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Periodontitis in diabetics: Is collaboration between physicians and dentists needed?

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Introduction

Results from numerous epidemiological and cross sectional studies over the past few decades indicate that diabetes mellitus (DM, both Type 1 and 2) increases the prevalence, incidence and severity of periodontitis[1-6] suggesting that diabetes predisposes subjects to periodontitis. In fact, periodontitis is now recognized as the 6th most common complication of diabetes[7]. Although the data are at times conflicting, several studies have shown that treatment of periodontitis results in an improved glycemic control in subjects who have DM[8-12] . Thus, these data suggest that periodontitis exacerbates diabetes and a "bi-directional relationship" exists between periodontitis and DM.[13] However, the mechanisms that explain this two-way relationship, especially the direct effect of periodontitis on DM condition, are not yet well understood.

Interestingly, results from several cross-sectional studies also suggest an association between the severity of diabetic end-organ complications and the presence of periodontitis. This paper will briefly review the current understanding of the association between periodontitis and T1 and T2 DM, and the possible effect of periodontitis on glycemic control and organ damage with the goal of promoting collaborative work between physicians and dentists in managing DM subjects with periodontal disease.

Type 1 Diabetes and periodontitis

Although the results from some studies indicate absence of periodontitis in T1DM subjects[14,15], several studies indicate that the prevalence of gingival inflammation and periodontitis in children with T1DM is approximately 10% [16,17] compared with less than 2% in children and adolescents overall,[18] suggesting that T1DM predisposes to periodontitis. In addition, the results from several studies indicate that the duration and/or severity of T1DM appear to be risk factors that impact the development of periodontitis[19,20] . As indicated, there are conflicting results to suggest an association exists between T1DM and the prevalence and/or severity of periodontitis and this may be due to the difference in assessment of periodontitis as well as confounding factors such as the dose and compliance with insulin treatment in the various studies resulting in different levels of glycemic control[21], and the frequency and quality of dental/periodontal care that T1DM subjects received. There have been a number of studies investigating the association between periodontitis and organ damage associated with T1DM. The results of these studies reveal that there is a greater incidence of ketoacidosis, retinopathy and neuropathy in patients with periodontitis compared with subjects without periodontitis[22] and more frequent

microvascular complications in subjects with severe gingival inflammation[23]. The presence of periodontitis was also found to be associated with significantly higher prevalence of proteinuria and cardiovascular diseases such as stroke, transient ischemic attacks (TIA) and angina in T1DM subjects[24]. In addition, it was reported that the severity of periodontitis is significantly correlated with the severity of diabetic retinopathy and that the risk of proliferative diabetic retinopathy is significantly higher in the presence of periodontal disease in DM (T1 or T2DM) subjects[25].

Although some studies have reported that treatment of severe periodontitis in T1DM subjects is not accompanied by better metabolic control[26,27], other prospective studies indicate that treatment of periodontitis/inflammation leads to either a significant reduction in insulin requirement or a reduction in HA1c levels[8,28,29]. These conflicting results may be due to variation in the severity of diabetic control among patients and/or severity of periodontitis and treatment modalities including the use of antibiotics. Collectively, these studies strongly suggest that there is an association between T1DM, periodontitis and concomitant organ damage. However, it can not be ruled out that poorly-controlled diabetic subjects or subjects with T1DM of long duration may have poorer oral hygiene and/or poorer compliance with dental appointments which may predispose them to more severe gingival inflammation and periodontitis. Nonetheless, an association between periodontitis and T1DM appears to exist and the reduction in inflammation that results from periodontal treatment may help improve glycemic control, as shown in prospective studies, and thus retard the progression of organ damage. Further research is needed in this respect to understand the mechanisms by which periodontitis impacts the diabetic condition and its augmenting effect on organ damage.

Type 2 Diabetes and periodontitis

The results of large epidemiological studies indicate that T2DM patients have a 3-4 times greater risk of developing destructive periodontitis than non-diabetic subjects[6,30] . The results from the third National Health and Nutrition Examination Survey (NHANES III) reported that the odds ratio of severe periodontitis in subjects with poorly-controlled T2DM (HbA1c > 9%) was 2.9 (90% CI: 1.4-6.03) compared with subjects without T2DM[31]. The underlying mechanisms for this association are still not certain. However, results from some studies indicate that inflammatory mediators and proteins modified by hyperglycemia such as advanced glycated end products (AGEs) produced as a result of DM might influence the periodontal condition in humans and animals[32-34]. These study results partially may explain the mechanism accounting for the effect of T2DM on periodontal condition observed in humans.

Published reports suggest that subjects with T2DM, especially uncontrolled T2DM, have more severe periodontitis and/or gingival inflammation than individuals with normoglycemia[31,35]. This is similar to the results from studies in T1DM subjects described above. Although the data are again at times conflicting,[36] there are a number of prospective studies that indicate that treatment of periodontitis/inflammation leads to an improved glycemic control (0.4 - 2.0% reduction in HbA1c value) in subjects with T2DM that lasts for 3 to 6 months following the treatment of periodontitis[10-12, 37-40] . An average HbAIc reduction of 1% is comparable to what oral T2DM medication can achieve[41]. The results from a meta-analysis, however, caution that this improvement in HA1c following the treatment of periodontitis may be due to limited robustness in the analysis due, in part, to the heterogeneity among studies[37].

