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Guest Editorial

Periodontal infections and diabetes mellitus: when will the puzzle be complete?

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The article in last month's issue of the *Journal of Clinical Periodontology* on the effects of periodontal therapy in patients with type 2 diabetes (Navarro-Sanchez et al. 2007) is the latest in a series of manuscripts that have been published in the journal in the past 12 months (Engebretson et al. 2006, 2007, Lalla et al. 2006, 2007a, Bakhshandeh et al. 2007, Davila-Perez et al. 2007, Lim et al. 2007, Jones et al. 2007a, b), shedding new light on the periodontitis–diabetes link. This is a welcome trend; research on this important and complex association is of prime significance.

This guest editorial reflects on the current evidence of the association between these two common chronic conditions, focuses on the topic of periodontal therapy effects on the diabetic state with the opportunity of the January issue Jones et al. (2007a, b) study, highlights the gaps in our knowledge and offers a view to important future research directions in the field.

Effects of Diabetes on the Periodontal Status

A review of the literature reveals decades of reports regarding the association between diabetes and periodontal diseases and a well-established consensus that diabetic patients are at significantly increased risk for periodontal complications. The available evidence has been summarized in multiple review articles over the years and more recently in a comprehensive manner by Taylor (2001) and Mealey & Oates (2006). An early meta-analysis of four studies including 3524 adults demonstrated a significant association between diabetes and periodontal diseases and estimated that diabetes increases the risk for periodontitis by twofold (Papapanou 1996). A recent meta-analysis of 23 studies including 19,245 individuals 5–78 years of age reported a higher severity but a similar extent of periodontal diseases in diabetes (Khader et al. 2006). However, a limitation of the latter report, acknowledged by its authors, was the inclusion of studies with significant heterogeneity, i.e., very different study populations and sizes, different diagnostic criteria and various parameters assessing periodontal status.

Similarly to what is well established for the other complications of diabetes, the level of metabolic control and the disease duration appear to play a role in the level of risk for periodontal diseases, but there is significant heterogeneity among diabetic individuals. In the February issue of the journal, a study by Lim et al. (2007) in 182 diabetic adults reported that the level of glycaemic control emerged as the most consistent risk factor associated with severity and extent of periodontitis. These findings concur previous findings in several reports, although some studies have found no such significant relationship. Additional evidence, especially from longitudinal follow-up studies, is necessary to conclusively demonstrate whether such a dose–response relationship exists.

Furthermore, although a lot has been accomplished in the research field of diabetes as a periodontitis risk factor thus far, many important questions remain still unanswered: which are the exact mechanisms involved in the pathogenesis of periodontitis in diabetes? What is the temporal association between the development of periodontitis and that of other diabetic complications? What is the level of risk and the mechanisms involved in special populations such as the young, those with gestational diabetes, the undiagnosed, those with pre-diabetes or those at risk for diabetes?

Effects of Periodontitis on the Diabetic State

Because diabetic individuals are at a higher risk for periodontitis, the questions of how to treat periodontitis in these individuals and, more importantly, what are the effects of periodontitis and its treatment on the diabetic state are natural ones.

Evidence on which periodontal treatment modalities are most successful in diabetic patients is scant, as is information on how these patients respond to surgical periodontal therapy, or long-term maintenance. These issues are pertinent given the established knowledge that wound healing is delayed and compromised in diabetes, and that the diabetic host response is characterized by an exaggerated inflammatory response to common stressors.

Moreover, our understanding of the less-studied part of the association, namely how periodontal infections

might affect the diabetic state, is rather limited. Four longitudinal studies thus far have demonstrated that severe periodontal disease at baseline is associated with poor metabolic control and the development of other systemic complications (i.e., cardiovascular disease and associated mortality, proteinuria and overt nephropathy/stage five chronic kidney disease) at follow-up (Taylor et al. 1996, Thorstenssson et al. 1996, Saremi et al. 2005, Shultis et al. 2007). However, it is critical to demonstrate whether treatment of periodontal disease has a positive systemic effect in patients with diabetes and to explore different therapeutic approaches to achieve such effect. Beyond the obvious implications because of the role of metabolic control in the development and/or progression of other complications, this is of essence in view of the accumulating evidence that direct infection of the vascular wall may impact atherosclerosis-related diseases, which are particularly relevant in the setting of diabetes. The issue becomes especially complicated as indeed the essential component of periodontal therapy, i.e., scaling and root planing, promotes the haematogenous spread of bacteria. Adjunctive antibiotic approaches may confer more positive systemic effects, and interference with host inflammatory responses, such as use of sub-antimicrobial tetracycline therapy, for example, may hold even more promise.

