Diabetes Mellitus & Periodontal Disease

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Abstract

The association between diabetes mellitus and periodontal disease has been studied in the last years, and several studies conclude that diabetes ellitus is a risk factor for the development of gingivitis and/or periodontitis in both diabetes type 1 and 2. In this review article we intend to demonstrate the possible association between diabetes mellitus and periodontal disease,assessing their main characteristics, the association with social status and the influence of periodontal disease control on Diabetes mellitus. Scientific research in recent years regarding this specific issue has allowed the establishment of a clear association between periodontal disease and diabetes mellitus among diabetics type 1 and 2. The main complications of diabetes mellitus are angiopathy, neuropathy, nephropathy and retinopathy.Several studies have demonstrated the oral manifestations of diabetes mellitus, assuming particular highlight the periodontal disease. There should be an interaction between general practitioners and dentists so that such patients have the appropriate preventive care and persistent periodontal therapy in specialized medical and dental clinics.

How to cite this Article: Singh S K, Ranjan N.Diabetes Mellitus & Periodontal Disease.HTAJOCD.2019

Introduction

Diabetes mellitus is a silent disease, which means that without medical tests the patient may be unaware of having this disorder. In an early stage, the patient may not present signs and symptoms compatible with the disease. It's a common disease worldwide, mainly in the United States of America (USA), affecting 7.6% of the adult population, between 30 and 69 years old, and 0.3% of pregnant women. Impaired glucose tolerance is observed in 12% of adults and 7% of pregnant women. It is estimated that about 50% of diabetic patients are unaware of the diagnosis. According to an international projection, due to a growing sedentary lifestyle,obesity and population ageing, diabetes will increase worldwide by over 50% in 2025.

Diabetes is in the top five of the highest mortality rate diseases in the world and is getting closer to the top of the list.Over the past 20 years the number of diabetics in North America has increased considerably. In 2005, there were about 20.8 million people with diabetes in the USA alone.According to the American Diabetes Association there are about 6.2 million people undiagnosed and about 41 million people who could be considered pre-diabetic.

Periodontal disease is an infectious inflammatory illness that may compromise gums and its attachment tissues, such as, cementum, periodontal ligament and alveolar bone. It is characterized by insertion loss of the periodontal ligament and bone destruction of adjacent tissue. The development of this process leads to teeth loss and destruction of the periodontal ligament by bacterial action. Dental plaque and calculus inflame these structures leading to the formation of periodontal pockets, thereby to tooth mobility.

Concerning oral pathologies, periodontal disease is one of the most prevalent oral diseases worldwide along with dental caries and is associated with various systemic diseases, particularly diabetes mellitus. In this review article we intend to demonstrate the possible association between diabetes mellitus and periodontal disease, assessing their main characteristics, associations with social status and influence of periodontal disease monitoring in diabetes mellitus.

Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases which is characterized by hyperglycemia. Its prevalence has been increasing in recent decades, both in developed and in developing countries.

Diabetes Can Be Classified Into The Following General Categories:

Type 1 Diabetes: It is characterized by changes in pancreatic β-cells, lack of insuline production and insulin secretion and tendency to ketoacidosis. It corresponds to 5% to 10% of cases, being more frequent among children and adolescents, with a peak incidence in both genders, between 11 and 14 years old, although it can occur in any age group. In most cases (85-90%) occur in patients with human leukocyte antigens, or associated with a strong genetic predisposition. The genetic predisposition linked to environmental factors, such as mumps virus and coxsackievirus B4 promotes a destructive autoimmune process, and highly selective pancreatic β-cells. When there is no evidence of autoimmunity it is considered idiopathic diabetes. The slowly progressive form generally occurs in adults and is referred as latent autoimmune diabetes of adults.

Type 2 Diabetes: It is the most common being responsible for 85% to 90% of cases and is characterized by a reduced sensitivity to insulin coupled with an insulin deficiency. Type 2 diabetes is more prevalent in patients aged over 40, obese and that do not practice physical exercise. Usually, most type 2 diabetics can use oral antidiabetic agents in the early years after diagnosis. However, they may need insulin for a good glycemic control through the years.

