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The Effect of Non-surgical Periodontal Therapy on Hemoglobin A_{1c} Levels in Persons with Type 2 Diabetes and Chronic Periodontitis: A Randomized Clinical Trial

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Abstract

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 non-surgical periodontal treatment reduces hemoglobin A_{1c} (HbA_{1c}) in persons with type 2 diabetes (DM) and moderate to advanced chronic periodontitis.

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Design, Setting and Participants—The Diabetes and Periodontal Therapy Trial (DPTT) is a 6-month, single-masked, randomized, multi-center clinical trial. Participants had DM, were taking stable doses of medications, had HbA_{1c} ≥7% and <9%, and untreated periodontitis. Five hundred fourteen participants were enrolled between November 2009 and March 2012 from diabetes and dental clinics and communities affiliated with five academic medical centers.

Intervention—The treatment group (n=257) received scaling and root planing plus chlorhexidine oral rinse at baseline, and supportive periodontal therapy at three and six months. The control group (n=257) received no treatment for six months.

Main Outcome Measure—Difference in HbA_{1c} change from baseline between groups at six months. Secondary outcomes included changes in probing pocket depths, clinical attachment loss, bleeding on probing, gingival index, fasting glucose, and the Homeostasis Model Assessment (HOMA2).

Results—Enrollment was stopped early due to futility. At 6 months, the periodontal therapy group increased HbA_{1c} 0.17% (1.0) (mean (SD)) compared to 0.11% (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% Confidence Interval (CI): -0.23%, 0.12%; p=0.55). Probing depth, clinical attachment loss, bleeding on probing and gingival index measures improved in the treatment group compared to the control group at six months with adjusted between-group differences of 0.33mm (95% CI: 0.26, 0.39), 0.31mm (95% CI: 0.23, 0.39), 16.5% (95% CI: 12.9, 20.0) and 0.28 (95% CI: 0.21, 0.35), respectively; all p values <0.0001).

Conclusions and Relevance—Non-surgical periodontal therapy did not improve glycemic control in patients with DM 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 HbA_{1c}.

Keywords

Diabetes; Diabetes Mellitus; Type 2; Periodontal Disease; Periodontitis; Glycated Hemoglobin; HbA_{1c}

Introduction

Emerging evidence implicates inflammation in the pathogenesis of type 2 diabetes (DM). [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 U.S. population over the age of 30 is estimated to have chronic periodontitis, with 38% having moderate or advanced disease. [5] Individuals with DM 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 periodontitis progression, [8,11,12] suggesting that level of glycemia is an important mediator of the relationship between diabetes and chronic periodontitis risk. Evidence that chronic periodontitis is in the causal pathway of DM, however, is observational, limited, and inconsistent.

Several small interventional studies have suggested that chronic periodontitis treatment may improve metabolic control of patients with DM. A meta-analysis of these clinical trials [13] found a non-significant weighted average decrease of HbA_{1c} three months following periodontal therapy of 0.38% (95% CI -1.5-0.7). A subsequent trial by Jones et al [14] involving 165 participants resulted in a mean non-significant reduction in HbA1c of 0.65% four months after periodontal therapy, but that study was underpowered. Therefore, the Diabetes and Periodontal Therapy Trial (DPTT) was designed to determine whether non-surgical periodontal therapy (scaling and root planing and supportive periodontal therapy), compared to no therapy, reduces HbA_{1c} at 6 months in persons with DM and moderate to advanced chronic periodontitis.

Methods

Trial design and setting

The Diabetes and Periodontal Therapy Trial (DPTT) was a multicenter, randomized, single-masked, clinical trial that enrolled participants from outpatient medical and dental clinics and communities of five 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 institutional review boards at each participating center, and all participants provided written informed consent. An independent Data and Safety Monitoring Board (DSMB) reviewed the safety data throughout the trial.

