

Confidential. Do not distribute. Pre-embargo material.

Original Investigation

The Effect of Nonsurgical Periodontal Therapy on Hemoglobin A_{1c} Levels in Persons With Type 2 Diabetes and Chronic Periodontitis

A Randomized Clinical Trial

Steven P. Engebretson, DMD, MS, MS; Leslie G. Hyman, PhD; Bryan S. Michalowicz, DDS, MS; Elinor R. Schoenfeld, PhD; Marie C. Gelato, MD, PhD; Wei Hou, PhD; Elizabeth R. Seaquist, MD; Michael S. Reddy, DMD, DMSc; Cora E. Lewis, MD, MSPH; Thomas W. Oates, DMD, PhD; Devjit Tripathy, MD; James A. Katancik, DDS, PhD; Philip R. Orlander, MD; David W. Paquette, DMD, MPH, DMSc; Naomi Q. Hanson, MS; Michael Y. Tsai, PhD

IMPORTANCE Chronic periodontitis, a destructive inflammatory disorder of the supporting structures of the teeth, is prevalent in patients with diabetes. Limited evidence suggests that periodontal therapy may improve glycemic control.

OBJECTIVE To determine if nonsurgical periodontal treatment reduces levels of glycated hemoglobin (HbA_{1c}) in persons with type 2 diabetes and moderate to advanced chronic periodontitis.

DESIGN, SETTING, AND PARTICIPANTS The Diabetes and Periodontal Therapy Trial (DPTT), a 6-month, single-masked, multicenter, randomized clinical trial. Participants had type 2 diabetes, were taking stable doses of medications, had HbA_{1c} levels between 7% and less than 9%, and untreated chronic periodontitis. Five hundred fourteen participants were enrolled between November 2009 and March 2012 from diabetes and dental clinics and communities affiliated with 5 academic medical centers.

INTERVENTIONS The treatment group (n = 257) received scaling and root planing plus chlorhexidine oral rinse at baseline and supportive periodontal therapy at 3 and 6 months. The control group (n = 257) received no treatment for 6 months.


MAIN OUTCOMES AND MEASURES Difference in change in HbA_{1c} level from baseline between groups at 6 months. Secondary outcomes included changes in probing pocket depths, clinical attachment loss, bleeding on probing, gingival index, fasting glucose level, and Homeostasis Model Assessment (HOMA2) score.

RESULTS Enrollment was stopped early because of futility. At 6 months, mean HbA_{1c} levels in the periodontal therapy group increased 0.17% (SD, 1.0), compared with 0.11% (SD, 1.0) in the control group, with no significant difference between groups based on a linear regression model adjusting for clinical site (mean difference, -0.05% [95% CI, -0.23% to 0.12%]; *P* = .55). Periodontal measures improved in the treatment group compared with the control group at 6 months, with adjusted between-group differences of 0.28 mm (95% CI, 0.18 to 0.37) for probing depth, 0.25 mm (95% CI, 0.14 to 0.36) for clinical attachment loss, 13.1% (95% CI, 8.1% to 18.1%) for bleeding on probing, and 0.27 (95% CI, 0.17 to 0.37) for gingival index (*P* < .001 for all).

CONCLUSIONS AND RELEVANCE Nonsurgical periodontal therapy did not improve glycemic control in patients with type 2 diabetes and moderate to advanced chronic periodontitis. These findings do not support the use of nonsurgical periodontal treatment in patients with diabetes for the purpose of lowering levels of HbA_{1c}.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00997178

JAMA. 2013;310(23):2523-2532. doi:10.1001/jama.2013.282431

 Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Steven P. Engebretson, DMD, MS, MS, Department of Periodontology and Implant Dentistry, New York University College of Dentistry, 345 E 24th St, 3W, New York, NY 10010 (spe2002@nyu.edu).

Confidential. Do not distribute. Pre-embargo material.

Emerging evidence implicates inflammation in the pathogenesis of type 2 diabetes.^{1,2} Chronic periodontitis, a destructive inflammatory disorder of the soft and hard tissues supporting the teeth,³ is a major cause of tooth loss in adults.⁴ Nearly half of the US population older than 30 years is estimated to have chronic periodontitis, with 38% having moderate or advanced disease.⁵ Individuals with diabetes are at greater risk for incident and prevalent chronic periodontitis and have more severe chronic periodontitis than individuals without diabetes.⁶⁻¹⁰ Well-controlled diabetes is associated with less severe chronic periodontitis and a lower risk for progression of periodontitis,^{8,11,12} suggesting that level of glycemia is an important mediator of the relationship between diabetes and risk of chronic periodontitis. Evidence that chronic periodontitis is in the causal pathway of diabetes, however, is observational, limited, and inconsistent.

Several small interventional studies have suggested that treatment of chronic periodontitis may improve metabolic control of patients with diabetes. A meta-analysis of these clinical trials¹³ found a nonsignificant weighted average decrease of 0.38% (95% CI, -1.5% to 0.7%) in glycated hemoglobin (HbA_{1c}) levels 3 months after periodontal therapy. A subsequent trial by Jones et al¹⁴ involving 165 participants resulted in a 0.65% mean nonsignificant reduction in HbA_{1c} levels 4 months after periodontal therapy, but that study was underpowered.

Therefore, the Diabetes and Periodontal Therapy Trial (DPTT) was designed to determine whether nonsurgical periodontal therapy (scaling and root planing and supportive periodontal therapy), compared with no therapy, reduces HbA_{1c} levels at 6 months in persons with type 2 diabetes and moderate to advanced chronic periodontitis.

Methods

Trial Design and Setting

The DPTT was a single-masked, multicenter, randomized clinical trial that enrolled participants from outpatient medical and dental clinics and communities of 5 academic medical centers in the United States. A more detailed description of the methods and rationale for the DPTT has been published elsewhere.¹⁵ The study protocol was approved by the institutional review boards at each participating center, and all participants provided written informed consent. An independent data and safety monitoring board reviewed the safety data throughout the trial.

Participants

Participants were recruited between November 2009 and March 2012. Men and women 35 years and older were eligible if they had physician-diagnosed type 2 diabetes of more than 3 months' duration, had an HbA_{1c} value between 7.0% and less than 9.0% at screening, had reported no changes in diabetes medications within the last 3 months, were in the care of a physician for their diabetes, agreed to not change diabetes medications during the trial unless

medically indicated, and agreed to avoid pregnancy during the trial. Participants required a diagnosis of moderate to advanced chronic periodontitis, defined as clinical attachment loss and probing depth of at least 5 mm in 2 or more quadrants of the mouth,¹⁶ a minimum of 16 natural teeth, and no periodontal treatment in the prior 6 months. Radiographs were used to confirm a diagnosis of chronic periodontitis. Participants needing treatment of extensive tooth decay, tooth abscesses, or other oral infection, such as teeth needing root canal therapy, were excluded. Additional exclusion criteria included limited life expectancy, diabetes-related emergency within 30 days, use of nonsteroidal anti-inflammatory drugs other than daily low-dose aspirin (75-325 mg), use of immunosuppressive medications, antibiotic use (>7 days within 30 days of enrollment), dialysis, risk of bleeding complications, or heavy alcohol consumption (>3 drinks/d for men and >2 drinks/d for women).