Other Specific Types of Diabetes Mellitus: Includes all diabetes cases in which the etiological factor is known, but having a lower incidence. For example, functional genetic defects of β cells with deficiency in insulin secretion; genetic defects in insulin action; diseases of exocrine pancreas (pancreatitis, trauma, infection, pancreatic cancer, hemochromatosis, cystic fibrosis); endocrine diseases that cause hyperglycemia (acromegaly); certain drugs and chemicals; viral infections; genetic syndromes (Down syndrome, Turner syndrome). Gestational diabetes: it is characterized by glucose intolerance diagnosed during pregnancy and may or may not persist after pregnancy. Women with increased body weight, over 25 years old and a familial history of diabetes mellitus have a medium or high risk for developing this type of diabetes, and thus should be monitored throughout pregnancy. In any form, the absence of insulin can cause chronic and acute metabolic disorders. Systemic and oral signs and symptoms aid in the evaluation and diagnosis of diabetes.

These signs and symptoms include polyuria, polydipsia, polyphagia, weight loss, fatigue, blurred vision, nausea, drowsiness, dehydration. Systemic chronic complications of diabetes mellitus affect multiple body systems and there may be cases of retinopathy, neuropathy, nephropathy, peripheral vascular diseases, coronary heart disease, central and peripheral nervous system and dermatological problems. In the oral cavity, the most frequent complications related to diabetes mellitus are: acetone breath, red furry tongue, increased asymptomatic parotid, gingival hypertrophy, alveolar resorption, tooth mobility, higher prevalence of stomatitis, increased incidence of dental caries due to the increase enamel hypoplasia and hypocalcification, increased susceptibility to oral candidiasis and angular cheilitis due to xerostomia.

Periodontal Disease

It is a disease in the oral cavity characterized by inflammation of teeth supporting tissues that evolve continuously, having periods of exacerbation and periods of remission.

There are two ways to classify this disease:

Gingivitis: It is characterized by soft tissues' inflammation but connective tissue remains attached to the tooth and does not occur insertion loss and if not promptly treated, may develop into periodontitis.

Periodontitis: It is the most severe form of periodontal disease affecting the deeper structures and is characterized by destruction of the periodontal ligament and apical migration of connective tissue. In a periodontal disease, accumulation of dental plaque leads to insertion loss due to resorption of the alveolar bone.Both forms are characterized by several signs and symptoms that should be analyzed during periodontal examination, in order to use the most appropriate therapy.

Gingivitis is clinically characterized by bleeding on probing, increased flow of crevicular fluid, hyperplasia, smooth and shiny gums, and radiologically by no bone loss. Peridontitis is clinically characterized by erythema and exudate, bleeding on probing, gingival recession, tooth mobility, insertion loss, furcation involvement halitosis; radiographic there is a horizontal and/or vertical bone loss that can be classified as mild, moderate or advanced.

Periodontal disease has become a worldwide public health issue affecting more the adult population. It usually starts as a gingivitis progressing quickly to a destructive periodontitis. Its development is influenced by multiple systemic, local and environmental factors.

Diabetes mellitus and periodontal disease are two common chronic diseases and, according to several research studies, are biologically interconnected. Periodontal disease is a result of micro vascular diabetes mellitus. There is scientific evidence showing that diabetes is a risk factor for gingivitis and periodontitis and that blood glucose control is crucial in this interaction. Thus, periodontal disease is clearly a clinical manifestation associated with several systemic diseases

including diabetes. There is supremacy of Gram -anaerobic bacteria in periodontal pockets and/or gingival sulcus that stimulate the immune system cells and consequently release inflammatory mediators. These mediators get into the bloodstream and increase inflammation present in diabetes and interfere with blood glucose levels' regulation, leading to development and aggravation of diabetic complications.

Thus, periodontal treatments like root scaling associated with antibiotic therapy, reduce periodontal pathogens, inhibit the secretion of inflammatory cytokines and also inhibit nonenzymatic glycosylation. It is important to submit diabetic patients to regular periodontal therapy in order to avoid reinfection and maintaining good metabolic control.

