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Periodontal and glycemic effects of nonsurgical periodontal therapy in patients with type 2 diabetes stratified by baseline HbA_{1c}

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Abstract: We evaluated the effects of nonsurgical periodontal therapy in 100 patients with type 2 diabetes and chronic periodontitis. The participants were classified as having good (n = 48) or poor (n = 52) glycemic control and were further randomly allocated to receive either scaling and root planning treatment group or no treatment (n = 50 each). The effect of nonsurgical periodontal therapy was compared among diabetic patients with good glycemic control, those with poor glycemic control, and 25 nondiabetic individuals. Periodontal and metabolic status was recorded at baseline, 3 months, and 6 months. In patients receiving treatment, periodontal parameters significantly improved and HbA_{1c} decreased by 10.8%. Improvements in gingival index and bleeding on probing were greater in the nondiabetic participants and the treated patients with good glycemic control than in the treated patients with poor glycemic control (P < 0.05). Regression analysis showed that improvement in periodontal status was independently associated with glycemic improvement. Nonsurgical periodontal therapy improved glycemic control and periodontal health in patients with type 2 diabetes. However, patients with poor baseline glycemic control had less clinical improvement than did those without diabetes and those with good glycemic control.
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Keywords: type 2 diabetes mellitus; hemoglobin A; glycated; chronic periodontitis.

Introduction

Diabetes is a pathologic consequence of many physiologic changes and leads to metabolic imbalance, hyperglycemia, and chronic inflammation, with potential effects on tissue integrity and repair (1). Type 2 diabetes mellitus (T2DM) is the most prevalent form of the disease and affects 90-95% of the diabetic population (2). Evidence suggests that individuals with T2DM, especially when inadequately controlled, have a higher risk of developing periodontitis than do normoglycemic individuals (3). Furthermore, destruction of periodontal tissues is more severe and extensive in those with moderately or poorly controlled diabetes than in those with good control (4,5).

Chronic inflammatory periodontal disease (periodontitis) is primarily an anaerobic microbial infection that results in loss of connective tissue and bone support and is a major cause of tooth loss in adults (5). There are few data on the effects of periodontal disease on metabolic control. However, research suggests that, as compared with periodontally healthy individuals, people with poor periodontal health, regardless of diabetes status, have a greater risk of worsening glycemic control. Periodontitis also seems to be linked to increased glycated hemoglobin

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(HbA_{1c}) in people without diabetes (6). Intervention studies of the effect of nonsurgical periodontal treatment in diabetic patients generally show improved periodontal status, while results concerning changes in glycemic status are rather contradictory. Some found significant improvements in glycemic control (7-19); others did not (20-26). Meta-analyses of intervention studies indicate a need for additional trials to clarify this relationship (27-30).

The present prospective study assessed 1) the effect of nonsurgical periodontal therapy in patients with T2DM and chronic periodontitis, 2) differences in clinical periodontal and metabolic responses to periodontal treatment among patients with good glycemic control, poor glycemic control, and nondiabetic individuals, and 3) differences in periodontal and metabolic status in T2DM patients with good and poor glycemic control over a period of 6 months without periodontal treatment.

Current classifications of periodontitis use mean probing pocket depth (PPD), mean clinical attachment level (CAL), or a particular cut-off point for PPD or CAL to define or classify periodontitis. PPD and CAL are linear measures and thus do not quantify the amount of inflamed periodontal tissue. The measure periodontal inflamed surface area (PISA) is derived from periodontal epithelial surface area (PESA) and expresses the surface area of bleeding pocket epithelium in square millimeters. It is believed to be better (face validity) than currently used criteria for classifying periodontitis. PISA was used in the present study to quantify periodontal inflammatory burden (31).