Data Collection

Data were collected by trained and certified study personnel; periodontal examiners were also calibrated before examining participants and annually thereafter.¹⁷ Study personnel recorded medical history, medication use, demographics, and lifestyle information. Race/ethnicity was self-reported using multiple-choice questions according to categories specified by the National Institutes of Health. Participants were allowed to provide options not included in the administered questions. Height, weight, and blood pressure were measured in duplicate. The oral examination included probing depth, clinical attachment loss, and bleeding on probing from 6 locations around each tooth, as well as plaque score and gingival index¹⁸ from 6 index teeth.

Study Procedures

Recruitment occurred during diabetes or dental care visits or by referral from community medical practices or local advertisements. Potential participants were screened for periodontitis and HbA_{1c} level. Eligible individuals were randomized using a permuted-block randomization scheme, stratified by clinical site, with block sizes of 2, 4, or 6.

Laboratory Measures

Fasting venous blood samples were collected prior to periodontal measures or therapy. Fresh whole-blood samples were refrigerated and sent on ice within 4 days to the study's core laboratory (University of Minnesota) for analysis of HbA_{1c} levels by high-performance liquid chromatography (Tosoh HPLC G7 Glycohemoglobin Analyzer, Tosoh Medics Inc). Serum and plasma aliquots were snap frozen and shipped on dry ice for analysis of levels of lipids, creatinine, and fasting glucose by enzymatic methods using a Roche Chemistry Analyzer (Roche Diagnostics Corp) and analysis of insulin levels by sandwich immunoassay using a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corp). Homeostasis Model Assessment (HOMA2) scores were calculated from fasting glucose and insulin values of noninsulin users using the HOMA2 Calculator version 2.2 (available at <http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/>).

Confidential. Do not distribute. Pre-embargo material.

Study Intervention

Initial treatment consisted of at least 160 minutes of scaling and root planing using curettes and ultrasonic instruments with local anesthesia during 2 or more sessions completed within 42 days of the baseline visit.¹⁵ Completeness of therapy was assessed by the study therapist and confirmed by a study periodontist. After treatment, the therapist provided oral hygiene instructions and dispensed chlorhexidine gluconate (0.12% oral rinse, twice daily for 2 weeks), toothbrush, toothpaste, and dental floss. Three and 6 months after the baseline visit, participants in the treatment group received oral hygiene instructions and scaling and root planing for approximately 1 hour during a single session. Participants in the control group received only oral hygiene instructions at the baseline and 3- and 6-month visits. Following their 6-month visit, control group participants were offered scaling and root planing.

Outcome Assessment

The primary study outcome was change in HbA_{1c} levels from baseline to 6 months. Secondary outcomes included change in 3-month HbA_{1c} levels and change in 3- and 6-month fasting glucose levels, HOMA2 scores, and clinical measures of chronic periodontitis. Change in diabetes medications at 3 and 6 months and the need for periodontal rescue therapy and diabetes rescue therapy were evaluated as safety outcomes. A change in medication was defined as more than 2-fold change in dosage for a hyperglycemic drug, more than 10% change in dosage for insulin, or addition or subtraction of an oral hyperglycemic agent or insulin.

Adverse Events and Safety Monitoring

Oral symptoms were recorded 2 weeks following treatment (treatment group) or baseline for the control group. Rescue therapy was administered to any participant who experienced progressive periodontitis.¹⁵ After the trial, participants were referred for follow-up periodontal care or additional treatment as needed.

Masking

Periodontal examiners and laboratory personnel who performed the HbA_{1c} analyses were masked to treatment group assignment.

Statistical Analyses

Sample size was estimated assuming a 0.6% (SD, 2%)¹⁹ or greater reduction in HbA_{1c} level from baseline to 6 months in the treatment group compared with the control group. Based on a 2-tailed, 2-sample *t* test and .05 type I error, a sample size of 468 participants was required to achieve 90% power. Assuming an attrition rate of 20%, the planned sample size was 600 participants (300 in each treatment group).

Baseline characteristics were summarized using means (SDs), medians (interquartile ranges), or both for continuous variables and using frequencies (percentages) for categorical variables. Mean periodontal measures (and changes) were computed as a per-person average and averaged across participants within each treatment group. Between-group baseline comparisons were based on 2-sample *t* tests or Wilcoxon Mann-

Whitney tests for continuous variables and on χ^2 tests for categorical variables.

The primary outcome, change in HbA_{1c} level, was analyzed using the intention-to-treat principle using linear extrapolation with multiple imputation to impute missing 6-month HbA_{1c} values. A sensitivity analysis using different approaches including no imputation, last observation carried forward, and multiple imputation showed similar results for the primary outcome and the treatment effect. The primary efficacy analysis was performed using linear regression models to evaluate 6-month change in HbA_{1c} level (follow-up – baseline) as the dependent variable, with treatment group as the independent factor (between-group difference defined as control – treatment) and clinical site as a covariate. Homogeneity of clinical site was evaluated using the *F* test based on a linear regression model. The secondary efficacy analysis used linear regression models that included selected baseline variables as covariates, eg, HbA_{1c} level, sex, age, race/ethnicity, smoking status, body mass index, use of diabetes medication, and duration of diabetes, to evaluate main effects of covariates; interactions with treatment group were tested using *F* tests.

A per-protocol analysis based on data available both at baseline and the 6-month visit was also performed without imputation. Subgroup analyses were preplanned for sex and race/ethnicity. Additional post hoc subgroup analyses were also conducted. Between-group comparisons in changes of 3-month HbA_{1c} levels and additional secondary outcomes (periodontal measurements [probing depth, clinical attachment loss, bleeding on probing, gingival index, and plaque score], fasting glucose level, fasting insulin level, HOMA2 insulin resistance, and HOMA2 β -cell function), weight, and blood pressure at the 3- and 6-month visits also used linear regression models.

P values less than .05 were adjusted for multiple comparisons using Bonferroni correction. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).

One futility analysis was planned after the first 300 participants completed their 6-month visit. Stopping guidelines were based on a 2-sided, independent *t* test and predetermined conditional power threshold.²⁰