Participants

Participants were recruited between November 2009 and March 2012. Men and women ages 35 years and older were eligible if they had physician-diagnosed DM of more than three months duration, an HbA_{1c} value >7.0% and <9.0% at screening, reported no changes in diabetes medications within the last 3 months, were under 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 while in the trial. Participants required a diagnosis of moderate to advanced chronic periodontitis defined as clinical attachment loss and probing depth of at least > 5mm 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 non-steroidal anti-inflammatory (NSAID) medications other than daily low dose aspirin (75-325mg), use of immunosuppressive medications, antibiotic use (>7 days within 30 days of enrollment), dialysis, risk of bleeding complications, or heavy alcohol consumption (>3 drinks/day for men and >2/day 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 life-style information.

Ethnicity was self-reported using multiple choice questions according to NIH-specified categories. 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 six locations around each tooth, and plaque index and gingival index[18] from six index teeth.

Study Procedures

Recruitment occurred during diabetes or dental care visits, or 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 four days to the study's core laboratory (University of Minnesota) for analysis of HbA_{1c} by high performance liquid chromatography (Tosoh HPLC G7 Glycohemoglobin Analyzer, Tosoh Medics, Inc, San Francisco, CA). Serum and plasma aliquots were snap frozen and shipped on dry ice for analysis of lipids, creatinine and fasting glucose by enzymatic methods on a Roche Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN), and insulin by sandwich immunoassay on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation). HOMA2 scores were calculated from fasting glucose and insulin values of non-insulin users using the HOMA2 Calculator version 2.2 (http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/).

Study Intervention

Initial treatment consisted of at least 160 minutes of scaling and root planing using curettes and ultrasonic instruments with local anesthetic during two 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. Following treatment, the therapist provided oral hygiene instructions and dispensed chlorhexidine gluconate 0.12% oral rinse (twice daily for two weeks), toothbrush, toothpaste and dental floss. Three and 6 months following the baseline visit, treatment group participants received scaling and root planing for approximately one hour during a single session, and oral hygiene instructions. Control group participants 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 the change in HbA_{1c} from baseline to 6 months. Secondary outcomes included 3-month change in HbA_{1c}, and change in 3- and 6-month fasting glucose, HOMA2 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 two-fold change in dosage for a hyperglycemic drug, or more than 10% for insulin, or by addition or subtraction of an oral hyperglycemic agent or insulin.

Adverse events and Safety Monitoring

Oral symptoms were recorded two weeks following treatment (treatment group) or baseline for the control group. Rescue therapy was performed on 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

The trial's sample size was estimated assuming a 6-month reduction from baseline in HbA_{1c} of 0.6% (SD 2%)[19] or greater in the treatment than control group. Based on a two-tailed, two-sample t-test and 0.05 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 for continuous variables by means (SD) and/or medians (interquartile ranges) and for categorical variables by frequencies (percentages). 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 two-sample t-tests or Wilcoxon Mann-Whitney tests for continuous, and χ^2 tests for categorical variables. The primary outcome, change in HbA1c, 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 HbA_{1c} change (follow-up - baseline) as the dependent variable, with treatment group as the independent factor and clinical site as a covariate. Homogeneity of clinical site was evaluated using the F-test based on linear regression model. The secondary efficacy analysis used linear regression models that included selected baseline variables as covariates, e.g. HbA_{1c}, gender, age, ethnicity, smoking status, body mass index, diabetes medication usage 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 pre-planned for gender and ethnicity. Additional post-hoc subgroup analyses were also conducted. Between-group comparisons in changes of 3- month $HbA1_C$ and additional secondary outcomes (periodontal measurements (probing depth, clinical attachment loss, bleeding on probing, gingival index and plaque index), fasting glucose, fasting insulin, 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 < 0.05 were adjusted for

multiple comparisons using Bonferroni's correction. All statistical analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC).

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

Results

Participants

1,756 individuals were screened and 514 were randomized from 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. Since the futility analysis t-test statistic for the primary outcome was -0.37, the DSMB recommended cessation of recruitment and continued follow up of enrolled participants.

Ninety-three percent of randomized participants completed the study with similar retention in the treatment (240/257) and control groups (236/257).