Materials and Methods

Study population

This randomized control trial was conducted from February 2010 to January 2012 in the Department of Periodontics and Oral Implantology at the Post Graduate Institute of Dental Sciences (PGIDS), Rohtak, India, in collaboration with the Department of Medicine, Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, India. This study was approved by the Institutional Review Board of Pandit Bhagwat Dayal Sharma University of Health Sciences, Rohtak (PGBOS/UHSR/Perio/04/2010/Dated 18.02.2010) and was carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki, as revised in 2008. On the basis of an expected mean difference in HbA_{1c} of approximately 0.4% between groups and a standard deviation of 0.4 (30), we calculated that at least 22 patients would be required in each group to detect a difference with 90% power and a two-sided type 1 error of 5% (32). A single examiner (R.K.S.) screened 324 patients who had been receiving treatment for at least 1 year after a diagnosis of T2DM. The inclusion criteria were an age of 45-60 years, presence of ≥12 teeth (excluding third molars), no change in medication use (oral hypoglycemics, insulin, etc.) during the 2 months before the study or during the study, and a clinical diagnosis of moderate or severe generalized chronic periodontitis (33). Moderate periodontitis was defined as two or more interproximal sites, not on the same tooth, with an attachment loss ≥4 mm, or two or more interproximal sites, not on same tooth, with probing depths ≥5 mm. Severe periodontitis was defined as two or more interproximal sites, not on the same tooth, with an attachment loss ≥6 mm, and one or more interproximal sites with a probing depth ≥5 mm. Patients were excluded if they had cardiovascular disease, chronic respiratory disease, rheumatoid arthritis, or any other systemic disease that could influence the course of periodontal disease; if they were pregnant or lactating; if they were current or ex-smokers; or if they had major diabetic complications or a history of systemic antibiotic use within the previous 3 months or periodontal treatment during the previous 6 months.

A total of 126 patients with T2DM satisfied the inclusion criteria, 26 of whom declined to participate in the study. The remaining 100 patients were stratified by HbA_{1c} level into those with good (G group; n = 48) and poor (P group; n = 52) glycemic control. An HbA_{1c} of <7% was used as the cutoff for this classification (34). These patients were then further randomly allocated to either the treatment group (T group; those receiving nonsurgical periodontal therapy in the form of scaling and root planning [SRP]) or the no-treatment group (NT group) (n = 50 each). Computer software was used to avoid a disparity in HbA_{1c} distribution between the two groups. A number from 1-100 was assigned to patients according to their recruitment date. Simultaneously, a comparator group of 25 well-matched nondiabetic individuals with chronic periodontitis who were otherwise systemically healthy (NoDM) was recruited from the Department of Periodontics, PGIDS. Participants in this group also received nonsurgical periodontal therapy (Fig. 1). The study participants thus comprised the following groups: 1) 23 individuals with good glycemic control who received SRP—the treatment/good glycemic control (TG group); 2) 27 patients with poorly controlled diabetes who received SRP—the treatment/poor glycemic control (TP group); 3) 25 individuals with good glycemic control who received periodontal treatment after completion of the study—the no-treatment/good glycemic control (NTG group); 4) 25 patients with poorly controlled diabetes

