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**Journal Title:** American Journal of the Medical Sciences  
**Volume:** Volume 351, Number 6  
**Publisher:** Elsevier | 2016-02-24, Pages 589-594  
**Type of Work:** Article | Post-print: After Peer Review  
**Publisher DOI:** 10.1016/j.amjms.2016.02.004  
**Permanent URL:** <https://pid.emory.edu/ark:/25593/s2zj1>

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Final published version: <http://dx.doi.org/10.1016/j.amjms.2016.02.004>

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*Accessed November 14, 2019 10:47 PM EST*



Published in final edited form as:

*Am J Med Sci.* 2016 June ; 351(6): 589–594. doi:10.1016/j.amjms.2016.02.004.

## 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, a cause of chronic inflammation, on inflammatory and bone turnover markers in patients with diabetes.

**Methods**—Using an investigator-administered questionnaire, we screened a cross-section of patients presenting for routine out-patient diabetes care. We recruited 22 subjects with periodontal disease. Inflammatory and bone turnover markers were measured at baseline and 3 months following periodontal disease treatment (scaling, root planing and sub-antimicrobial dose doxycycline).

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Conflict of Interest: None of the authors have any potential conflicts of interest relevant to this article to declare.

Some of the findings included in this article were presented in poster format at the American Diabetes Association Annual Conference, Boston, MA, 5-9 June 2015.

**Results**—There were non-significant reductions in high sensitivity C-reactive protein (6.34 to 5.52 mg/L,  $p=0.626$ ) and tumor necrosis factor-alpha (10.37 to 10.01 pg/ml,  $p=0.617$ ). There were non-significant increases in urinary C-terminal telopeptide (85.50 to 90.23 pg/ml,  $p=0.684$ ) and bone-specific alkaline phosphatase (7.45 to 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 periodontal disease in patients with diabetes resulted in non-significant lowering of inflammatory markers and non-significant increase in bone turnover markers. However, adherence to doxycycline therapy resulted in better treatment effects.

### Keywords

Periodontal disease; diabetes complications; inflammation markers; bone turnover markers

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### 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<sup>12</sup>. Chronic periodontal bacterial infection results in the continuous release of inflammatory mediators in the systemic circulation<sup>3-7</sup>. Patients with diabetes have a higher prevalence and severity of POD when compared to the general population<sup>389</sup>. Increased systemic inflammation is known to cause several of the vascular complications of diabetes<sup>310-12</sup>. Inflammation also results in increased bone resorption, decreased bone mineral density and increased fracture risk<sup>613-15</sup>.

It is known that patients with diabetes have a higher prevalence of osteoporosis<sup>16</sup>. However, the exact mechanism for bone disease in diabetes is not well understood. Treatment for POD results in reduced inflammation<sup>1718</sup>, 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 non-surgical techniques on biomarkers of inflammation and bone turnover. Our overall hypothesis was that, if inflammation can be reduced through treatment for POD, this has the potential to reduce the bone loss and bone-related complications which are more common in patients with diabetes.

### 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<sup>19</sup> 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 regular dental evaluations, lack of regular personal dental care, or any positive answer to a past history of deep cleaning, loose teeth, tooth sensitivity or gum bleeding when brushing.

Inclusion criteria were:

- Current and past evidence of POD
- At least 20 teeth in place
- Type 1 or type 2 diabetes with duration of 2 or more years
- Receiving stable treatment for diabetes with A1C between 6 and 10%
- Not receiving treatment with anti-inflammatory medications
- Not currently a smoker
- Not on treatment with thiazolidinediones
- No previous diagnosis or treatment of osteoporosis
- Not currently undergoing treatment for POD

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

### Study Procedures

Half of subjects identified with POD were treated immediately following enrollment over a 3-month period (treatment period), while 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 1). The group that did not receive immediate treatment for POD, served as control while those that were followed 3 months after completing treatment served to examine any delayed effects of treatment (delayed follow-up period). Treatment for diabetes was stable with no changes to their diabetes medications during the course of the study.