Baseline characteristics were similar between groups and were reflective of individuals with DM and periodontitis (Table 1). Forty-seven percent (224/514) of participants used oral hypoglycemic agents alone, 16% (80/514) insulin alone, and 35% (179/514) both. Only 2% (11/514) were not taking diabetes medications.

Primary outcome

HbA_{1c} did not change significantly between baseline and the 3-month or 6-month visits in either the treatment or control group (Figure 2 and Table 2) and the target six-month reduction of HbA1c 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, 6-month HbA_{1c} change did not differ significantly between the treatment and control groups (adjusted 6-month treatment effect (95% CI) = -0.05% (-0.23%, 0.12%); p=0.55). Three-month results were similar. No significant differences in Hba1c results across centers were found (p= 0.44 (intention to treat); p=0.59 (per protocol) based on F-test for homogeneity from the linear regression model).

Secondary outcomes

A per protocol linear regression analysis evaluating change in HbA_1c did not reveal HbA_{1c} differences between groups at either time point (adjusted treatment effect (95% CI) =-0.07% (-0.26%, 0.13%); p= 0.50) (Table 2).

Using linear regression models, all periodontal clinical parameters improved significantly at 3 months and were sustained at 6 months in the treatment but not the control group. (Figure 3 and e-Table 2). At 6 months, mean (95% CI) probing depth improved by 0.42 mm (0.36, 0.48) in the treatment group compared to 0.14mm (0.08, 0.21) in the control group (adjusted treatment effect (95% CI) of 0.33mm (0.26, 0.39); p (Bonferroni's correction) <.0001). In

the treatment group, bleeding on probing decreased by 19.0% (15.7, 22.4) (mean (95% CI)) compared with 5.9% (2.3, 9.6) for the control group (adjusted difference (95% CI): 16.5% (12.9, 20.0); p (Bonferroni's correction) <.0001). Clinical attachment loss and gingival index measures also improved more in the treatment group compared to the control group (adjusted between-group differences were 0.31mm (95% CI: 0.23, 0.39) and 0.28 (95% CI: 0.21, 0.35), respectively; both p values <0.0001). A post-hoc subgroup comparison of treatment groups by response tertiles likewise revealed no significant differences between groups at any time point (eTable 1). Changes in blood pressure, weight, fasting glucose, fasting insulin and HOMA2 sensitivity (%s) and HOMA2 β-cell function (%β) are summarized in eTable 3. All 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, 55% (128/233) in the treatment group and 60% (137/229) 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/pain than the controls (40.2% (102/254) and 28.1% (72/257) respectively; p <0.01(based on chi-square test), and thermal sensitivity (31.9% (81/254) vs. 18.3% (47/257), respectively (p <0.01(based on chi-square 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 multi-center, randomized, clinical trial to investigate the effect of periodontal therapy on measures of glycemic control in patients with DM and chronic periodontitis. Despite its effectiveness in improving clinical measures of periodontitis, periodontal therapy did not significantly change HbA_{1c} after 3 or 6 months in the treatment group, and no differences in HbA_{1c} change were observed between the treatment and control groups. Findings were similar in the intent-to-treat and the per-protocol analysis. Likewise, periodontal therapy had no significant effect on fasting glucose or the HOMA2 score. 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, though not specifically evaluated in our study, periodontal therapy may be considered in patients with DM 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% CI 0.54- 0.19) but significant reduction in HbA_{1c} following periodontal therapy.[23] A number of features of the present study may account for these differences. First, all previous trials were small, while DPTT had greater than 90% power to detect a clinically meaningful difference between groups in HbA_{1c} change from baseline of 0.6%, even with early cessation of trial enrollment. Secondly, 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 absence of differences in HbA_{1c} outcome. This aspect of the DPTT study design was critical since medications may have profound short-term influence on HbA_{1c} levels and have not been adequately documented in previous studies. Also, meta-analyses of small trials have been reported to be subject to high false positive rates. [24-26] Finally, it is possible that periodontal inflammation and infection in fact do not influence glycemic control. Indeed, the results of this trial indicate that glycemic control worsened, although not significantly, six months following study therapy.