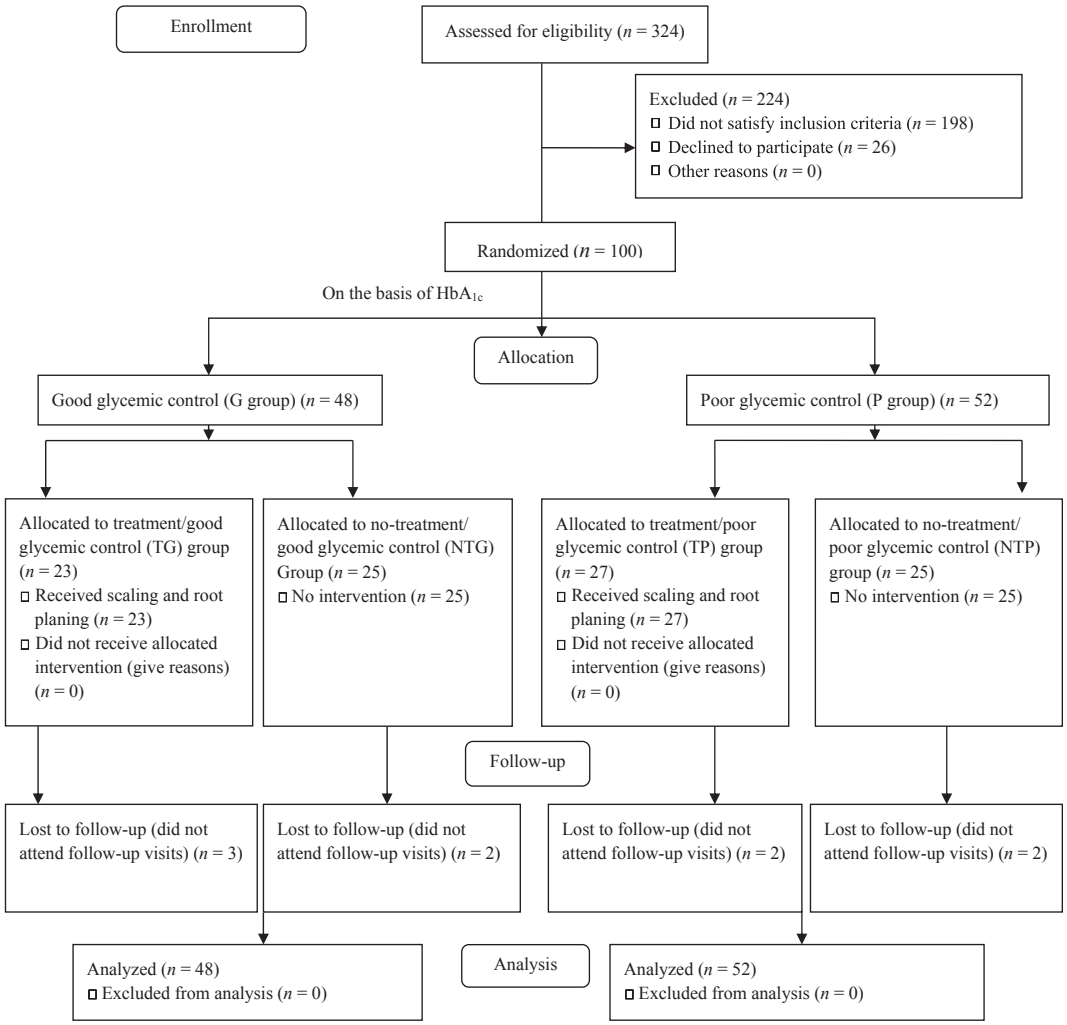

Fig. 1 Enrollment and participation of the study participants.

who received periodontal treatment after completion of the study—the no-treatment/poor glycemic control (NTP group); and 5) 25 nondiabetic individuals who received SRP (NoDM group). Individuals in the NoDM group were matched (in terms of age, sex, body mass index (BMI), number of teeth) with individuals in the treatment groups who had good and poorly controlled diabetes (TG and TP groups).

Participants were followed for 6 months and were assessed at baseline, 3 months, and 6 months. Detailed systemic examinations rather than self-reports were relied upon to determine participants' medical status. Plasma lipid profile, glucose level, liver enzyme levels, and thyroid function were evaluated. Information on age, sex, smoking status, duration of diabetes, family history, and medication use was obtained through interviews. Anthropometric evaluation included measurements of weight (kg) and height (m) for estimating BMI in kg/m^2. All patients were informed of the study methods in detail and were given the opportunity to ask questions and express their concerns and were included in the study only after giving written consent. A single examiner (S.C.N.), blinded to the group allocation, was responsible for recording periodontal parameters throughout the study. The examiner (S.C.N.) was assessed for intra-examiner reproducibility for PPD, location of the gingival margin (LGM) and CAL on six sites per tooth, excluding third molars, for 10 patients. A second assessment was done 3 h after the first. Reproducibility of the data collection was determined for each site by calculating the percentage of examined sites for which scores were identical or within 1 mm. The examiner was blinded to the results of the previous evaluation, and both sets of periodontal assessments were found to be in agreement (92%). Periodontal treatment of patients in treatment groups was carried out by a different trained examiner (P.K.K.), to avoid any bias in the evaluations.