Results

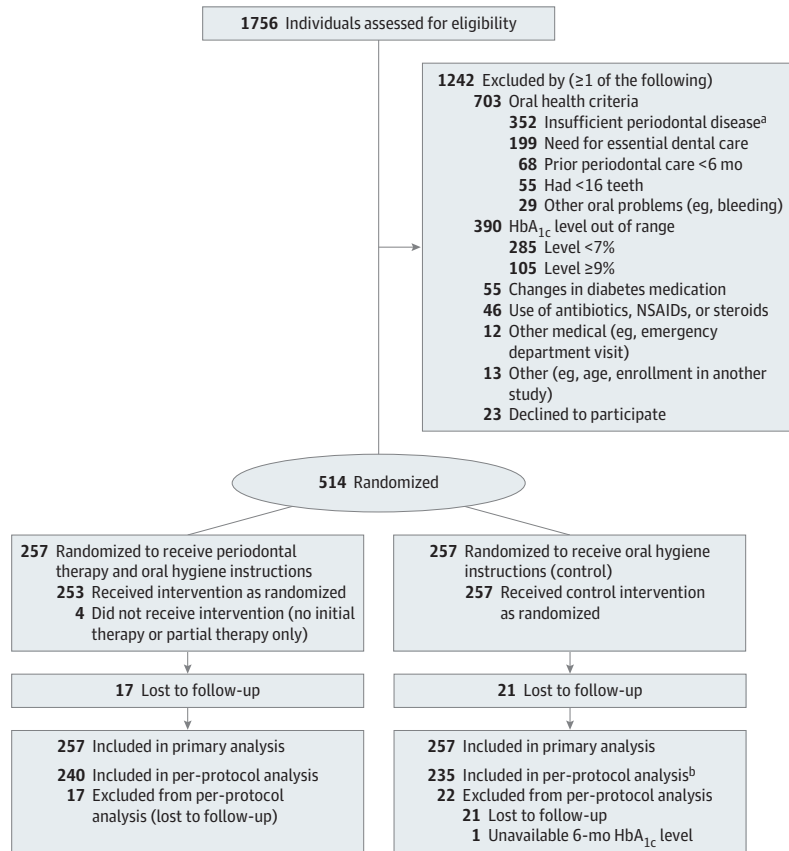
Participants

1756 individuals were screened and 514 were randomized between November 2009 and March 2012 (Figure 1), at which time enrollment was stopped because of futility. The guidelines for terminating DPTT for futility were based on a primary conditional power threshold of 40% and required an observed interim test statistic less than -0.12 . Because the futility analysis *t* test statistic for the primary outcome was -0.37 , the data and safety monitoring board recommended cessation of recruitment and continued follow-up of enrolled participants.

Of the 514 participants randomized, 476 (93%) completed the study, with similar retention in the treatment (240/257) and control (236/257) groups. Baseline characteristics were

Confidential. Do not distribute. Pre-embargo material.

Figure 1. Study Flow



HbA_{1c} indicates glycated hemoglobin; NSAID, nonsteroidal anti-inflammatory drug. ^aDefined as participants needing treatment of extensive tooth decay, tooth abscesses, or other oral infections. ^bFollowing their 6-month visit, participants in the control group were offered scaling and root planing. Two hundred twenty-nine participants received periodontal therapy after the 6-month visit; 7 refused periodontal therapy.

similar between groups and were reflective of individuals with type 2 diabetes and periodontitis (Table 1). Of the 514 randomized participants, 244 (47%) used oral hypoglycemic agents alone, 80 (16%) used insulin alone, and 179 (35%) used both. Only 11 (2%) were not taking diabetes medications.

Primary Outcome

Levels of HbA_{1c} did not change significantly between baseline and the 3-month or 6-month visits in either the treatment or the control group (Figure 2 and Table 2), and the target 6-month reduction of HbA_{1c} level of 0.6% or greater was not achieved. In the intention-to-treat analysis of the primary outcome based on a linear regression model including clinical site as a covariate, change in HbA_{1c} levels at 6 months did not differ significantly between the treatment and control groups (adjusted 6-month treatment effect, -0.05% [95% CI, -0.23% to 0.12%]; *P* = .55). Three-month results were similar. No significant differences in HbA_{1c} levels across centers were found (*P* = .44 [intention to treat] and *P* = .59 [per protocol], based on an F test for homogeneity from the linear regression model).

Secondary Outcomes

Similar to the intention-to-treat analysis, a per-protocol linear regression analysis evaluating change in HbA_{1c} levels also did not reveal between-group differences in HbA_{1c} values at 6

months (adjusted treatment effect, -0.07% [95% CI, -0.26% to 0.13%]); *P* = .50 (Table 2). Results at 3 months were also similar.

Using linear regression models, all periodontal clinical parameters improved significantly at 3 months and were sustained at 6 months in the treatment group but not in the control group (Figure 3 and eTable 2 in Supplement). At 6 months, mean probing depth improved by 0.4 mm (95% CI, 0.4 to 0.5) in the treatment group compared with 0.1 mm (95% CI, 0.1 to 0.2) in the control group (adjusted between-group difference, 0.3 mm [95% CI, 0.2 to 0.4]; Bonferroni-corrected *P* < .001). In the treatment group, mean bleeding with probing decreased by 19.0% (95% CI, 15.7% to 22.4%), compared with 5.9% (95% CI, 2.3% to 9.6%) in the control group (adjusted between-group difference, 13.1% [95% CI, 8.1% to 18.1%]; Bonferroni-corrected *P* < .001). Clinical attachment loss and gingival index measures also improved more in the treatment group compared with the control group (adjusted between-group differences, 0.2 mm [95% CI, 0.1 to 0.4] and 0.3 mm [95% CI, 0.2 to 0.4], respectively; *P* < .001 for both). A post hoc subgroup comparison of treatment groups by response tertiles likewise revealed no significant between-group differences in change in HbA_{1c} levels at any point (eTable 1 in Supplement).

Changes in blood pressure, weight, fasting glucose level, fasting insulin level, HOMA2 sensitivity (%s), and HOMA2 β-cell

Confidential. Do not distribute. Pre-embargo material.

Table 1. Baseline Participant Characteristics

Characteristic	Treatment (n = 257)	Control (n = 257)
Age, mean (SD), y	56.7 (10.5)	57.9 (9.6)
Women, No. (%)	114 (44.4)	123 (47.9)
Race/ethnicity, No. (%)		
African American/black	76 (29.6)	70 (27.2)
White	140 (54.5)	140 (54.5)
Hispanic	81 (31.5)	85 (33.1)
Other (eg, Native American, Asian)	41 (16.0)	47 (18.3)
Smoking history, No. (%)		
Never	129 (50.2)	144 (56.0)
Former	89 (34.6)	86 (33.5)
Current	39 (15.2)	27 (10.5)
Diabetes factors, mean (SD)		
HbA _{1c} , No. (%)		
<7.0	12 (4.7)	10 (3.9)
≥7.0 to <8.0	143 (55.6)	154 (59.9)
≥8.0 to <9.0	93 (36.2)	86 (33.5)
≥9.0 to <10	9 (3.5)	7 (2.7)
Fasting glucose, median (IQR), mg/dL	150 (125-174)	147 (122-172)
Duration of diabetes, mean (SD), y	12.3 (8.2)	11.3 (8.4)
Fasting insulin, excluding insulin use, median (IQR), pmol/L ^a	95 (61-138)	88 (61-133)
HOMA2 insulin sensitivity, excluding insulin use, median (IQR), %S ^{a,b}	50.1 (34.1-77.0)	53.9 (38.0-79.0)
HOMA2 β-cell function, excluding insulin use, median (IQR), %β ^{a,b}	55.5 (34.1-76.2)	52.0 (36.7-76.0)
Hypoglycemic medications, No. (%)		
No diabetes medications	7 (3)	4 (2)
Oral agents only	117 (46)	127 (49)
Insulin only	40 (16)	40 (16)
Combination of medications	93 (37)	86 (33)
Anthropometrics, mean (SD)		
Weight, kg	99.5 (24.3)	97.5 (21.7)
BMI ^c	34.7 (7.5)	34.2 (6.7)
Blood pressure, mean (SD), mm Hg ^d		
Systolic	133.1 (20.7)	135.1 (20.4)
Diastolic	78.8 (12.3)	78.8 (10.9)
Cardiovascular disease factors		
Lipids, excluding statin use, median (IQR), mg/dL ^e		
Total cholesterol	189 (162-211)	185 (161-212)
LDL-C	113 (92-135)	108 (94-130)
HDL-C	46 (38-53)	41 (37-48)
Triglycerides ^d	117 (89-169)	126 (93-231)
Creatinine, median (IQR), mg/dL	0.81 (0.68-1.0)	0.81 (0.67-0.98)
Periodontal measurements, mean (SD) ^f		
No. of teeth, count/person	25.4 (3.7)	24.7 (3.6)
Probing depth, mm	3.3 (0.6)	3.3 (0.7)
Mean sites/person, by probing depth category		
≥4	51.3 (27.3)	49.2 (27.5)
≥5	28.9 (21.6)	28.0 (22.3)
≥7	3.5 (6.3)	3.5 (8.2)
% sites/person, by probing depth category		
≥4	33.8 (17.6)	33.6 (18.7)
≥5	19.0 (14.2)	19.3 (15.6)
≥7	2.3 (4.2)	2.5 (6.1)