The largest previous trial of periodontal treatment and glycemic control (n=157) reported a non-statistically significant HbA1c reduction of 0.36% in the treatment compared with the control group after three months. [27] Another study of 132 male Veterans Administration participants[14] failed to demonstrate a positive effect on glycemic control. The results of the DPTT are consistent with the latter study.

Possible limitations to the present study should be considered. Our periodontal treatment did not include systemic or topical antibiotics nor was any participant treated surgically due to 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 metabolic syndrome likewise did not achieve a reduction in glycemic control.[28] While probing depths and clinical attachment levels were significantly improved in the treatment group, dental plaque and bleeding score improvements were only modest and indicate that changing oral hygiene habits remains a challenge. A subgroup comparison by tertiles of response, however, did not reveal HbA_{1c} differences even among those with the largest improvements in periodontal parameters. Since DPTT participants were enrolled with $HbA_{1c} > 7\%$ and $<9\%$, we cannot rule out the possibility that individuals with values outside of this range might experience HbA_{1c} reduction following periodontal treatment.

The DPTT had a number of strengths. The sample size was sufficient to ensure adequate statistical power to detect a meaningful clinical difference in HbA_{1c}. 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. Diabetes medication changes 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 of other multi-center trials of non-surgical therapy in non-diabetic populations. [29,30] The DPTT core laboratory responsible for the centralized analysis of blood samples is a reference laboratory for the analysis of HbA_{1c} in North America.[31]

Conclusions

In conclusion, this multi-centered randomized clinical trial of non-surgical periodontal treatment for participants with DM and chronic periodontitis did not demonstrate a benefit to measures of glycemic control. Although periodontal treatment improved clinical measures of chronic periodontitis in patients with DM, the findings do not support the use of nonsurgical periodontal treatment for the purpose of lowering HbA_{1c}.

DPTT Study Group

DPTT Study Group

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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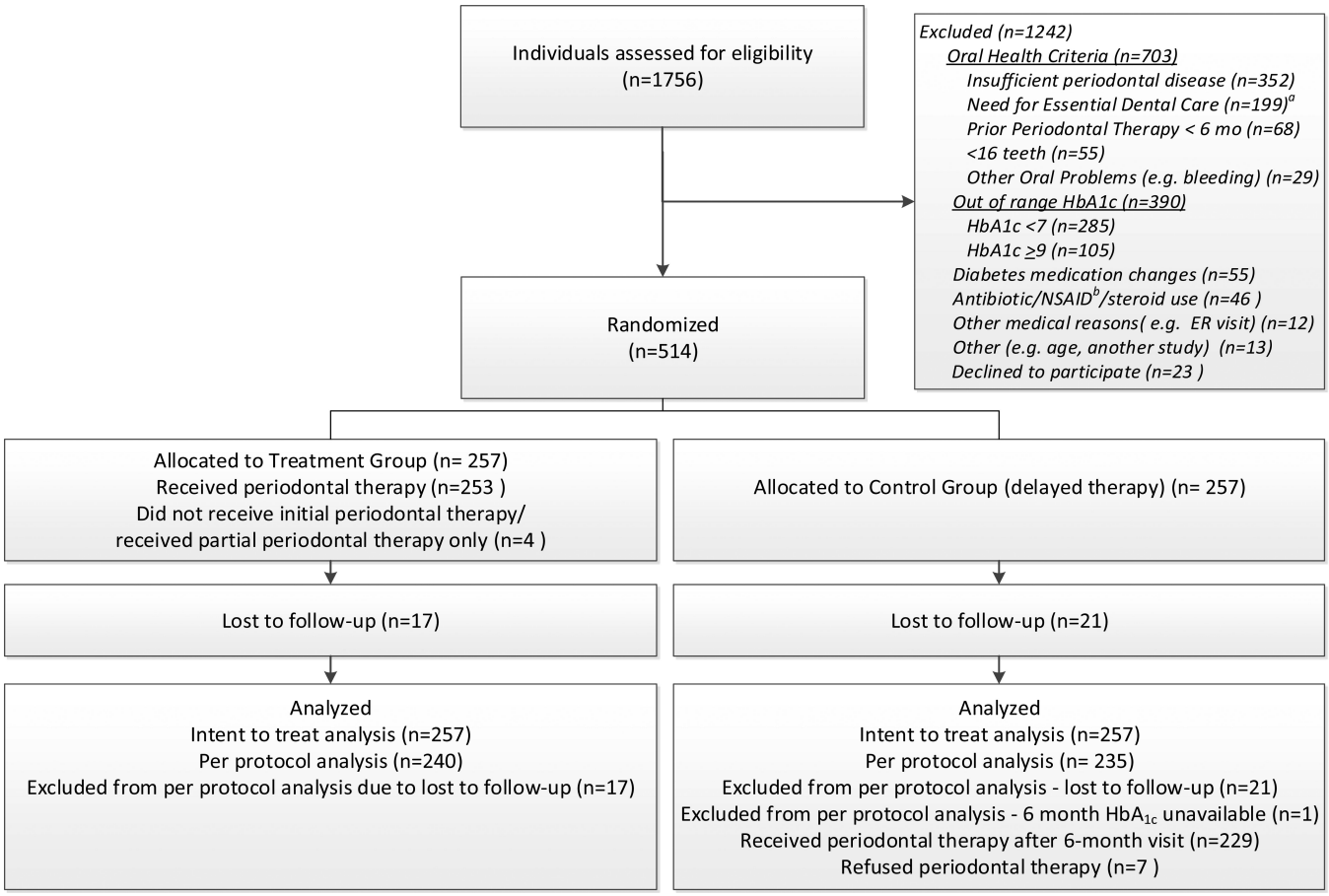

