Changes in Inflammatory and Bone Turnover Markers After Periodontal Disease Treatment in Patients With Diabetes

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ABSTRACT

Background: The underlying mechanisms for increased osteopenia and fracture rates in patients with diabetes are not well understood, but may relate to chronic systemic inflammation. We assessed the effect of treating periodontal disease (POD), a cause of chronic inflammation, on inflammatory and bone turnover markers in patients with diabetes.

Materials and Methods: Using an investigator-administered questionnaire, we screened a cross-section of patients presenting for routine outpatient diabetes care. We recruited 22 subjects with POD. Inflammatory and bone turnover markers were measured at baseline and 3 months following POD treatment (scaling, root planing and subantimicrobial dose doxycycline).

Results: There were nonsignificant reductions in high-sensitivity C-reactive protein (6.34–5.52 mg/L, $P = 0.626$) and tumor necrosis factor-alpha (10.37–10.01 pg/mL, $P = 0.617$). There were nonsignificant increases in urinary C-terminal telopeptide (85.50–90.23 pg/mL, $P = 0.684$) and bone-specific alkaline phosphatase (7.45–8.79 pg/mL, $P = 0.074$). Patients with >90% adherence with doxycycline were 6.4 times more likely to experience reduction in tumor necrosis factor-alpha ($P = 0.021$) and 2.8 times more likely to experience reductions in high-sensitivity C-reactive protein ($P = 0.133$).

Conclusions: Treatment of POD in patients with diabetes resulted in nonsignificant lowering of inflammatory markers and nonsignificant increase in bone turnover markers. However, adherence to doxycycline therapy resulted in better treatment effects.

Key Indexing Terms: Periodontal disease; Diabetes complications; Inflammation markers; Bone turnover markers. **[Am J Med Sci 2016;351(6):589–594.]**

INTRODUCTION

Periodontal disease (POD) is associated with poor dental care, resulting in chronic inflammation around the teeth with destruction of supporting tissues, including alveolar bone and, ultimately, tooth loss if untreated.[1,2] Chronic periodontal bacterial infection results in the continuous release of inflammatory mediators in the systemic circulation.[3-7] Patients with diabetes have a higher prevalence and severity of POD when compared to the general population.[3,8,9] Increased systemic inflammation is known to cause several of the vascular complications of diabetes.[3,10-12] Inflammation also results in increased bone resorption, decreased bone mineral density and increased fracture risk.[6,13-15]

It is known that patients with diabetes have a higher prevalence of osteoporosis.[16] However, the exact mechanism for bone disease in diabetes is not well understood. Treatment of POD results in reduced inflammation,[17,18] but it is unknown if this translates to better outcomes for bone disease in patients with diabetes. There is limited outcome-based evidence to support the recommendation of aggressive management of POD in patients with diabetes.

The purpose of this pilot study was to determine the effect of treating POD in patients with diabetes using nonsurgical techniques on biomarkers of inflammation and bone turnover. Our overall hypothesis was that, if inflammation can be reduced through treatment of POD, this has the potential to reduce the bone loss and bone-related complications that are more common in patients with diabetes.

MATERIALS AND METHODS

Subjects

The study was conducted at a university outpatient clinic and involved a consecutive, purposeful sample of patients with diabetes presenting for their routine care. Prospective participants were screened with an investigator-administered questionnaire[19] to determine their eligibility. Patients with responses suggestive of POD who met inclusion criteria and agreed to participate in the study were referred for a full dental examination to confirm presence of POD. Questionnaire responses that were considered to suggest the presence of POD included: not having dental insurance, not going for

