and severe forms of this condition can follow a systemic response of the bacteria and bacterial result products that are outspread due to the collapse of the periodontal apparatus that is composed from the ligament attachment around the tooth, the gingival tissues and bone. The interdependency between periodontal disease and diabetes is an example that a systemic disease can predispose to oral infection, and then once that infection is settled, the oral infection can augment the progression of systemic disease [3]. In addition, it is possible for oral infection to act as a metabolic stressor that may amplify the systemic disease. For a better understanding of the molecular and cellular mechanisms responsible for this kind of cyclical association, it is important to identify physiological changes related with periodontitis and diabetes that produce a cumulative effect when the two diseases coexist. Accumulation of advanced glycation end products (AGEs) as a consequence of the chronic hyperglycemic state of diabetes, associated with the existence of infection and an exacerbated host response, may furnish a viable explanation for the clinical outcomes found in diabetic patients with periodontal disease [4].

**Mechanism by which diabetes may influence the periodontium**

To enable an interrelationship between periodontal diseases and diabetes, a biologically presumable mechanism has to be evident to certify the pathobiology of the interactions. A wide evidence base is available to define these potential mechanisms, many of which are astounding similar to those related with the classic diabetic complications, like: nephropathy, macrovascular diseases, neuropathy, retinopathy and slow wound healing. The importance of the evidence has led some to indicate that periodontitis should be included among the “classic” complications of diabetes [5]. Patients with diabetes have an oral bacterial flora similar to the flora found in subjects without diabetes, but their response to infection is different. It has been shown that patients with diabetes have markers of systemic inflammation and it has been established that this inflammatory state can carry to increased destruction of the chronically infected periodontium. These markers include increased levels of fibrinogen, C-reactive protein and decreased albumin. Not
only do patients with diabetes have elevated levels of systemic pro-inflammatory mediators but the local tissues of the periodontium is also affected by raised levels of inflammation. An example of local inflammation occurs when monocytes have an increased production of cytokines in response to insult; even after removal of the offending stimulus the increase in inflammatory mediators remains [6]. However, patients with diabetes have high systemic and local inflammation, which contributes to the destruction of the periodontium. Therefore, the lack of significant differences in potential pathogens indicate that alterations in the host immune-inflammatory response may have a high influence on the high prevalence and severity of periodontal destruction found in diabetes. The activity of immune cells, macrophages, monocytes, and neutrophils is modified in diabetes. Neutrophil chemotaxis, phagocytosis and adherence are often altered, which may block bacterial killing in the periodontal pocket and augment periodontal destruction. Even if the function of neutrophils is often altered in diabetes, the immune cell line monocyte/macrophage may present up-regulation in response to bacterial antigens. The hyper responsiveness of macrophages/monocytes results in significantly elevated production of pro-inflammatory cytokines and mediators. Peripheral blood monocytes of diabetic patients produce increased levels of tumor necrosis factor-alpha (TNF-a) due to antigens coming from Porphyromonas gingivalis compared to monocytes coming from non-diabetic control patients. These results are supported in a diabetic animal model in which inoculation of P. gingivalis produced an extended inflammatory response. Interestingly, this extended inflammatory response was discovered to be independent of the pathogenic component parts of the inoculated organisms and directly connected to TNF alfa stimulation. Because of the gingival crevicular fluid is a serum transudate, high serum levels of inflammatory mediators related with diabetes are reflected in similarly elevated levels of these mediators in gingival crevicular fluid. The levels of cytokines in the gingival crevicular fluid are also associated to glycemic control in diabetes. In a recent study of diabetic patients with periodontitis, the subjects with HbA1c levels more than 8% had crevicular fluid levels of interleukin-1 beta (IL-1b) nearly twice as high as patients with HbA1c levels <8%. The net response of these alterations of the host defense in diabetes is elevated in attachment loss, periodontal inflammation and also in bone loss [7]. In addition, patients with diabetes have an altered response to injury healing and an defective immune response. Fibroblast function is impaired due to the elevated levels of glucose and collagen availability is decreased. The diminished fibroblast function and collagen availability alter the healing reaction in diabetics. The immune response, which is considered a characteristic feature of diabetes, includes abnormal adherence, chemotaxis and phagocytosis of neutrophils. This ensures an altered environment in which oral bacteria can expand; that way, systemic and local inflammation can slow the recovery and an aberrant immune response contribute to destruction of the periodontium in diabetic patients [8]. Diabetic subjects tend to suffer from periodontitis with high alveolar bone loss caused by decreased immune reaction and slow tissue recovering. Periodontal pathogens such as several cytokines (TNF-alpha, IL-1 and IL-6) and P. gingivalis lipopolysaccharide...
(P-LPS) stimulate osteoclast differentiation in gingival connective tissue, alveolar bone resorption advances and the result is tooth loss. It is certified that the incidence of periodontitis is two to three times increased in diabetic subjects than in non-diabetic patients. Lately, many researches established that periodontitis affected diabetic disease, periodontal pathogen like P-LPS and TNF-alpha possibly increase insulin resistance by inhibiting glucose incorporation into smooth muscle cells. The clinical study revealed that serum C-reactive protein (CRP) value increased in periodontitis patients and that periodontal treatment improved the level of HbA (1C) in diabetic subjects. These data suggest that periodontal pathogen influenced systemic conditions and these are partly ameliorated by periodontal therapy. Also, periodontal pathogen may promote atherosclerosis formation. Further research are necessary to clarify the relationship between periodontal disease and diabetes [9].