### Periodontal measures

Initial dental examination was conducted by one 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 for POD was non-surgical and included scaling and root planing, removal of supragingival and subgingival calculus and plaque, and oral low-dose (sub-antimicrobial) doxycycline 20 mg twice daily for 90 days. Other dental conditions that could contribute to periodontal inflammation were also addressed during treatment (for example, 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:

- Serum glycohemoglobin A1 c (A1C)
- Serum high-sensitivity C-reactive protein (hs-CRP)
- Serum tumor necrosis factor alpha (TNF- $\alpha$ )
- Urinary C-terminal telopeptide (CTX)
- Serum bone-specific alkaline phosphatase (BSAP)

Blood samples were collected at baseline and at 3 and 6 months after enrollment (Figure 1). Samples were collected in the morning and in a fasting state. All subjects included in the final analysis had pre- and post-POD treatment biomarker assay.

Detailed procedures for sample collection, storage and assay have been published previously <sup>19</sup>.

### Statistical analysis

The sample size was estimated assuming an effect size of 1.1, equivalent to an 18% or greater reduction in hemoglobin A1C levels from baseline to post-POD treatment, using baseline A1C levels specified in Rudolph and Hirsch <sup>20</sup>. Based on a one-tailed, paired t-test and 0.05 significance level, a sample size of 11 participants per subgroup was required to achieve this effect size with 80% power. Similarly, based on baseline C-reactive protein levels found in Pejcic et al. <sup>21</sup>, sample sizes of 11 for each subgroup would also enable detection of an effect size of 1.1 in pre/post-POD treatment C-reactive protein levels with 80% power at a one-sided significance level of 0.05. Assuming an attrition rate of 10%, the planned sample size was 12 for each subgroup, for a total of 24 participants receiving POD treatment.

All periodontal and biomarker variables were summarized using means for the continuous variables and frequencies/percentages for the categorical variables. Dental measures were computed as a per-person average initially across sites, and those means were then averaged across subjects, similar to the method detailed in Engebretson et al. <sup>22</sup>. Comparisons of demographic characteristics, and mean dental and biomarker measures between the treatment and control groups at baseline and at 3 months were completed via two-sample t-tests or Wilcoxon Mann-Whitney U-tests for the continuous variables and via Chi-square tests for the categorical variables, in order to determine that the two groups did not significantly differ from each other, so that their data could be effectively combined for the pre- and post-POD treatment analyses. Comparisons between dental measures and biomarker levels at the beginning and end of each relevant study period (control period, treatment period, and/or delayed follow-up period) were completed via paired t-tests or Wilcoxon signed rank tests.

The alpha value was set at  $p < 0.05$ , and all statistical analyses were performed using SPSS version 22.0 (IBM).

## Results

### Participants

A total of 202 patients with diabetes were screened. The first 24 subjects that initially met inclusion criteria were assigned to the control or treatment group based on the order of their enrollment (odd-numbered enrollees were assigned to the treatment group, and even-numbered enrollees were assigned to the control group). Two subjects met one or more exclusion criteria, so 22 subjects (12 in treatment group and 10 in control group) had periodontal treatment and completed the study.

Mean age and duration of diabetes for our sample were  $58.86 \pm 14.6$  years and  $17.14 \pm 12.6$  years, respectively. Eighteen subjects (81.8%) had type 2 diabetes, 14 (63.6%) were male, 50.0% were former smokers, and the average body mass index (BMI) was  $32.81 \pm 8.7$  kg/m<sup>3</sup> (Table 1).

### Periodontal measures

The results of the pre- and post-POD treatment periodontal measures are summarized in Table 2. Average pre-POD treatment clinical attachment loss was  $2.98 \pm 0.64$  mm, average pre-POD treatment probing depth was  $2.75 \pm 0.61$  mm, and average pre-POD treatment percentage of sites bleeding upon probing was  $39.1 \pm 20.4\%$ . After POD treatment, mean probing depth had decreased by 0.22 mm ( $p = 0.004$ ), mean percentage of sites bleeding upon probing had decreased by 16.7% ( $p < 0.001$ ), and clinical attachment loss had a non-significant decrease of 0.11 mm ( $p = 0.168$ ).

### Biomarker measures

The mean A1C, hs-CRP, TNF- $\alpha$ , CTX and BSAP levels during each study period are detailed in Table 3. While POD treatment was deemed successful, based on the periodontal measures, none of the biomarker measures demonstrated statistically significant changes immediately following POD treatment. A1c declined from  $7.64 \pm 1.08\%$  to  $7.56 \pm 1.30\%$  ( $p = 0.421$ ), TNF declined from  $10.37 \pm 3.45$  pg/ml to  $10.01 \pm 3.95$  pg/ml ( $p = 0.617$ ), CRP declined from  $6.34 \pm 8.92$  mg/L to  $5.52 \pm 6.79$  mg/L ( $p = 0.626$ ), CTX increased from  $85.50 \pm 15.18$  pg/ml to  $90.23 \pm 20.92$  pg/ml ( $p = 0.684$ ) and BSAP increased from  $7.45 \pm 5.05$  pg/ml to  $8.79 \pm 6.55$  pg/ml ( $p = 0.074$ ).