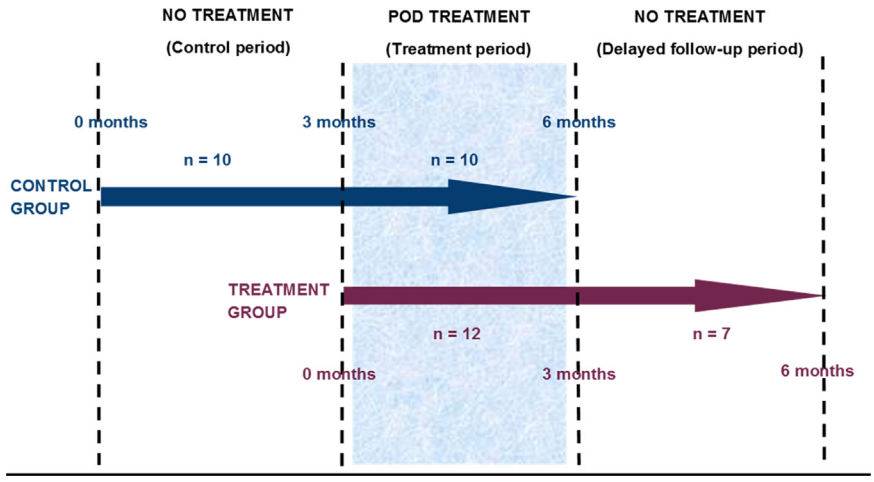

FIGURE. Flow diagram of group assignment and collection of outcome measures (dashes). POD, periodontal disease.

regular dental evaluations, lack of regular personal dental care or any positive answer to a history of deep cleaning, loose teeth, tooth sensitivity or gum bleeding while brushing.

Inclusion criteria were the following:

(1) Current and past evidence of POD
(2) At least 20 teeth in place
(3) Type 1 or type 2 diabetes with duration of 2 or more years
(4) Receiving stable treatment of diabetes with serum glycohemoglobin A1c (A1C) between 6% and 10%
(5) Not receiving treatment with anti-inflammatory medications
(6) Not currently a smoker
(7) Not on treatment with thiazolidinediones
(8) No previous diagnosis or treatment of osteoporosis
(9) Not currently undergoing treatment of POD

The study was approved by the university institutional review board and all study participants reviewed and signed an informed consent before enrollment.

Study Procedures

Half of subjects identified with POD were treated immediately following enrollment over a 3-month period (treatment period), wheras the remaining subjects were observed without treatment for 3 months (control period), after which they were then treated. The group treated first also had another follow-up visit 3 months after treatment was completed, for biomarker evaluation (Figure). The group that did not receive immediate treatment of POD served as control, wheras those who were followed 3 months after completing treatment served to examine any delayed effects of treatment (delayed follow-up period). Treatment of diabetes was stable with no changes to their diabetes medications during the course of the study.

Periodontal Measures

Initial dental examination was conducted by 1 provider to confirm the presence of POD. Evaluation included probing depths, clinical attachment loss, bleeding upon probing, furcation involvement, tooth mobility and panoramic oral radiographs. Treatment of POD was nonsurgical and included scaling and root planing, removal of supragingival and subgingival calculus and plaque and oral low-dose (subantimicrobial) doxycycline 20 mg twice daily for 90 days. Other dental conditions that could contribute to periodontal inflammation were also addressed during treatment (eg, the extraction of hopeless teeth). Outcome measures for POD treatment included probing depth, clinical attachment loss and bleeding upon probing. These were assessed at baseline, 6 weeks after treatment and 3 months after treatment by the same study dentist. Dental hygiene and adherence to doxycycline were reinforced during the 6 weeks follow-up visit. Subjects' self-reported adherence to doxycycline was assessed during follow-up and at the end of the study.

Biomarker Measures

The biomarkers assayed included:

(1) A1C
(2) Serum high-sensitivity C-reactive protein (hs-CRP)
(3) Serum tumor necrosis factor-alpha (TNF-α)
(4) Urinary C-terminal telopeptide (CTX)
(5) Serum bone-specific alkaline phosphatase (BSAP)

Blood samples were collected at baseline and at 3 and 6 months after enrollment (Figure). Samples were collected in the morning and in a fasting state. All subjects included in the final analysis had pre-POD and post-POD treatment biomarker assay. Detailed procedures for sample collection, storage and assay have been published previously.[19]