(continued)

Confidential. Do not distribute. Pre-embargo material.

Table 1. Baseline Participant Characteristics (continued)

Characteristic	Treatment (n = 257)	Control (n = 257)
Clinical attachment loss, mm	3.5 (0.8)	3.5 (0.9)
Mean sites/person, by clinical attachment loss category		
≥4	60.1 (30.7)	57.5 (30.7)
≥5	35.9 (25.9)	33.6 (26.0)
≥7	6.6 (9.7)	6.9 (11.9)
% sites/person, by clinical attachment loss category		
≥4	40.3 (21.1)	39.5 (21.3)
≥5	24.3 (18.2)	23.4 (18.6)
≥7	4.7 (7.3)	5.0 (9.2)
Bleeding on probing, % sites/person	61.2 (24.1)	59.6 (26.0)
Gingival index, mean sites/person	1.4 (0.4)	1.4 (0.4)
Plaque score, % sites/person	86.7 (17.9)	84.5 (20.8)
Self-reported overall health, No. (%)		
Excellent-very good	50 (19.5)	59 (23.0)
Good	123 (47.9)	138 (53.7)
Fair-poor	84 (32.6)	60 (23.3)
Other medical history, No. (%)		
Angina	21 (8.2)	11 (4.3)
Myocardial infarction	22 (8.6)	21 (8.2)
Stroke	12 (4.7)	12 (4.7)
Hypertension	180 (70.0)	184 (71.6)
Kidney disease	14 (5.4)	12 (4.7)
Other medication use, No. (%)		
Blood pressure	202 (78.6)	210 (81.7)
Cholesterol	172 (66.9)	170 (66.1)

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA2, Homeostasis Model Assessment; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; creatinine levels to μmol/L, multiply by 88.4.

^a Limited to noninsulin users: n = 133 in treatment group, n = 138 in control group.

^b Calculated using the HOMA2 calculator version 2.2 (available at <http://www.dtu.ox.ac.uk/homacalculator/index.php>).

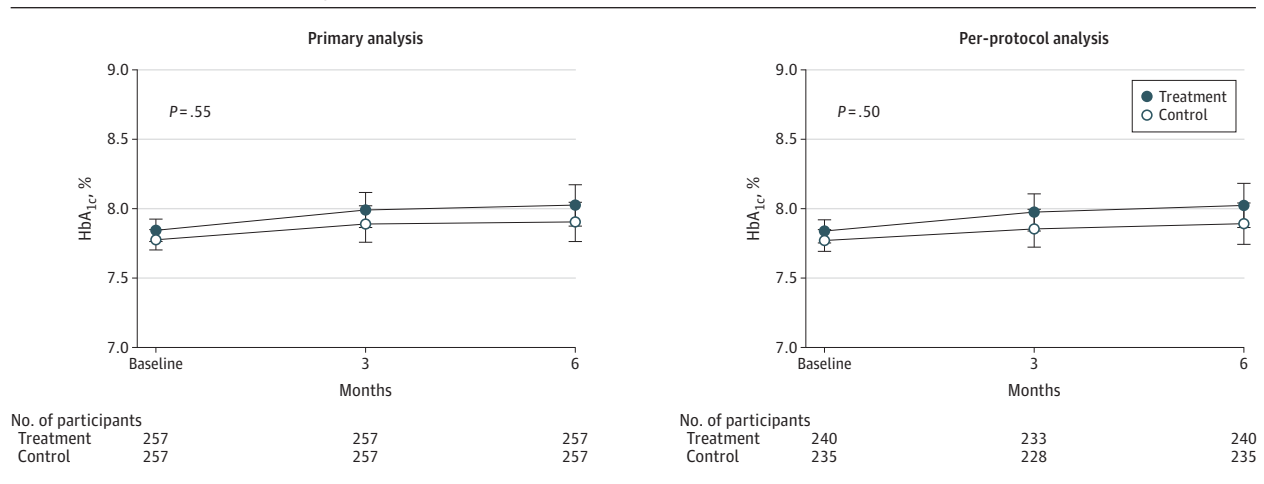
^c Calculated as weight in kilograms divided by height in meters squared.

^d Includes blood pressure measurements for all participants independent of reported blood pressure medication use.

^e Nonstatin users: n = 85 in treatment group, n = 87 in control group.

^f Each periodontal measurement was evaluated on 6 sites of each tooth. A participant-based summary measurement was determined by first calculating an average of the 6 sites per tooth and then calculating an average for all teeth assessed for that participant.

Figure 2. Glycated Hemoglobin (HbA_{1c}) Levels at Baseline and Follow-up



Error bars indicate ±2 SEs. P values comparing 6-month change in HbA_{1c} levels between the 2 treatment groups were based on t tests from linear regression

models, with 6-month change in HbA_{1c} level as a dependent variable and treatment group and clinical site as covariates.

function (%β) are summarized in eTable 3 in Supplement. All of these measurements remained stable during follow-up, with no significant differences between groups. Of the 462 participants with medication data available at all study visits, 128 of 233 (55%) in the treatment group and 137 of 229 (60%) in the control group had no protocol-defined changes in diabetes medications during the study.

Safety

The DPTT was a low-risk study, and no study-related serious adverse events occurred. Two weeks after completion of treatment or baseline, the treatment group experienced more soreness, tenderness, or pain than the controls (102/254 [40.2%] and 72/257 [28.1%], respectively; P = .004 by χ² test), and more thermal sensitivity (81/254 [31.9%] vs 47/257 [18.3%], respec-

Confidential. Do not distribute. Pre-embargo material.