Decreases in A1C, hs-CRP, and TNF- $\alpha$  during the treatment period were observed in 54.5%, 59.1%, and 54.5% of subjects, respectively. Increases in CTX and BSAP were observed in 50.0% and 54.5% of subjects, respectively. However, when the data were stratified by level of doxycycline adherence (>90% vs. <90% adherence), decreases in A1C, hs-CRP, and TNF- $\alpha$  were observed in 70.6% of adherent subjects for all three measures, with those subjects who were >90% doxycycline-adherent being 6.4 times more likely to experience A1C and TNF- $\alpha$  decreases after POD treatment ( $p = 0.021$ ) and 2.8 times more likely to experience a hs-CRP decrease after POD treatment ( $p = 0.133$ ) than subjects who were <90%

adherent with the doxycycline regimen. Similar improvements in the percentage of subjects with increases in CTX and BSAP were not observed when examining only the >90% doxycycline-adherent subjects.

During the “delayed follow-up period” (3 months after completion of active POD treatment), we observed significant reductions in both hs-CRP (4.19 to 2.34 mg/L,  $p=0.028$ ) and TNF- $\alpha$  (10.83 to 5.96 pg/ml,  $p=0.038$ ). The bone turnover markers (CTX and BSAP) displayed non-significant reductions during this delayed follow-up period (92 to 81.43 pg/ml,  $p=0.107$  and 6.91 to 6.51 pg/ml,  $p=0.238$  respectively) (Table 3).

## Discussion

There is an under appreciation of the significant relationship between diabetes and periodontal disease (POD) among medical providers and endocrinologists caring for patients with diabetes<sup>23-26</sup>. Despite a higher prevalence of POD and the known association of POD with increased inflammation in patients with diabetes, there are no specific recommendations for intensive management of POD in patients with diabetes<sup>27,28</sup>. Current evidence suggests that chronic systemic inflammation contributes to the vascular and bone complications of diabetes<sup>310-1315</sup>. However, there is inadequate evidence to demonstrate that treatment for POD results in significant reductions in inflammation and complications from diabetes<sup>29-31</sup>. Demonstrating that effective treatment for POD results in improvement in outcomes of patients with diabetes will be a basis for developing treatment guidelines. In this study, we explored how biomarkers of inflammation and bone turnover in patients with diabetes changed following nonsurgical treatment of POD.

We demonstrated that our approach to the treatment of POD was effective, with reductions in probing depths and bleeding upon probing, both key indices of POD. Following treatment, we observed a trend in improvement in A1C from baseline; however, the observed change in A1C was not significant from baseline. Engebretson et al. compared changes in A1C between two groups of patients with diabetes and POD following treatment in one of the groups. This study was stopped early due to futility. Their treatment for POD had consisted of scaling, root planing, and chlorhexidine oral rinse<sup>22</sup>. In another pilot study, treatment of POD with a sub-antimicrobial dose of doxycycline in conjunction with conventional POD therapy in patients with diabetes resulted in significant reduction in A1C<sup>32</sup>. The significant downward trend in A1C in the patients who were adherent to doxycycline treatment that we observed in this study supports the use of doxycycline as adjunct therapy in the treatment for POD. Similarly, the reduction in inflammatory markers following treatment was not significant from baseline in our patients but was more pronounced among the patients with >90% adherence with doxycycline. Furthermore, the reduction in inflammation seemed to be sustained even after completion of active POD treatment with significant decreases in hs-CRP and TNF- $\alpha$  during the delayed follow-up period. This suggests that the effect of treatment for POD on systemic inflammation may be sustained for several months after treatment is completed. This sustained improvement may be a direct effect of treatment or the consequence of better dental care that was learned during treatment.

Regardless, these observations support the hypothesis that treatment of POD, a chronic inflammatory state, will result in a reduction in systemic inflammation, similar to other published reports<sup>1718</sup>.