Prevalence of Gingivitis & Periodontitis in Relation to Diabetes

The prevalence of periodontitis in the United States is subject to controversy. Current data suggest that the prevalence of periodontitis has decreased across ethnicity, sex, and age-groups to < 10%. Different interpretations of the same data suggest, however, that up to 50% of U.S. adults may suffer from various degrees of periodontitis. The prevalence of periodontitis is significantly higher among middle-aged people with diabetes than in similar-aged people without diabetes. Analysis of data from the third National Health and Nutrition Examination Survey has revealed that a self-reported family history of diabetes, hypertension, high cholesterol, and clinical evidence of periodontal disease bears a probability of 27–53% that the patient has undiagnosed diabetes. Analysis of periodontal status in people with type 1 or type 2 diabetes from a population-based German study has demonstrated an association between both types of diabetes and tooth loss. Attention to oral disease in addition to medical conditions by both medical and dental care providers will improve the ability to identify individuals unaware of their diabetic status. Dentists should establish referral patterns, communicate with physicians, and use dental screening as a tool for referral of patients with severe gingival or periodontal inflammation. It would be advantageous if blood glucose assessments were performed in dental offices for patients at risk for type 2 diabetes. Likewise, physicians should refer patients with type 2 diabetes to dentists for treatment of gingival or periodontal inflammation. This is especially important because the pathophysiology of periodontal inflammation is not limited to the oral cavity and can have important effects on glycemic control. Indeed, periodontitis has been identified as the sixth complication of diabetes.

Pathophysiology of Periodontitis as a Complication of Diabetes

The oral cavity, as part of the gastrointestinal tract, is populated by a diverse and large microbiota and has been identified as a location with a more dense bacterial colonization than any other organ. Teeth provide a nonshedding surface with a complex biofilm containing bacteria that are in balance with the host, but bacterial species with high virulence can also be identified.

Periodontitis has a complex infectious etiology, and the establishment of infection is usually slow. A bacterial biofilm of both aerobic and anaerobic bacteria, including > 500 species, may be found in periodontal pockets around teeth. Bacteremia is rarely identified in periodontitis. However, endotoxins from bacteria identified in periodontal pockets and associated with periodontitis can be found in serum in > 30% of nondiabetic patients who present with early signs of periodontitis.

In general, the bacterial infection in periodontitis does not differ between nondiabetic patients and those with type 2 diabetes. However, the immune response to periodontal bacterial infection does differ in that patients with type 2 diabetes do not develop antibodies to pathogens associated with periodontitis. Many of the anaerobic bacteria associated with periodontitis have a lipopolysaccharide (LPS) capsule with endotoxins and heat-shock proteins. Pretreatment profiles of serum antibody titers to different heat shock proteins and LPS levels from Porphyromonas gingivalis, an anaerobe commonly found in periodontitis lesions, can predict the outcome of periodontal therapy in patients with diabetes such that those with elevated titers have a more favorable treatment outcome.Unpublished data based on 282 subjects, among whom 9.3% had type 2 diabetes with similar severity of periodontitis, suggest that patients with type 2 diabetes may have fewer bacteria in periodontal pockets but the same severity of disease. These data suggest that the inflammatory response to infection in people with type 2 diabetes is more severe than in nondiabetic subjects (G.R.P, unpublished observations). This may be explained by a lack of ability to produce functional antibodies against bacteria in periodontal infection. This is illustrated in the diagram in Figure 2, which includes four bacterial species associated with periodontitis.

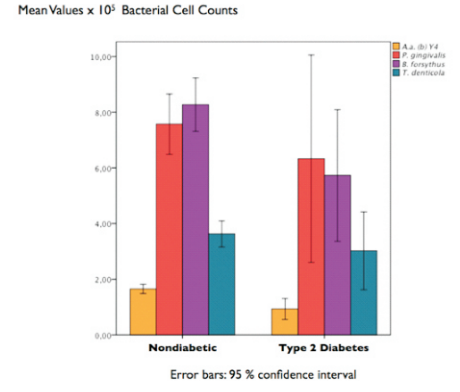

Figure 2. Levels of select bacteria associated with periodontitis in periodontal pockets of subjects without a diagnosis of diabetes and in subjects with type 2 diabetes. A similar severity of periodontitis, but with lower bacterial counts, was identified in subjects with diabetes for A. actinomycetemcomitans serotype Y4 (A.a (b) Y4), P. gingivalis, T. forsythia, and T. denticola, all associated with periodontitis.