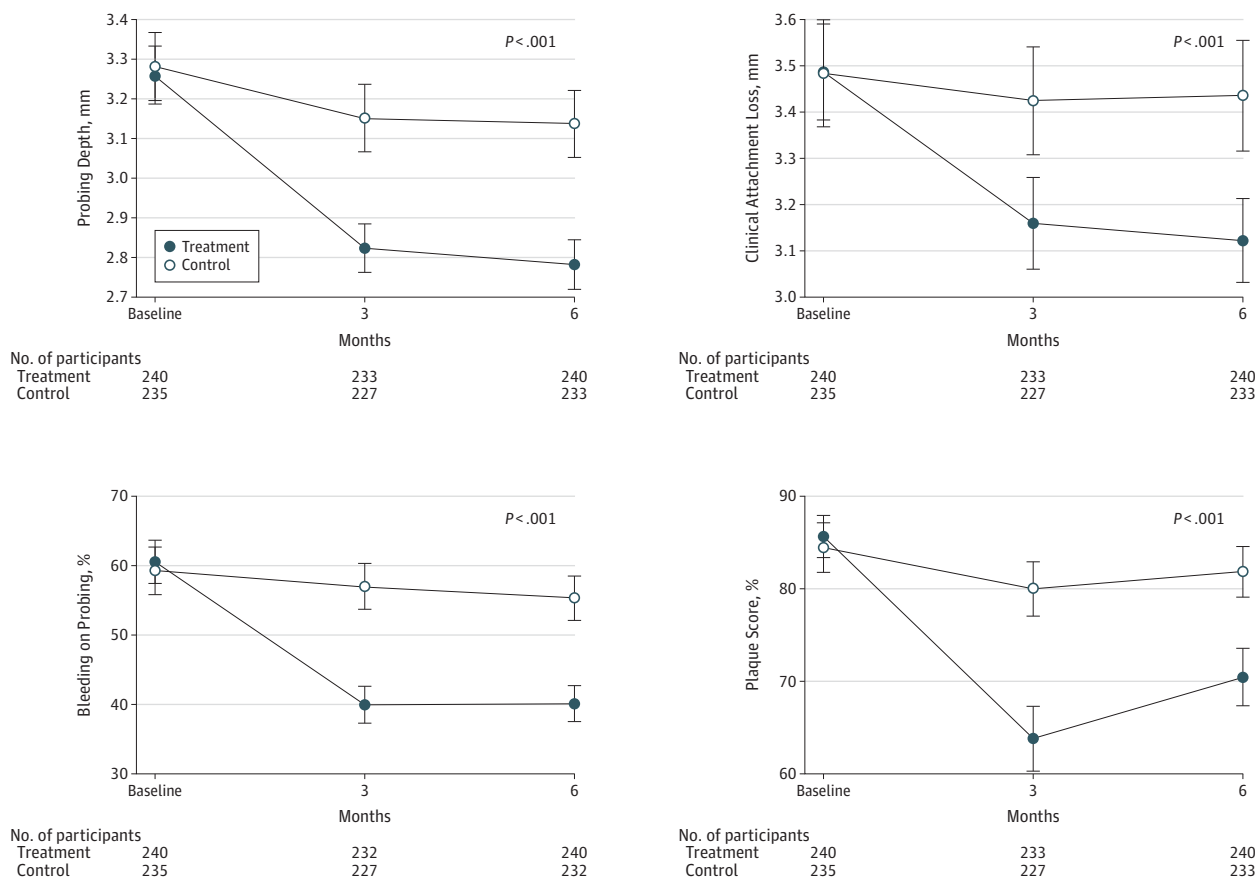
Table 2. Three-Month and 6-Month Change in Glycated Hemoglobin (HbA_{1c}) Levels by Treatment Group

Analysis	Baseline, Mean (SD)		Mean Change (95% CI) ^a					
	Treatment	Control	3 Months		P Value	6 Months		P Value
			Treatment	Control		Treatment	Control	
Intent to treat	n = 257	n = 257	n = 257	n = 257		n = 257	n = 257	
HbA _{1c} , %	7.84 (0.65)	7.78 (0.60)	0.14 (0.02 to 0.27)	0.11 (-0.02 to 0.24)	.64	0.15 (-0.01 to 0.30)	0.09 (-0.06 to 0.25)	.55
Per protocol ^b	n = 240	n = 235	n = 233	n = 228		n = 240	n = 235	
HbA _{1c} , %	7.84 (0.65)	7.77 (0.60)	0.13 (-0.01 to 0.26)	0.08 (-0.05 to 0.22)	.57	0.15 (-0.02 to 0.32)	0.09 (-0.09 to 0.26)	.50

^a Change calculated as 3-month (or 6-month) values minus baseline. Mean changes and 95% CIs were determined from linear regression models with 3-month and 6-month changes in HbA_{1c} levels included as dependent variables, treatment group as an independent factor, and the clinical site as a covariate; P values were based on t tests comparing mean changes between the 2 groups.

^b Analyses were based on all participants with HbA_{1c} data at the 6-month visit (n = 240 in the treatment group, n = 235 in the control group). Six participants in the treatment group and 7 in the control group missed their 3-month visit. HbA_{1c} data were not available for 1 additional treatment group participant at 3 months.

Figure 3. Periodontal Measurements at Baseline and Follow-up (Per-Protocol Analysis)



Error bars indicate ±2 SEs. P values comparing 6-month changes in periodontal outcomes between the 2 treatment groups were based on t tests from linear

regression models, with 6-month periodontal change as a dependent variable and treatment group and clinical site as covariates.

tively; P < .001 by χ^2 test). These symptoms are commonly reported following scaling and root planing.¹⁴ Few participants (4/241 in the treatment group and 5/236 in the control group) required generalized periodontal rescue therapy during the study.

Discussion

The DPTT is to our knowledge the largest multicenter randomized clinical trial to investigate the effect of periodontal therapy

Confidential. Do not distribute. Pre-embargo material.

on measures of glycemic control in patients with type 2 diabetes and chronic periodontitis. Despite its effectiveness in improving clinical measures of periodontitis, periodontal therapy did not significantly change HbA_{1c} levels after 3 or 6 months in the treatment group, and no differences in changes in HbA_{1c} levels were observed between the treatment and control groups. Findings were similar in the intention-to-treat and the per-protocol analyses. Likewise, periodontal therapy had no significant effect on fasting glucose levels or HOMA2 scores. Current treatment guidelines^{21,22} do not include periodontal therapy as a means of achieving glycemic control, and the results of our study support those treatment guidelines. However, although not specifically evaluated in our study, periodontal therapy may be considered in patients with diabetes for reasons other than glycemic control, such as for benefits to tooth retention and masticatory function.

These results are in contrast to recently published meta-analyses that showed a modest (−0.36% [95% CI, −0.54% to −0.19%]) but significant reduction in HbA_{1c} levels following periodontal therapy.²³ A number of features of the present study may account for these differences. First, all previous trials were small, whereas the DPTT had greater than 90% power to detect a clinically meaningful 0.6% between-group difference in change of HbA_{1c} level from baseline, even with early cessation of trial enrollment. Second, our trial enrolled participants who were under the care of a physician for their diabetes and who were within a range of HbA_{1c} values that would be less likely to trigger a change in medications during the study period. The DPTT enrollment criteria excluded individuals who had experienced a recent change in hypoglycemic medications, and we monitored changes of hypoglycemic medication and insulin during the study period. Changes in diabetes medications during the DPTT were similar between treatment groups and may in part account for the absence of differences in HbA_{1c} outcome. This aspect of the DPTT study design was critical, because medications may have profound short-term influence on HbA_{1c} levels and have not been adequately documented in previous studies. Third, meta-analyses of small trials have been reported to be subject to high false-positive rates.^{24–26} Fourth, it is possible that periodontal inflammation and infection do not influence glycemic control. Indeed, the results of this trial indicate that glycemic control worsened, although not significantly, 6 months after study therapy.