Figure 1.

DPTT Participant Flow Chart

[a] Essential Dental Care – defined as participants needing treatment of extensive tooth decay, tooth abscesses, or other oral infections: [b] Non-steroidal anti - inflammatory drug

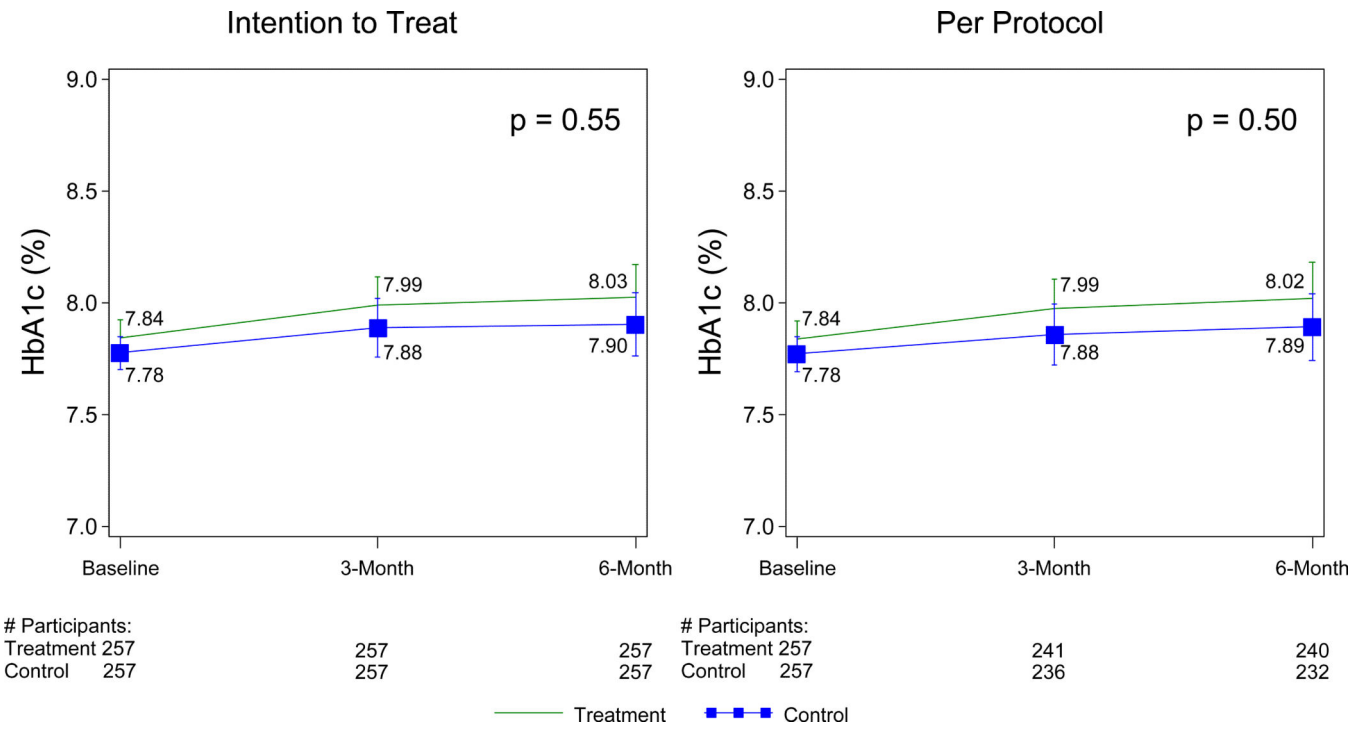

Figure 2.

Hemoglobin A_{1c} Levels at Baseline and Follow-up Mean values and standard errors are presented at each visit.

P-values comparing 6-month change in Hb A_{1c} between the two treatment groups were based on t-tests from linear regression models with 6-month HbA_1c change as a dependent variable, treatment group and Clinical Site as covariates.