Regarding the effects of POD treatment on bone turnover, there were non-significant increases in both the CTX (a marker of bone resorption) and BSAP (a marker of bone formation) in the immediate post-treatment period. However, both biomarkers had nonsignificant declines during the delayed follow-up period (3 months after active POD treatment). Although there were trends to suggest increased bone remodeling immediately after POD treatment, our findings suggest that the effect of POD treatment on the bone turnover markers in this study was limited. However, based on the reduction in the levels of inflammatory markers that we observed and the known impact of chronic inflammation on the bone<sup>613-15</sup>, we suspect that the trend in bone turnover markers that we observed may represent early positive changes on the bone.

### Limitations

Although our sample size was based on a sound power calculation, a study with a larger sample size and longer duration of follow up for POD would be required to determine if the trends seen with this pilot study are significant.

The poor adherence with the doxycycline regimen by some of our patients limited the overall impact of POD treatment. The duration of POD treatment, as well as the small number of subjects who returned for the delayed follow-up visit (n=7), may not have been adequate to appreciate the full impact of POD treatment on our chosen outcome measures.

Our study only looked at changes in biomarker levels, which may not necessarily translate to actual clinical outcomes.

### Conclusions

Treatment of POD in patients with diabetes resulted in non-significant lowering of A1C and inflammatory markers and non-significant increase in bone turnover markers. We observed better treatment effects in patients that were adherent to doxycycline treatment. Given known connection between inflammation and diabetes complications, a larger study with greater attention to patient adherence is required to further explore the trends in biomarkers that we observed following treatment of POD in this study.

### Acknowledgments

This study was funded by NIH/NIGMS grant #1U54GM104944-01.

Some of the findings included in this article were presented in poster format at the American Diabetes Association 75<sup>th</sup> Scientific Sessions, Boston, MA, 5-9 June 2015.

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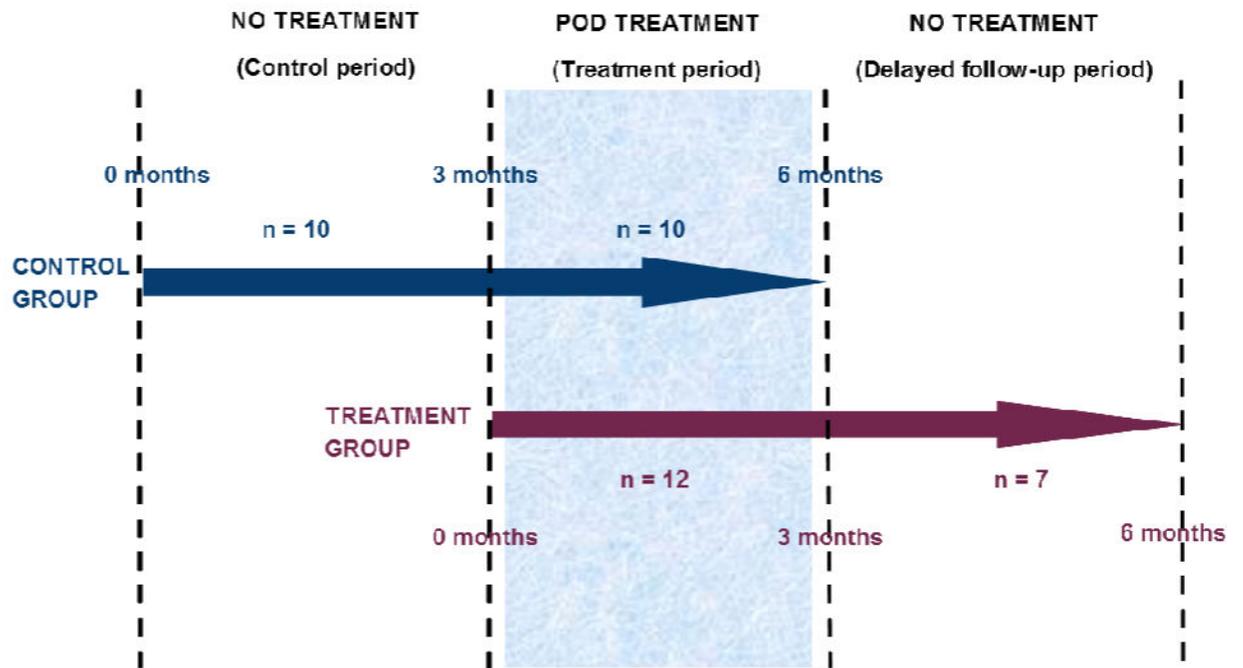
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## Abbreviations