The largest previous trial of periodontal treatment and glycemic control (n = 157) reported a statistically significant 0.36% reduction in HbA_{1c} levels in the treatment group compared with the control group after 3 months.²⁷ Another study including 132 male Veterans Administration participants¹⁴ failed to demonstrate a positive effect on glycemic control. The results of the DPTT are consistent with those from the latter study.

Possible limitations of the DPTT study should be considered. Our periodontal treatment did not include systemic or topical antibiotics, and no participants were treated surgically because of the difficulties of standardizing a surgical protocol. Systemic antibiotics were not used so as not to confound the effects of the study intervention. However, a recent study that administered systemic antibiotics in addition to scaling and root planing in patients with the metabolic syndrome likewise did not achieve an improvement in glycemic control.²⁸ Although probing depths and clinical attachment levels were significantly improved in the treatment group, improvements in plaque and bleeding scores were only modest and indicate that changing oral hygiene habits remains a challenge. A subgroup comparison by tertiles of response, however, did not reveal differences in HbA_{1c} levels even among participants with the largest improvements in periodontal parameters. Because DPTT participants were enrolled with HbA_{1c} levels between 7% and less than 9%, we cannot rule out the possibility that individuals with values outside of this range might experience HbA_{1c} reduction following periodontal treatment.

The DPTT does, however, have a number of strengths. The sample size was sufficient to ensure adequate statistical power to detect a meaningful clinical difference in HbA_{1c} level. The study population was geographically and ethnically diverse, increasing generalizability of the results. A thorough screening and enrollment process ensured that participants met eligibility criteria and retention was high, with 93% of participants completing the trial. Changes in diabetes medications were monitored during follow-up. Periodontal treatment was conducted under supervision, averaging 190 minutes of treatment per individual, and resulted in a positive effect on clinical measures of periodontitis among participants in the treatment group. The magnitude of clinical change achieved was consistent with results from other multicenter trials of nonsurgical therapy in populations without diabetes.^{29,30} The DPTT core laboratory responsible for the centralized analysis of blood samples is a reference laboratory for the analysis of HbA_{1c} values in North America.³¹

Conclusions

This multicenter randomized clinical trial of nonsurgical periodontal treatment for participants with type 2 diabetes and chronic periodontitis did not demonstrate a benefit for measures of glycemic control. Although periodontal treatment improved clinical measures of chronic periodontitis in patients with diabetes, the findings do not support the use of nonsurgical periodontal treatment for the purpose of lowering levels of HbA_{1c}.

ARTICLE INFORMATION

Author Affiliations: Department of Periodontology and Implant Dentistry, New York University, New York, New York (Engelbreton); Department of Developmental and Surgical Sciences, University of Minnesota, Minneapolis (Michalowicz);

Department of Medicine, University of Minnesota, Minneapolis (Seaquist); Department of Periodontology, University of Alabama at Birmingham (Reddy); Department of Medicine, University of Alabama at Birmingham (Lewis); School of Dentistry, University of Texas at San

Antonio (Oates); Department of Medicine, University of Texas—San Antonio Health Science Center (Tripathy); Department of Periodontics, University of Texas at Houston (Katancik); Department of Internal Medicine, University of Texas—Houston Health Science Center (Orlander);

Confidential. Do not distribute. Pre-embargo material.

Department of Endocrinology, University of Texas—Houston Health Science Center (Orlander); Department of Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, New York (Hyman, Schoenfeld, Gelato, Hou); Stony Brook University School of Dental Medicine, Stony Brook, New York (Paquette); Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis (Hanson, Tsai).

Author Contributions: Drs Engebretson and Hyman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Engebretson, Hyman, Michalowicz, Schoenfeld, Seaquist, Oates.

Acquisition of data: Engebretson, Michalowicz, Schoenfeld, Gelato, Seaquist, Reddy, Lewis, Oates, Tripathy, Orlander, Paquette, Hanson, Tsai.

Analysis and interpretation of data: Engebretson, Hyman, Michalowicz, Schoenfeld, Gelato, Hou, Seaquist, Reddy, Oates, Katancik, Orlander.

Drafting of the manuscript: Engebretson, Hyman, Michalowicz, Schoenfeld, Gelato.

Critical revision of the manuscript for important intellectual content: Engebretson, Hyman, Michalowicz, Schoenfeld, Hou, Seaquist, Reddy, Lewis, Oates, Tripathy, Katancik, Orlander, Paquette, Hanson, Tsai.

Statistical analysis: Hyman, Schoenfeld, Hou.

Obtained funding: Engebretson, Hyman, Michalowicz, Schoenfeld, Oates, Katancik.

Administrative, technical, or material support: Engebretson, Hyman, Michalowicz, Schoenfeld, Gelato, Seaquist, Lewis, Oates, Tripathy, Katancik, Orlander.

Study supervision: Engebretson, Hyman, Michalowicz, Schoenfeld, Gelato, Seaquist, Reddy, Oates, Katancik, Paquette.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gelato reported receiving travel/meeting expenses from the Endocrine Society. Dr Seaquist reported serving as a board member and President Elect of Science and Medicine for the American Diabetes Association; serving as a consultant for AMG Medical, sanofi-aventis, SkyePharma, and Merck; receiving grants or grants pending from the American Diabetes Association, Eli Lilly, and the National Institutes of Health; and receiving payment for lectures from the Japan Diabetes Society, the American Diabetes Association, Intellyst Medical Education, Pediatric Academic Societies, the Association of Specialty Professors, and the International Society for Neurochemistry. Dr Lewis reported receiving a grant or grant pending from Novo Nordisk. Dr Katancik reported serving as a consultant for the Texas Healthy Baby Initiative 2011 and receiving a grant or grant pending, and travel/meeting expenses, from Zimmer Dental. Dr Paquette reported serving as a board member for Colgate-Palmolive; receiving a speakers honorarium from Colgate-Palmolive; and serving as a consultant for MIS Implant Technologies.

Funding/Support: The DPTT study was funded through cooperative agreements grants U01 DE018902 (Dr Engebretson) and U01 DE018886 (Dr Hyman) from the National Institute of Dental and Craniofacial Research, National Institutes of Health.