This observation is consistent with the general perception of an increased susceptibility to infection among patients with type 2 diabetes. Periodontal infections trigger the release of pro-inflammatory cytokines both at the site of the periodontal infection and throughout the endothelial cell system. Studies of gingivitis in humans with or without type 1 diabetes have shown that both diabetic and nondiabetic subjects react to experimental plaque accumulation with gingival inflammation.

However, subjects with type 1 diabetes develop an earlier and more severe local inflammatory response to a comparable bacterial challenge.

Further studies have shown that two biological markers of inflammation, IL-1b and MMP-8, which are typically elevated in the fluid from inflamed periodontal pockets, are more elevated in people with diabetes. People with type 2 diabetes also have higher levels of several other cytokines (i.e., interferon-γ, osteoprotegrin, tumor necrosis factor-α (TNF-α), and interleukin at the site of periodontal infection but also exhibit a down regulation of interleukin 4.

An increasing severity of periodontitis has been linked to the development of glucose intolerance, likely because of increased inflammation leading to increase in interleukin-6 (IL-6). The liver is an important target for IL-6 action, leading to an increased inflammatory response with impaired insulin signaling and action and resultant decreased insulin production.

Patients with impaired insulin production are therefore unable to control for IL-6 activation and the enhanced inflammation induced by IL-6.Elevated IL-6 serum levels have been identified in people with untreatedchronic periodontitis.21 These studies suggest that the presence of elevated serum levels of pro-inflammatory cytokines in patients with type 2 diabetes caused by periodontitis may aggravate inflammatory responses in other organs commonly affected inpatients with diabetes. Other pathological factors in diabetes affecting the periodontal tissue are linked to elevated glucose levels in serum with development of advanced glycation end-products (AGEs), altered lipid mechanisms, and oxidative stress.Data suggest that AGEs present in diabetic gingiva can be associated with oxidative stress.Clinical data have suggested that the presence of AGEs in patients with diabetes is associatedwith the biofilm on teeth, indicating an increased risk for periodontal damage.

Association Between Diabetes Mellitus And Periodontal Disease

Several studies demonstrate an association between diabetes mellitus and periodontal disease. Following, there is a summary of some studies suggesting the association between these two disorders (Table 1) and another one that shows several studies presenting diabetes' control due to periodontal therapy performed in diabetic patients (Table 2).

Conclusions

Patients with diabetes are usually poorly informed about the relationship between periodontitis and diabetes.Therefore, health care providers of patients with diabetes should be aware of this link and inform their patients about the need for good oral health.

Referral of patients with uncontrolled diabetes for dental evaluation and periodontal treatment may result in better control of blood glucose levels. Although a survey of the oral cavity should be included in a thorough medical examination, health care providers other than those within the dental team usually are not aware of what clinical signs of periodontitis to consider. An increased redness of the gum tissues along the teeth is a classic sign of gingivitis, a condition that indicates that there is an active inflammatory response to bacterial infection. The use of a toothbrush or a toothpick to gently touch the gums of diabetic patients with inflammation will provoke bleeding that

will cease within minutes. Health care providers should suggest a thorough dental examination if such bleeding is common throughout a patient's mouth. Also, the presence of white or gray deposits on teeth suggests that dental treatment may be necessary. Spacing between upper front teeth and mobile teeth are other signs of periodontitis. Likewise, dentists and dental hygienists should refer their patients who respond poorly to initial periodontal therapy or have advanced periodontitis without obvious signs of poor oral hygiene for diabetes screening. In fact, it might be advantageous for dental offices to monitor the blood glucose levels of patients considered to be at risk for diabetes.