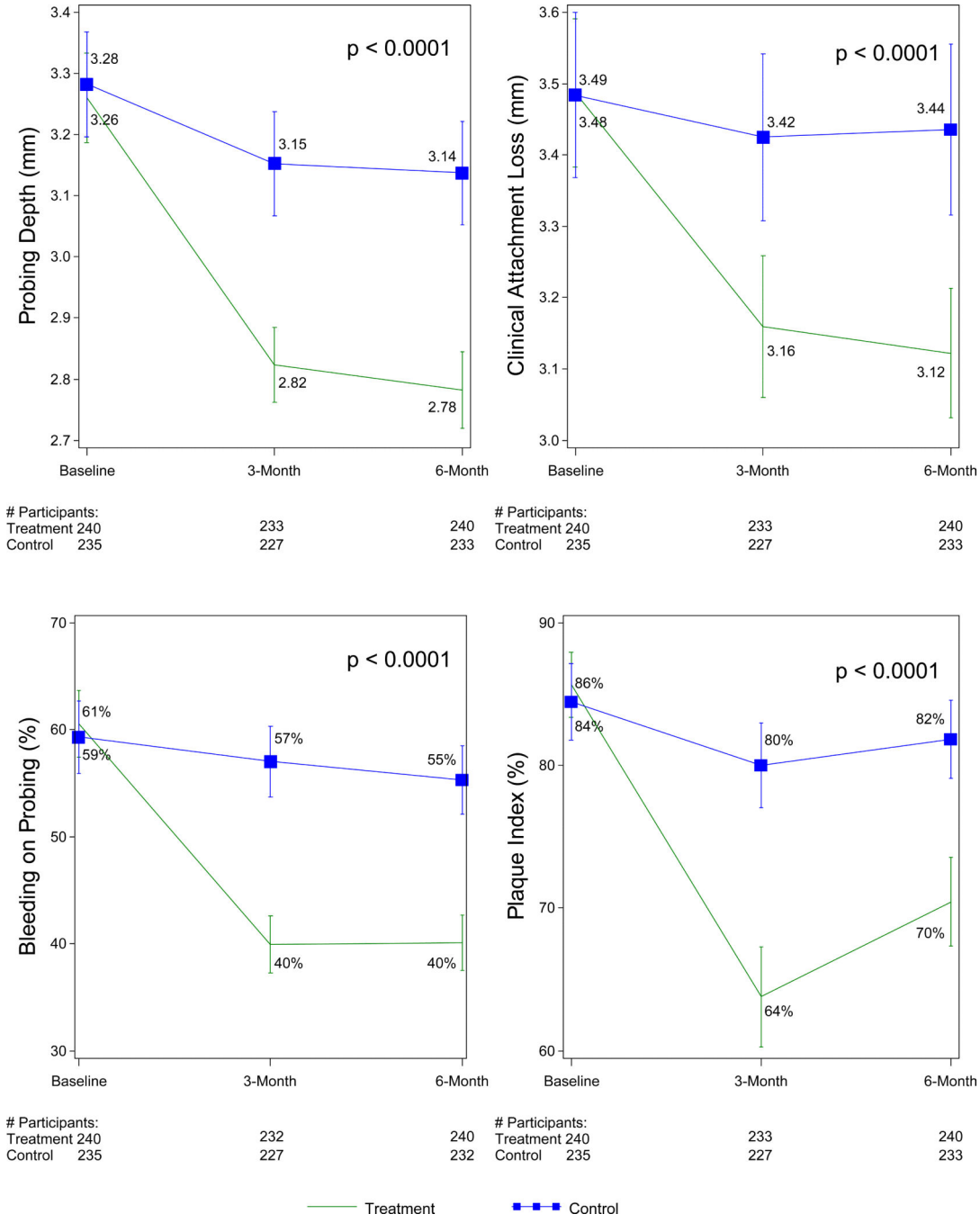

Figure 3.

Periodontal Measurements at Baseline and Follow-up (Per Protocol)

Mean values and standard errors are presented at each visit.

P-values comparing 6-month changes in periodontal outcomes between the two treatment groups were based on t-tests from linear regression models with 6-month periodontal change as a dependent variable, treatment group and Clinical Site as covariates.

Table 1

General Baseline Characteristics of DPTT Participants by Study Group

Characteristics	Treatment Group (N=257)	Control Group (N=257)
Age, mean (sd), years	56.7 (10.5)	57.9 (9.6)
Female, No. (%)	114 (44.4)	123 (47.9)
Race, No. (%)		
African American/ Black	76 (29.6)	70 (27.2)
White	140 (54.5)	140 (54.5)
Other(e.g., Native American, Asian)	41 (16.0)	47 (18.3)
Hispanic, No. (%)	81 (31.5)	85 (33.1)
Smoking history, No. (%)		
Never smoked	129 (50.2)	144 (56.0)
Former	89 (34.6)	86 (33.5)
Current	39 (15.2)	27 (10.5)
Diabetes factors, mean (SD)		
HbA1c, %	7.8 (0.65)	7.8 (0.60)
HbA1c, 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, mg/dL , median	150	147
IQR	(125 – 174)	(122 – 172)
Duration of diabetes, years	12.3 (8.2)	11.3 (8.4)
Fasting insulin, (pmol/L), excluding insulin use[a]		
median	95	88
IQR	(61 – 138)	(61 – 133)
HOMA2 insulin sensitivity (%S), excluding insulin use[a,b]		
median	50.1	53.9
IQR	(34.1 – 77.0)	(38.0 – 79.0)
HOMA2 β-cell function (%β), excluding insulin use [a,b]		
median	55.5	52.0
IQR	(34.1 – 76.2)	(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, kg/m^2	34.7 (7.5)	34.2 (6.7)
Blood pressure[c], mean(sd), mm Hg		