Role of the Sponsor: The National Institutes of Health had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

DPTT Study Group: Stony Brook University: Steven Engebretson, DMD, MS, MS (study chair); Marie Gelato, MD (diabetes consultant); Baljit Moonga, PhD (assistant to study chair [7/2008-3/2010]); Ruth Tenzler, RN, BSN, CCRC (assistant to study chair [4/2010-present]). **Coordinating Center:** Stony Brook University Medical Center: Leslie Hyman, PhD (principal investigator [PI]); Elinor Schoenfeld, PhD (co-PI); Li Ming Dong, PhD, (lead biostatistician [7/2009-6/2010]); Melissa Fazzari, PhD (lead biostatistician [5/2011-5/2012]); Wei Hou, PhD (lead biostatistician [11/2012-present]); Gail Lerner, MS (data analyst [1/2010-1/2013]); Hao Chen, PhD candidate (student data analysis [1/2012-present]); Soyoun Lee, PhD candidate (student data analysis [11/2012-present]); Colette Knuth, PhD (study coordinator [3/2009-8/2010]); Jayme Mendelsohn, MA (data entry [9/2009-12/2010]); Gabriel Pietrzak, MPH (study coordinator [12/2010-11/2011]); Catherine Hytner, BA (assistant study coordinator [5/2011-1/2013]); Lisa Snelling, BA (assistant study coordinator [8/2011-5/2013]); Sakeena Ahmed (data entry [1/2009-8/2010]); Maria Rodriguez (data entry [7/2008-12/2012]); Michael Merin (data entry [9/2010-4/2011]); Joanna Merin (data entry [3/2011-6/2012]); Leanne Merrill, MA (data entry [11/2011-6/2013]); Lydia Seib, AAS (administrative assistant [8/2008-present]). **Clinical Centers:** *University of Alabama at Birmingham:* Michael Reddy, DMD, DMSc (PI); Cora Lewis, MD, MSPH (diabetologist); Nicolaas Geurs, DDS, MS (masked periodontal examiner); Phillip Vassilopoulos, DDS (backup masked examiner); Adrian Abrahams, DMD (study therapist [8/2009-6/2011]); Jennifer Doobrow, DMD (study therapist [8/2009-7/2010]); Maria Geisinger, DDS, MS (study therapist and phlebotmist); Simha Kukunooru (study therapist [8/2009-7/2010]); Curry Leavitt, DMD (study therapist [8/2009-7/2010]); Juan Pardo, DDS (study therapist [8/2009-6/2011]); Ramzi Abou Arraj, DDS (study therapist); Anoth Reganato (study therapist [8/2009-7/2010]); Kristi Simmons, DMD (study therapist [8/2009-6/2011]); Erik Unger, DDS (study therapist [8/2009-6/2011]); Jennifer Bain, DMD (study therapist); Kathleen Beaudry, DMD (study therapist [10/2009-8/2012]); Michael Nguyen, DDS (study therapist [2/2010-6/2012]); Ruben Saucedo, DDS (study therapist [11/2010-6/2012]); Jared Bauerle, DMD (study therapist [3/2011-present]); Michael Madigan, DMD (study therapist [3/2011-6/2013]); Thanos Ntounis, DDS (periodontal resident [3/2011-6/2013]); Maninder Kaur, BDS, MS (clinical research assistant [5/2011-6/2013]); Alvin Stevens, DMD (study therapist [7/2011-present]); Susanna Goggin, DMD (study therapist [10/2011-present]); Lillie Pitman, DMD (study therapist [10/2011-present]); Kyle Trammel, DMD (study therapist [10/2011-6/2013]); C. Peterson (study therapist [1/2012-present]); Sandra Haigh, BS, MS (study coordinator); Javetta Jackson (study/clinic coordinator [8/2009-4/2011]); Erin Finch, BSN (study coordinator/administrator [10/2011-4/2012]); Sheila Akers (assistant clinical coordinator); Vivian Stoyanova Grant (study/clinic coordinator [3/2011-5/2012]); Sushma Acharya,

BDS (assistant clinical coordinator [4/2011-8/2011]); Stephanie McLean, MS (study coordinator [10/2011-present]); Janet Turman, BS (recruiter); Jackie Roche (recruiter [2/2010-3/2012]); Charlotte Bragg, BA, MS, RD (recruiter [8/2009-10/2010]); Rupa Rajanna, BDS (assistant clinic coordinator [8/2009-8/2010]); Elizabeth Bolton (administrative assistant). *University of Minnesota/Hennepin County Medical Center (HCMC):* Bryan Michalowicz, DDS (PI); Anthony DiAngelis, DMD, MPH (PI-HCMC); Elizabeth Seaquist, MD (diabetologist PI); Judy Danielson, RDH (masked periodontal examiner); Pat Lenton, RDH, BS, MA (recruiter/retention backup study therapist); Larry Wolff, DSS, PhD (backup examiner [2/2010-present]); Pamela Thibado, RDH (treatment/recruiter 2/2010-9/2012); Satya Molletti (dentist/therapist [4/2010-11/2012]); Leslie Long-Simpson (study coordinator); Yolanda Okorocho, LPN (study recruiter/clinic coordinator/blood draw); Brian Hadfield (assistant clinical coordinator/blood draw/processing); Lindsay Bartels (recruiter [5/2010-5/2012]); Carol Dunn (dental assistant); Kelly Meyer, RDH (treatment/recruitment [10/2009-6/2010]); Kristina Reibel, RDH (recruiter [10/2009-5/2010]); Andi Jordan, RDH (recruiter [5/2010-12/2010]); R. Hedge (6/2010-5/2011); Ophelia Herrera (interpreter/interviewer [8/2010-2/2011]); E. Romero (2/2011-3/2011); Suban Mohamed (recruiter [7/2011-11/2012]); Cyndee Stull, BS (recruiter [10/2011-12/2011]). *University of Texas Health Science Center at San Antonio:* Thomas Oates, DMD, PhD (PI); Devjit Tripathy, MD (diabetologist); Peggy Alexander, DDS (masked examiner); David Lasho; DDSM, MSD (masked periodontal examiner); H. Gregory (10/2010-12/2010); Guy Huynh-Ba, DMD (therapist [9/2010-4/2013]); Jo Ann Jordan, RDH (study coordinator); Sandra Pena (3/2010-4/2013); Cassandra Pacheco-Vera, DA (research assistant [8/2011-4/2013]); Ashley Munoz (dental assistant, blood processing and shipping [1/2010-5/2011]). *Stony Brook University (site became active 9/2010):* David Paquette, DMD, MPH, DMSc (PI [10/2011-present]); Steven Engebretson, DMD, MS, MS (PI [9/2010-10/2011]); Marie Gelato, MD (diabetes consultant); Chindanout (Tok) Sayasith, RDH, BSDH (masked periodontal examiner); Ying Gu, DDS (backup masked examiner [2/2011-12/2012]); Anita Roth, RDH, BSDH (study therapist/recruiter); Alice Urbankova, DDS, MUDr (study therapist); Maria Ryan, DDS, PhD (study therapist/recruiter [10/2011-12/2012]); Janet Tuthill, RDH, MA (study therapist [12/2011-12/2012]); Jill Hughes, DC, BS (study coordinator); Suman Grewal, PhD (blood processing and measurement/data recording); Ruth Tenzler, RN, BSN, CCRC (backup study/clinical coordinator/study phlebotomist); Bahar Houshmand, DDS, MS (blood processing and measurement/data recording [10/2011-6/2012]); Vincent Iacono, DMD (periodontal consultant [4/2011-12/2012]). *University of Texas Health Science Center at Houston (site became active 8/2011):* James Katancik, DDS, PhD (PI [8/2011-6/2012]); Bing-Yan Wang, DDS, MS, PhD (PI [8/2012-4/2013]); Phillip Orlander, MD (diabetes investigator); Sridhar Eswaran, BDS, MS (masked periodontal examiner); Kavitha Parthasarathy, BDS, MS (masked periodontal examiner); Robin Weltman, DDS, MS (masked examiner); Meggan Wehmeyer, DDS (study therapist); Ali Arastu, DMD (3/2012-4/2013); Rosemary Thomas, DMD

Confidential. Do not distribute. Pre-embargo material.