In Summary

- Diabetes and periodontitis are both common chronic diseases in adults and specifically in older individuals.
- There is substantial evidence of the impact of periodontitis on systemic inflammatory markers.
- Periodontal treatment of patients with diabetes may have limited effects on slightly elevated A1C levels, but in patients with more severe diabetes, such treatment may reduce A1C levels significantly if coordinated with blood glucose control.
- Signs of periodontal inflammation, including gingivitis, can be assessed easily by all medical health care providers.
- Patients with periodontitis with severe gingival inflammation who do not respond to routine periodontal therapy should be screened for diabetes.
- By communicating and coordinating the treatment of diabetic patients, medical and dental care providers have an opportunity to provide better care of their patients.

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Table 1 & 2

Authors	Study Design	Methods	Results
Hugoson et al.	Cohort	82 patients with type 1 diabetes (long term). 72 patients with type 1 diabetes (short term). Periodontal probing, premolars & molars xrays for periodontal evaluation.	Long-term type I diabetics have more tooth surfaces with periodontal pockets higher than 6mm than nondiabetics
Emrich et al.	Cross-sectional	1342 patients with type 2 diabetes & 1877 non diabetic patients, aged between 15-55 years old. Periodontal evaluation by age. probing & analysis of alveolar bone loss	Type 2 diabetics have a higher risk of periodontal disease regardless their
Thorstensson et al.	Cross-sectional	Evaluation by probing, clinical characteristics of the gum, the alveolar bone level. 83 patients with type 1diabetes and 99 nondiabetic patients, aged between 40-69 years old	Diabetes mellitus is a risk factor for the development and progression of periodontitis.
Tervonen et al.	Cross-sectional	35 patients with type 1 diabetes and 10 nondiabetic patients aged 29. Bone loss assessment. It has been considered glycemic control, duration &severity of diabetes.	Increased bone loss in type I diabetics & more significant in long term diabetics.
Mattout et al.	Cross-sectional	71 patients with type 2 diabetes and 2073 nondiabetic patients, aged between 35-75 years old. Assessment of gingivitis,periodontal pockets, periodontal attachment loss. Fasting blood glucose levels.	Periodontal disease is more severe in type 2 diabetics.
Bascones-Martínez et al	Literature review		There is an increased severity of periodontal disease in diabetics. Periodontal disease is considered to be the 6th major complication related to diabetes mellitus.
Kumar et al.[	Literature review		There is a clear association between the periodontal disease's severity and diabetes mellitus

Authors	Methods	Periodontal treatment	Metabolic control	Results
Iwamoto et al.[30]	13 patients with type 2 diabetes, aged between 19-65 years old	Local minocycline in periodontal pockets.	HbA1c	The treatment with minocycline was effective in improving metabolic control in diabetics.
Skaleric et al	10 patients with type 1 diabetes &10 nondiabetic patients,aged between 26-58 years old. Duration of study:24 months	Scaling. Minocycline microspheres in pockets greater than 5mm.	HbA1c	Decrease HbA1c
Janket et al	456 patients with type 1 & 2 diabetes. Duration of study: 25years	Scaling Antibiotic therapy	HbA1c	
Schara et al.[	10 patients with type 1 diabetes, aged 38. Duration of study:10 months	Scaling Oral chlorhexidine	HbA1c	Decrease in HbA1c after 3 months of treatment.
Faria-Almeida et al.[	10 diabetics and 10 nondiabetic patients, aged between 35-70 years old. Duration of study:6 months.	Scaling	HbA1c	Significant decrease in HbA1c.
Darré et al.[	9 clinical trials with 485 type 1 and 2 diabetics.	Periodontal treatment	HbA1c	Decrease HbA1c
Kormantzos	30 patients with type 2 diabetes &30 nondiabetic patients, aged between 40-75 years old. Duration of study:6 months	Non-surgical periodontal treatment every 7 days	HbA1c	Non-surgical periodontal treatment effective in patients with type2 diabetes & moderate or severe periodontal disease because there was a reduction in HbA1c levels
Wang et al	19 clinical trials with 143 patients having periodontal disease & type 2 diabetes mellitus.	Periodontal treatment with antibiotics and periodontal curettage	HbA1c	Insufficient scientific evidence to justify a direct relationship between periodontal therapy and metabolic control