The first meta-analysis attempting to quantify the effects of periodontal therapy on the level of metabolic control in diabetic individuals was reported in 2005 (Janket et al. 2005). A total of 456 patients, from 10 longitudinal periodontal intervention studies, were included in the analysis and the overall weighted average decrease in actual HbA1c levels was 0.38% (95% CI: -1.5, 0.7). A larger, but still not statistically significant, effect was seen in type 2 patients (average change 0.66%, CI: -2.2, 0.9) and also with the addition of antimicrobials in the treatment protocol of type 2 individuals (average change 0.71%, CI: -2.3, 0.9).

Whether periodontal therapy has a differential effect on HbA1c across baseline levels of metabolic control (poor, moderate, good) is an important question, but it was unfortunately not adequately addressed in this report. The authors reported that ''the type of control did not manifest any substantial difference in the level of HbA1c ($p = 0.82$)'' without any further explanation. The authors also suggested that future studies should focus on type 2 patients only and this should be more feasible, as type 2 diabetes is much more prevalent, and affected patients usually have poor glycaemic control. Undeniably, there are difficulties with studying type 1 diabetes in this particular setting: these are *usually* younger individuals (and thus at a lower risk for periodontitis), have an overall more disciplined life style (and may be more cooperative with oral health-care habits) and have tighter metabolic control at baseline (thus improvements may be more difficult to achieve). Furthermore, multiple insulin adjustments (especially in those on an insulin pump) can confound potential periodontal therapy results on HbA1c levels even within short follow-up periods.

Nevertheless, studies including type 1 patients remain extremely important and any results in type 2 individuals will eventually need to be extended and validated across all diabetic patients. Let us not forget that irrespective of diabetes type, it has been conclusively demonstrated that hyperglycaemia is what drives most complications in affected individuals and this is the reason why glycaemic levels as close to the non-diabetic range as possible is the essential treatment strategy in both types of diabetes. Therefore, type of disease or aetiology might be less important than the lifetime exposure to hyperglycaemia (i.e., the overall host burden). The treatment strategy in type 2 patients is arguably broader, including lipid lowering and antihypertensive measures. This further substantiates the concept that in both disease types, the potential effects of periodontal treatment should also be examined on other outcomes, beyond Hb1Ac levels. Obviously, development and/or progression of other systemic complications is the most important endpoint, albeit the most difficult to study as it will require long-term prospective follow-up studies. Insulin requirements, lipid levels/profile, serum CRP, TNF-α, or other systemic biomarkers consistent with a pro-inflammatory, or pro-atherogenic and pro-thrombotic profile in these high-risk individuals are alternative relevant endpoints. Indeed, in a pilot study of 10 diabetic individuals with moderate to severe periodontitis that were treated with full-mouth subgingival debridement, we observed a reduction in $CD14^+$ blood monocytes, the percentage of TNF-α-releasing macrophages and the serum levels of high-sensitivity CRP and E-selectin (Lalla et al. 2007b). Iwamoto et al. (2001) reported reduction in serum TNF-α with periodontal therapy consisting of mechanical debridement and local minocycline in 13 diabetic patients, and these reductions strongly correlated with improvement in HbA1c levels. The findings in these two pilot studies are of importance given the systemic implications of inflammation and the link with insulin resistance, respectively, in diabetic individuals. Furthermore, such studies offer a first glimpse on *how* periodontal therapy may potentially impact the diabetic state.