Periodontal disease is a silent devastating disease and the first stage may not be taken seriously by the patient because at first the early symptoms are less concerning. It is a group of inflammatory conditions that can damage the periodontal apparatus, cementum, collagen fibrils on the root surface of the tooth and also a layer of calcified interfibrillar matrix. Out of this group gingivitis and chronic periodontitis are the most frequent conditions seen clinically. According to one the U.S. survey, 50% of the adults individuals are affected by gingivitis, whereas chronic periodontitis is estimated to affect 35% of adults, moderate to advanced forms of the condition is estimated to affect approximately 13% to 15% of adults population [10]. These chronic conditions are more severe, more prevalent, and advance more rapidly when they occurs concurrently. A variety of epidemiologic research studies have proven that periodontitis is more frequent and severe in both type 1 and type 2 diabetes mellitus that in non-diabetics. In a wide scale meta-analysis in which participated 3,500 adults, the relationship between periodontal disease and non-insulin dependent diabetes was studied and it was reported a statistically significant association between periodontitis and diabetes. Since 1986 Tervonen and Knuuttila suggested a elevated risk for periodontitis among diabetic subjects. Furthermore, the risk is found to be associated with the duration of diabetes and the the level of diabetic control. In a big epidemiological study made in the U.S. (NHANES III), individuals with low controlled diabetes had a 2,9-fold elevated risk of developing periodontitis compared to non-diabetic patients; conversely, patients with good controlled diabetes had no significant elevate risk of developing periodontitis. The same risk has been certified in a longitudinal study of Gila River Indian adult population. In fact, one study has showed that diabetic subjects are five times more likely to have a partially edentulous than non-diabetic controls [11]. In another separate research, the risk of periodontitis is increased by a factor 2,1 to 3 in subjects with diabetes. Many studies made on the Pima Indian population in Arizona well known with a very high prevalence of type 2 diabetes mellitus shows an increased prevalence of periodontal disease in subjects with insulin dependent diabetes mellitus. These results are also reported in a study of non-insulin dependent diabetic Turkish adult population. Firatlı observed since 1997 the similar results in a study made on 44 type 1 diabetes children and adolescents and with 20
healthy controls subjects over 5 years [12]. The interrelationship between periodontal disease and diabetes seems to be very powerful within Aboriginal individuals. Several research studies in separate ethnical groups have found conclusive evidences that the prevalence, severity and the progression of the periodontal disease are significantly higher in individuals with diabetes. Periodontitis is more than a localized oral infection. The relationship between the diabetes and periodontitis indicate the predisposition of systemic condition to oral infection and also vice versa [13].

Periodontal disease as a risk factor for patients with diabetes. Recognition of subgingival plaque as a microbial biofilm has considerably added to our understanding of the pathophysiology of periodontal condition. In microbial biofilms, bacteria are incorporated in an extracellular matrix and bind to one another and/or to a surface [14]. Bacterial adhesion is fundamental to establish the subgingival biofilm, and the pathogenic potential of this biofilm is caused by the growth and maturation of the bacteria in question. Also, this bacteria constantly banish part of their cell structure components into the crevicular area. The cell wall structures of Gram-negative bacteria are essential in the pathogenesis of periodontal condition. These structures are vesicles with protein content and lipopolysaccharides that form part of the normal turnover of the cell wall of these microorganisms and can initiate the innate host response. The structure of the biofilm offers favorable conditions for the survival of the bacteria that form it, in spite of an intact host immune system. The virulence factors of these microorganisms are responsible for activating the sequence of pathogenic events in periodontal condition. Periodontal microorganisms, in particular Tannerella forsythia (T.f.) and Porphyromonas gingivalis (P.g.), were found to augment Matrix metallopeptidase 9 (MMP-9) in gingival crevicular fluid and serum [15]. According to the pathogenic model suggested in periodontal disease might elevate the already increased cytokine levels in diabetic subjects and thereby contribute to systemic inflammation. Increased formation and accumulation of AGEs in tissues is the most common feature of diabetic complications. The adhesion of these molecules to neutrophils produces a hyperinflammatory state that intensify the response to cytokines. These preliminarily activated neutrophils also show a intensified response on making contact with lipopolysaccharide (LPS) of gram-negative bacteria in the subgingival biofilm, and the consequent initiating of the inflammatory cascade augments the destruction of periodontal connective tissue and the severity of diabetes [16].