<b>POD</b>	Periodontal disease
<b>A1C</b>	Serum glycohemoglobin A1c
<b>Hs-CRP</b>	Serum high-sensitivity C-reactive protein
<b>TNF- <math>\alpha</math></b>	Serum tumor necrosis factor alpha
<b>CTX</b>	Urinary C-terminal telopeptide
<b>BSAP</b>	Serum bone-specific alkaline phosphatase
<b>BMI</b>	Body mass index



**Figure 1.** Flow diagram of group assignment and collection of outcome measures (dashes). POD = periodontal disease.

**Table 1**  
**Characteristics of 22 study participants**

<b>Demographics</b>	<b>Mean (<math>\pm</math> SD), or frequency (%)</b>
Age, in years	58.86 ( $\pm$ 14.6)
Gender (female)	8 (36.4%)
BMI	32.81 ( $\pm$ 8.7)
Race (Caucasian)	8 (36.4%)
Ethnicity (Hispanic)	9 (40.9%)
<b>Diabetes status</b>	
Diabetes duration, in years	17.14 ( $\pm$ 12.6)
Type 2 diabetes	18(81.8%)
<b>Dental status</b>	
Number of teeth (out of 32)	26.91 ( $\pm$ 3.4)
Last dentist visit, in months	39.00 ( $\pm$ 54.2)
Have dental insurance	8 (36.4%)

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**Table 2**  
**Summary of pre- and post-POD treatment mean dental measures for all 22 study participants**

	Pre-treatment	Post-treatment	p-value
<b>Probing depth</b>	2.75mm	2.53mm	0.004 *
<b>Clinical attachment loss</b>	2.98mm	2.87mm	0.168
<b>Bleeding upon probing</b>	39.08%	22.37%	<0.001 *

\* Significant at  $p < 0.05$

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**Table 3**  
**Summary of mean ( $\pm$  standard deviation) biomarker measures during each study period**

Control period, n=10			
Biomarker	Baseline	3-months	p-value
A1C	7.35% ( $\pm$ 0.67)	7.31% ( $\pm$ 0.80)	0.788
TNF	9.81 pg/ml ( $\pm$ 3.35)	9.08 pg/ml ( $\pm$ 1.75)	0.528
CRP	5.30 mg/L ( $\pm$ 4.85)	4.38 mg/L ( $\pm$ 4.25)	0.575
CTX	88.40 pg/ml ( $\pm$ 21.80)	83.2 pg/ml ( $\pm$ 10.86)	0.959
BSAP	9.29 pg/ml ( $\pm$ 8.21)	9.05 pg/ml ( $\pm$ 7.16)	0.878
Treatment period, n=22			
Biomarker	Pre-treatment	Post-treatment	p-value
A1C	7.64% ( $\pm$ 1.08)	7.56% ( $\pm$ 1.30)	0.421
TNF	10.37 pg/ml ( $\pm$ 3.45)	10.01 pg/ml ( $\pm$ 3.95)	0.617
CRP	6.34 mg/L ( $\pm$ 8.92)	5.52 mg/L ( $\pm$ 6.79)	0.626
CTX	85.50 pg/ml ( $\pm$ 15.18)	90.23 pg/ml ( $\pm$ 20.92)	0.684
BSAP	7.45 pg/ml ( $\pm$ 5.05)	8.79 pg/ml ( $\pm$ 6.55)	0.074
Delayed follow-up period, n=7			
Biomarker	Immediate post-treatment	3-months post-treatment	p-value
A1C	7.53% ( $\pm$ 2.00)	7.16% ( $\pm$ 1.34)	0.307
TNF	10.83 pg/ml ( $\pm$ 4.71)	5.96 pg/ml ( $\pm$ 1.45)	0.038 *
CRP	4.19 mg/L ( $\pm$ 4.20)	2.34 mg/L ( $\pm$ 2.20)	0.028 *
CTX	92.00 pg/ml ( $\pm$ 24.89)	81.43 pg/ml ( $\pm$ 11.73)	0.107
BSAP	6.91 pg/ml ( $\pm$ 2.40)	6.51 pg/ml ( $\pm$ 1.82)	0.238

\* Significant at  $p < 0.05$