(3/2012-4/2013); Janelle Headley, RN (study/clinic coordinator); Adriana Cavender, BA/Registered Dental Assistant (study/clinic coordinator); Nathaniel J. Harrison, BSN (recruiter); T. Dancsak (12/2011-4/2013); Matt Galpin (Medical Assistant through the military [4/2012-4/2013]); Monika Ruscheinsky, MS, CPhT (study/clinic coordinator [4/2012-4/2013]). *University of Minnesota Core Laboratory*: Michael Tsai, PhD (PI); Naomi Hanson, MS, CLS, (NCA), MT (ASCP) (laboratory coordinator/technical supervisor); Maren Nowicki, CLS (technical supervisor); Van H. Le, CLS (clinical laboratory scientist). **Executive Committee**: Steven Engebretson, DMD, MS, MS (chair); Leslie Hyman, PhD; MarieGelato, MD; Bryan Michalowicz, DDS; Holli Hamilton, MD, MPH (ex officio); Jane Atkinson, DDS (ex officio). **Steering Committee**: Steven Engebretson, DMD (chair); Leslie Hyman, PhD; Marie Gelato, MD; Bryan Michalowicz, DDS; Holli Hamilton, MD (ex officio); Jane Atkinson, DDS (ex officio); Elinor Schoenfeld, PhD; Li Ming Dong, PhD; Melissa Fazzari, PhD; Wei Hou, PhD; Elizabeth Seaquist, MD; Michael Reddy, DMD, DMSc; Cora Lewis; Thomas Oates; Devjit Tripathy, MD; James Katanick, DDS, PhD; Bing-Yan Wang, DDS, MS, PhD; Phillip Orlander, MD.

Additional Contributions: We wish to acknowledge the contributions of the following individuals to the DPTT study: *Data and Safety Monitoring Board*: John C. Gunsolley, DDS, MS, Virginia Commonwealth University School of Dentistry(chair); Vivian A. Fonseca, MD, FRCP, Tulane University Health Sciences Center; Judith A. Jones, DDS, MPH, DScD, Boston University Henry M. Goldman School of Dental Medicine; Daniel F. Heitjan, PhD, University of Pennsylvania, Perelman School Of Medicine; James B. Meigs, MD, MPH, Harvard Medical School; Jane C. Atkinson, DDS, National Institute of Dental and Craniofacial Research (ex officio); and Holli Hamilton, MD, MPH, National Institute of Dental and Craniofacial Research/NIH (ex officio). Members of the data and safety monitoring board, except ex officio members, were compensated for their participation.

REFERENCES

- Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE. The effects of salsalate on glycemic control in patients with type 2 diabetes. *Ann Intern Med*. 2010;152(6):346-357.
- Goldfine AB, Fonseca V, Shoelson SE. Therapeutic approaches to target inflammation in type 2 diabetes. *Clin Chem*. 2011;57(2):162-167.
- Page RC, Engel LD, Narayanan AS, Clagett JA. Chronic inflammatory gingival and periodontal disease. *JAMA*. 1978;240(6):545-550.
- Hirschfeld L, Wasserman B. A long-term survey of tooth loss in 600 treated periodontal patients. *J Periodontol*. 1978;49(5):225-237.
- Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *J Dent Res*. 2012;91(10):914-920.
- Soskolne WA, Klinger A. The relationship between periodontal diseases and diabetes: an overview. *Ann Periodontol*. 2001;6(1):91-98.
- Taylor GW, Loesche WJ, Terpenning MS. Impact of oral diseases on systemic health in the elderly: diabetes mellitus and aspiration pneumonia. *J Public Health Dent*. 2000;60(4):313-320.
- Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. *Community Dent Oral Epidemiol*. 2002;30(3):182-192.
- Löe H. Periodontal disease: the sixth complication of diabetes mellitus. *Diabetes Care*. 1993;16(1):329-334.
- Tervonen T, Oliver RC. Long-term control of diabetes mellitus and periodontitis. *J Clin Periodontol*. 1993;20(6):431-435.
- Tervonen T, Knuutila M. Relation of diabetes control to periodontal pocketing and alveolar bone level. *Oral Surg Oral Med Oral Pathol*. 1986;61(4):346-349.
- Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. *J Am Dent Assoc*. 1993;124(12):71-76.
- Janket SJ, Wightman A, Baird AE, Van Dyke TE, Jones JA. Does periodontal treatment improve glycemic control in diabetic patients?. *J Dent Res*. 2005;84(12):1154-1159.
- Jones JA, Miller DR, Wehler CJ, et al. Does periodontal care improve glycemic control? the Department of Veterans Affairs Dental Diabetes Study. *J Clin Periodontol*. 2007;34(1):46-52.
- Engebretson S, Gelato M, Hyman L, Michalowicz BS, Schoenfeld E; DPTT Study Group. Design features of the Diabetes and Periodontal Therapy Trial (DPTT): a multicenter randomized single-masked clinical trial testing the effect of nonsurgical periodontal therapy on glycosylated hemoglobin (HbA_{1c}) levels in subjects with type 2 diabetes and chronic periodontitis. *Contemp Clin Trials*. 2013;36(2):515-526.
- Armitage GC; Research, Science and Therapy Committee of the American Academy of Periodontology. Diagnosis of periodontal diseases. *J Periodontol*. 2003;74(8):1237-1247.
- Lenton PA. *Examiner Guide to Measuring Periodontal Parameters and Indices*. Vol 1. Minneapolis: University of Minnesota Press; 1998.
- Löe H. The gingival index, the plaque index and the retention index systems. *J Periodontol*. 1967;38(6)(suppl):610-616.
- Engebretson SP, Hey-Hadavi J. Sub-antimicrobial doxycycline for periodontitis reduces hemoglobin A_{1c} in subjects with type 2 diabetes. *Pharmacol Res*. 2011;64(6):624-629.
- Lan KK, Wittes J. The B-value: a tool for monitoring data. *Biometrics*. 1988;44(2):579-585.
- American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36(suppl 1):S11-S66.
- Mealey BL, Oates TW; American Academy of Periodontology. Diabetes mellitus and periodontal diseases. *J Periodontol*. 2006;77(8):1289-1303.
- Engebretson S, Kocher T. Evidence that periodontal treatment improves diabetes outcomes. *J Periodontol*. 2013;84(4)(suppl):S153-S169.
- Ioannidis JP. Why most published research findings are false. *PLoS Med*. 2005;2(8):e124.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
- Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
- Sun WL, Chen LL, Zhang SZ, Wu YM, Ren YZ, Qin GM. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. *Intern Med*. 2011;50(15):1569-1574.
- López NJ, Quintero A, Casanova PA, et al. Effects of periodontal therapy on systemic markers of inflammation in patients with metabolic syndrome. *J Periodontol*. 2012;83(3):267-278.
- Caton JG, Ciancio SG, Blieden TM, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol*. 2000;71(4):521-532.
- Williams RC, Paquette DW, Offenbacher S, et al. Treatment of periodontitis by local administration of minocycline microspheres: a controlled trial. *J Periodontol*. 2001;72(11):1535-1544.
- Little RR, Rohlfing CL, Sacks DB; National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A_{1c} measurement and goals for improvement. *Clin Chem*. 2011;57(2):205-214.