Periodontitis also appears to have an effect on organ damage and mortality in T2DM patients. For example, recent data indicate that the death rate from diabetic nephropathy in

subjects with severe periodontal disease is 8.5 times as high as that in individuals with healthy periodontal tissues or mild or moderate periodontal disease after adjustment for age, sex, and duration of diabetes. In addition, subjects with severe periodontal disease have a 3.2 times greater risk of cardio-renal mortality compared with patients with healthy periodontal tissues or mild or moderate periodontal disease[42]. Thus, this study suggests that co-morbidity of severe periodontitis and T2DM is a risk factor for severe complications of T2DM leading to premature death from renal and cardio-renal complications. However, it cannot be discounted that subjects suffering from T2DM and nephropathy may be at greater risk of developing severe periodontitis.

The effect of periodontitis on nephropathy and end-stage renal disease (ESRD) in a cohort of Pima and Tohono O'ldham Indians who were >25 years old and suffering from T2DM was also investigated. These subjects received one or more periodontal examinations and were monitored for up to 22 years[43]. The results of this study suggest that periodontitis predicts development of overt nephropathy and ESRD in T2DM subjects.

Thus, results from a number of studies suggest that a relationship exists between T2DM and periodontitis, and co-morbidity with these 2 diseases may increase the severity of diabetic end organ damage possibly resulting in higher mortality. Conversely, metabolic control of T2DM is viewed as critical to this co-morbidity since it influences not only organ damage associated with T2DM, but also affects the severity of periodontitis and gingival inflammation. Finally, the collective results suggest that treatment of periodontitis may be helpful in improving glycemic control and hence preventing or delaying organ damage. However, more mechanistic studies are necessary to determine the effect of periodontitis on T2DM.

Possible mechanisms underlying these two way relationships

One of the mechanisms by which diabetes appears to influence the periodontal condition is via production of AGEs. AGEs are known to activate host cells such as monocytes/ macrophages and endothelial cells leading to release of proinflammatory cytokines as well as proteases which contribute to destruction of gingival tissues and tooth supporting bone.[44,45] The expression level of the AGE receptor (RAGE) in subjects with both T2DM and periodontitis is higher compared to the level in non-diabetic subjects with periodontitis.[46] These data support one mechanism that operates from the DM to periodontitis direction in two-way relationship.

The primary etiology of periodontitis is bacteria and their byproducts, including lipopolysaccharides (LPS). LPS, in particular through activation of TLR4, results in transcriptional activation of genes encoding proinflammatory cytokines including TNFα, IL1β and IL-6.[47] TLR4 is one of the pattern recognition receptors whose function is to recognize products of bacteria and viruses and to initiate inflammatory and immune responses to infection. A number of studies have demonstrated that periodontitis lesions release high levels of these cytokines. Therefore, the basic premise underlying the potential influence of periodontitis on the diabetic condition is that proinflammatory cytokines or LPS released locally in gingiva may enter the systemic circulation and influence insulin target organs/tissues in distant sites[48]. Since TNFα is known to impair insulin signaling and cause insulin resistance[49], it is hypothesized that periodontitis via production of TNFα and possibly other cytokines influences the diabetic condition.

Animal studies are useful to determine the precise mechanisms of these proposed relationships. For example, elegant studies in which AGE-RAGE interaction was blocked by sRAGE or Receptor activator of nuclear factor kappa-B ligand (RANKL)-Receptor activator of nuclear factor (RANK) interaction was blocked by osteoprotegerin (OPG) in diabetic

animals demonstrated that AGE and RANKL influence rapid alveolar bone loss in diabetics in animal model systems[32, 50].

The mechanisms that underlie the reverse relationship i.e. the effect of periodontitis on the diabetic condition are also emerging using animal model systems. For example, induction of periodontitis in prediabetic rats causes impaired glucose tolerance[51, 52]. In addition, induction of periodontitis accelerates the development of insulin resistance and the onset of T2DM in animals fed a high fat diet[48]. However, as mentioned above, more research is necessary to understand the inter-relationship between periodontitis and DM, especially the effect of periodontitis on the course of DM progression and end organ damage.

Conclusion

Although some inconsistencies exist due to difficulties in controlling a number of confounding factors in human clinical studies, available data suggest that there is a close association between periodontitis and DM. This relationship is bi-directional and supported by human cross sectional studies, prospective studies and by animal model systems. The results from recent studies using animal models indicate that periodontitis does influence the progression of diabetes. Thus, treatment of periodontitis to reduce low-grade systemic chronic inflammation that exists in DM subjects may help glycemic control and help reduce the extent of organ damage. Large scale human prospective studies as well as animal model systems to determine mechanisms that delineate the effects of periodontitis on DM are necessary. Lastly, communication between physicians, endocrinologists and dentists/periodontists is critical for providing optimal care for DM patients. When this is achieved, we can look forward to a better understanding of the interactions between these two extremely prevalent diseases and, perhaps, a better control of hyperglycemia and end organ damage in diabetic patients.

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