Periodontal treatment and glycaemic control in patients with diabetes. Although the relationship between periodontal and diabetes condition is not enough questioned in the current literature, the effect of periodontal treatment on metabolic control in diabetic patients and the effect of the metabolic control of diabetes on periodontal condition remains controversial. In general, periodontal treatment is a important priority in patients for whom periodontal condition may pose a health risk and this includes diabetic subjects. A number of studies have evaluated whether the use of systemic antibiotics ameliorate the periodontal prognosis and metabolic control in diabetic subjects. Mechanical periodontal therapy with 100 mg doxycycline has reduced...
HbA1c with 0.6% in type-2 diabetic subjects. Tetracyclines and their derivatives appear to have an important role in the inhibition of tissue destruction enzymes. Hence, doxycycline appears to be a powerful modifier of the response to periodontal treatment in diabetic subjects by inhibiting non-enzymatic glycosylation of extracellular proteins, indicating that it has an equal effect on haemoglobin glycosylation [17]. Treatment of periodontitis using a association of mechanical therapy, scaling and root planning, plus systemic tetracycline antibiotics has been demonstrated to have important reductions in HbA1c values - indicative of improved glycaemic control. Also, a research study by Miller and colab. demonstrated that mechanical periodontal therapy associated with adjunctive systemic doxycycline resulted in a decreasing with 0.6% HbA1c values in a group of Hispanic patients with type 2 diabetes [18]. Iwamoto and colab. associated mechanical periodontal therapy with local application of minocycline gel to each periodontal pocket, every week for a month, in a group of patients with type 2 diabetes. Following this treatment, the number of bacteria existing in periodontal pockets was highly reduced, serum TNF-α levels were decreased with 0.49pg/mL and glycemic control, quantified by HbA1c values was also improved [19]. Grossi and colab. reported results of periodontal therapy in a group of Pima indians with type 2 diabetes. An association of ultrasonic root debridement with systemic doxycycline, 100mg per day for two weeks, decreased P. gingivalis to nondetectable levels in all patients who tested positive at baseline after three months of treatment. In addition, there was a important improvement in periodontal attachment and a 1% decrease in the level of HbA1c, three months after the ending of the treatment. These results are in contrast with a number of researches cited by Grossi in which diabetic patients treated with mechanical periodontal therapy, scaling and root planning, without adding adjunctive systemic antimicrobials, failed to improve glycemic control. Therefore, a mechanical periodontal therapy associated with systemic doxycycline seems to ameliorate glycemic control in many diabetic subjects with periodontitis. This is in contrast to the periodontal treatment of patients without diabetes, where systemic antimicrobials are not usually used and are not necessary for a successful treatment. Also, it should be noted that the treatment with systemic tetracyclines alone have been proven to suppress or inhibit activity of collagenase in the gingival crevicular fluid of diabetic subjects with periodontitis. Therefore, a limited number of interventional studies have demonstrated that treatment of periodontal infection and the consequent reduction in bacterial load and pro-inflammatory molecules may have as result an improved glycemic control in diabetic patients. Also, these data indicate that other periodontal therapies designed to consistently free the patient of periodontal pathogens should bring similar benefits [20].

Conclusion

Periodontitis is a common complication in individuals with diabetes. The relationship between these two diseases appears bidirectional insofar that the existance of one disease tends to promote the other and that the management of either may help the treatment of the other. The two diseases, periodontitis and diabetes, may stimulate the chronic
release of proinflammatory cytokines that have a harmful effect on periodontal tissues. The chronic systemic increase of proinflammatory cytokines determined by periodontitis may even predispose subjects to the development of type 2 diabetes mellitus. Mechanical treatment of periodontitis, scaling and root planing, associated with short-term administration of tetracycline, can temporarily ameliorate glycemic control in diabetic subjects, especially in those with advanced stages of periodontitis and low glycemic control before treatment. The biochemical mechanisms indicated by these research studies show that other periodontal procedures designed to rid subjects of periodontal pathogens can also improve the management of diabetes. Therefore, we suggest that periodontal patients with diabetes should be consulted and treated by a periodontist [21].

REFERENCES


17. Antonio Bascones-Martinez 1, Paula Matesanz-Perez 1, Marta Escribano-Bermejo 1,