The study design and initial findings from the first multi-site single-blinded randomized-controlled clinical trial exploring the effects of a single course of periodontal therapy (scaling/root planing and systemic doxycycline) on glycaemic control were published in the January issue of the journal (Jones et al. 2007a, b). In this moderately sized study, the vast majority of subjects were poorly controlled type 2 males, who attended four VA hospitals in New England. Using the cut-off of 8.5% for baseline HbA1c as an inclusion criterion, 265 (58%) of the eligible and interested in participating patients were excluded. The authors adopted this strategy because ''it clearly left room for improvement and included a broad range of poor control''. Indeed, baseline HbA1c was one of the parameters that showed a strong association with improvement at follow-up; however, including any patient above the 7% treatment goal would still be clinically relevant and would have significantly increased power. In this case, differences between patients presenting with poor *versus* good metabolic control at baseline could still be explored in subsequent analyses. One hundred and ninety-three patients were randomized in immediate or deferred treatment groups and 132 completed the whole study. Effects on HbA1c levels after the first 4 months are reported in the January article for the 165 subjects who completed this arm.

The study's primary outcome was change in HbA1c from baseline at 4 months, and when analysed as a continuous variable, non-significant differences in both the unadjusted and adjusted models were revealed

(differences in mean HbA1c change were in the order of 0.14% in the model adjusted for baseline HbA1c, duration and older age, but not for insulin requirements). The percentages of subjects with clinically relevant improvements in HbA1c (of 0.5% and 1%) were also assessed. Interestingly, subjects who received therapy were more likely to achieve the 0.5% and 1% reductions, although statistical significance was not achieved. This was coupled by a trend for higher numbers of patients with decreased insulin requirements (among the 52% who used insulin at baseline) in the treatment group. Similarly, more of the untreated subjects received increases in insulin during the 4-month period.

Based on the a priori power analysis presented, for an effect size δ of 0.04 (δ = difference in mean change between groups divided by the overall standard deviation), 200 subjects would be needed (80% power at the 5% level). This effect size was probably chosen based on previously published evidence where *absolute* HbA1c reductions observed with periodontal therapy ranged from 0.4% to 0.9%. However, the effect size achieved in the current study was much smaller, only 0.11. Possible reasons for the small effect size may include the fact that periodontal destruction at baseline was not very severe and that approximately 60% of the initially deep sites were still present at 4 months. Re-evaluation at a later time point may reveal improved periodontal healing. Thus, findings at the 8- and 12-month follow-ups, and also in the groups that received continuous treatment for 12 months, are much anticipated. Interestingly, as the authors state in their discussion, detection of a 10% difference between the two groups in the proportion of subjects with HbA1c improvement of at least 1% (using an adjusted model) would require 362 patients per group, a rather feasible sample size for a future multi-centre clinical trial. As a final point, the Jones et al. study represents a major effort and serves an important role: it shows that periodontal therapy holds promise for inducing a positive effect on the diabetic state and offers valuable information for the design of future multi-centre clinical trials.

Taken together, it is apparent that results from large, multi-centre clinical trials with multiple treatment modalities and multiple endpoints/outcomes could provide important and much-needed support for the concept that periodontitis may affect the diabetic state, which may eventually initiate new clinical approaches to the management of diabetic patients.

From Evidence to Clinical Practice

A chasm between what is known and current primary care practices has been well described for many chronic diseases (Bodenheimer et al. 2002). We now have evidence that although growing understanding of the diabetes–oral link supports an increased primary and preventive role for dentists in diabetes, this knowledge has not translated to real changes in clinical practice. Work from our group has shown, for the first time, that rates of proactive management of patients with diabetes by general dentists and periodontists alike are actually quite low (Kunzel et al. 2005, 2006). Dentists tend to inquire, discuss and inform, but do not get very actively involved in the management of these patients. Confidence, involvement with colleagues and medical experts and professional responsibility are influential predictors of active management for periodontists; variables pertaining to patient relations are significant predictors for general dentists (Kunzel et al. 2007).

More research to better understand the level of awareness, attitudes and orientations of health-care providers (both dentists and physicians), and even patients themselves, when it comes to diabetes and its relationship with periodontal diseases, is warranted. There is clearly room for improvement in clinical practice, and looking ahead, research towards developing clinical support systems for dentists (and dental hygienists, physicians, nurses, diabetes educators, dieticians) and also programmes that facilitate the interaction and synergy among all health-care providers involved in the care of diabetic individuals is of essence.

Conclusion

The puzzle of the periodontal infections–diabetes relationship is large, and due to the multi-factorial, complex aetiopathogenesis of both disease entities involved, it is a difficult one to solve. More, better-informed, coordinated and focused effort is necessary, in order to add the many missing pieces and hopefully make some difference in the lives of those affected.

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