Characteristics	Treatment Group (N=257)	Control Group (N=257)
Systolic	133.1 (20.7)	135.1 (20.4)
Diastolic	78.8 (12.3)	78.8 (10.9)
Cardiovascular disease factors, mg/dL, median IQR		
Cholesterol, median, IQR, excluding statin use[d]		
Cholesterol	189	185
IQR	(162 – 211)	(161 – 212)
Low-density lipoprotein	113	108
IQR	(92 – 135)	(94 – 130)
High density lipoprotein	46	41
IQR	(38 – 53)	(37 – 48)
Triglycerides, median, excluding statin use[d]	117	126
IQR	(89 – 169)	(93 – 231)
Creatinine, median	0.81	0.81
IQR	(0.68 – 1.0)	(0.67 – 0.98)
Periodontal measurements[e], mean (SD)		
Number of teeth (count/person)	25.4 (3.7)	24.7 (3.6)
Probing depth (PD) (mm, mean sites/person)	3.3 (0.6)	3.3 (0.7)
# sites		
≥4mm	51.3 (27.3)	49.2 (27.5)
≥5mm	28.9 (21.6)	28.0 (22.3)
≥7mm	3.5 (6.3)	3.5 (8.2)
% sites		
≥4mm	33.8 (17.6)	33.6 (18.7)
≥5mm	19.0 (14.2)	19.3 (15.6)
≥7mm	2.3 (4.2)	2.5 (6.1)
Clinical Attachment loss (CAL) (mm, mean sites/person)	3.5 (0.8)	3.5 (0.9)
# sites		
≥4mm	60.1 (30.7)	57.5 (30.7)
≥5mm	35.9 (25.9)	33.6 (26.0)
≥7mm	6.6 (9.7)	6.9 (11.9)
% sites		
≥4mm	40.3 (21.1)	39.5 (21.3)
≥5mm	24.3 (18.2)	23.4 (18.6)
≥7mm	4.7 (7.3)	5.0 (9.2)
Bleeding on probing (BOP) (% sites/person)	61.2 (24.1)	59.6 (26.0)
Gingival Index (GI) (mean sites/person)	1.4 (0.4)	1.4 (0.4)
Plaque Index (PLA) (% 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. (%)		

Characteristics	Treatment Group (N=257)	Control Group (N=257)
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)

[a] Limited to non-insulin users: n=133 treatment group; 488 n=138 control group

[b] HOMA2 - calculated using the HOMA2 calculator version 2.2 (http://www.dtu.ox.ac.uk/homacalculator/index.php).

[c] Includes blood pressure measurements for all participants independent of reported blood pressure medication use.

[d] Non-statin users: n=85 Treatment Group; n=87 Control Group

[e] 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 six sites per tooth and then calculating an average for all teeth measured for that participant.

Table 2

3-month and 6-month Change in HbAlc by Treatment Group

	Baseline		3- month Change (Δ=3-month - Baseline)			6- month Change (A=6-month - Baseline)		
	Treatment	Control	Treatment	Control		Treatment	Control	
Study Outcome	**mean (SD)**	**mean (SD)**	**mean[a] 95% C.I.)**	**mean[a] (95% C.I.)**	***p volue*[a]**	**mean[a] (95% C.I.)**	**mean[a] (95% C.I.)**	***p volue*[a]**
Intent to Treat	**N=257**	**N=257**	**N=257**	**N=257**		**N=257**	**N=257**	
HbA1c(%)	7.84 (0.65)	7.78 (0.60)	0.14 *(0.02, 0.27)*	0.11 *(−0.02, 0.24)*	***0.64***	0.15 *(−0.01, 0.30)*	0.09 *(−0.06, 0.25)*	***0.55***
Per protocol[b]	**N=240**	**N=235**	**N=233**	**N=228**		**N=240**	**N=235**	
HbA1c(%)	7.84 (0.65)	7.77 (0.60)	0.13 *(−0.01, 0.26)*	0.08 *(−0.05, 0.22)*	***0.57***	0.15 *(−0.02, 0.32)*	0.09 *(−0.09, 0.26)*	***0.50***

[a]Mean changes and 95% CI's were determined from linear regression models with 3-month and 6-month change in HbAjC 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 two groups.

[b]Per protocol: Analyses were based on all participants with HbAlc data at the 6-month visit (n=240 in the Treatment group, n=235 in the Control Group). 6 participants in the Treatment Group and 7 in the Control Group missed their 3 month visit. HbAlc data were not available for one additional Treatment Group participant at 3 months.