Clinical periodontal examination

Assessments were done by using a manual, calibrated periodontal probe (Williams Probe, Hu-Friedy Manufacturing Co., Chicago, IL, USA). Clinical parameters were recorded at six sites per tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual/palatal, midlingual/palatal, distolingual/palatal), excepting the third molars. Bleeding on probing (BOP) was recorded as present (score 1) if it occurred within 30 s of probing and absent (score 0) if no bleeding occurred. Periodontal probing depth (PPD) was defined as the distance from the gingival margin to the base of the clinical pocket. LGM was recorded with respect to the cementoenamel junction (CEJ). CAL was defined as the distance from the CEJ to the base of the clinical pocket. CAL, LGM, and PPD were recorded in millimeters, and measurements were rounded to the nearest millimeter. A Microsoft Excel spreadsheet was used to facilitate PISA calculation, using the procedure detailed on the website www.parsprototo.info. After recording the CAL measurements at six sites per tooth in the spreadsheet, mean CAL was calculated for each tooth and subsequently entered into an inbuilt formula for conversion of linear CAL measurements to the attachment loss surface area (ALSA) for that specific tooth (35). Then, recession measurements at six sites per tooth were recorded and the software calculated the mean recession for each tooth, which was entered into the appropriate formula for conversion of linear recession measurements to the recession surface area (RSA) for that specific tooth (35). Then, the RSA for a particular tooth is subtracted from the ALSA of that tooth to determine the PESA for that specific tooth, i.e., PESA = ALSA − RSA.

Because PESA also includes healthy pocket epithelium, which does not contribute to the inflammatory burden of periodontal tissues, PESA does not itself quantify the surface area of inflamed pocket epithelium. Therefore, the PESA for a particular tooth is then multiplied by the proportion of sites around the tooth that are affected by BOP, which results in the PISA for that tooth. Finally, the sum of all individual PISA scores around individual teeth is calculated, which represents the total PISA within a patient's mouth. PESA and PISA scores are expressed in mm^2. Plaque index (PI) (36) and gingival index (GI) (37) were recorded at four sites per tooth (mesiobuccal, midbuccal, distobuccal, and midlingual/palatal). These parameters were recorded at baseline and 3 and 6 months after completion of periodontal therapy in the treatment groups (TG, TP, and NoDM groups) and at baseline, 3 months, and 6 months in the no-treatment groups (NTG and NTP groups).

Periodontal treatment

Individuals in the treatment groups (TG, TP, and NoDM groups) were given oral hygiene instructions at baseline followed by nonsurgical periodontal treatment comprising four SRP sessions over a maximum of 2 weeks, using standard rigid Gracey curettes (Hu-Friedy Manufacturing Co.) and an ultrasonic scaler (Suprasson P5 Booster, Satelec-Acteon group., Merignac, France). Oral hygiene instructions were reviewed at each visit, and additional supportive SRP was done when necessary. The patients were instructed to use only mechanical cleansing aids throughout the study. Periodontal treatment was performed in the no-treatment group (NT group) after completion of the study (after 6 months).

Metabolic parameters

HbA_{1c} was determined by using a latex agglutination inhibition assay and an autoanalyzer (Konelab clinical chemistry analyzers, Thermo Scientific., Milan, Italy), and blood glucose determination was done using a glucose oxidase–peroxidase method (glucose *in vitro* diagnostic kit, Siemens., Vadodara, Gujarat, India) at the Department of Biochemistry, PGIMS, Rohtak. Laboratory staffs were blinded to the allocation groups. Metabolic assessments were done at baseline, 3 months, and 6 months. Absence of diabetes was confirmed in nondiabetic patients.

Statistical analysis

All 125 patients were included in the statistical analysis. The nine patients who withdrew after 3 months (five from T group and four from NT group) were included in intention-to treat analysis by carrying their last observation forward (38). Mean PI, GI, PPD, CAL, PESA, and PISA were calculated for each participant and each group. For BOP, the percentage of positive sites was obtained for the patient, and a mean value was then calculated for the group. The Kolmogorov-Smirnov test was used to confirm normality of the data distribution. Because data were normally distributed, differences between groups were assessed using one-way analysis of variance, with Tukey's post-hoc test and the independent *t*-test for ordinal data and the chi-square test for dichotomous data. Repeated-measures ANOVA was used to compare baseline values with follow-up values in the same group. Partial correlations of change in HbA_{1c} (ΔHbA_{1c}) with baseline HbA_{1c} and group (T, NT groups) were performed after adjustment for confounders, including age, sex, duration of diabetes, and BMI. Multiple linear regression analysis was done using ΔHbA_{1c} as the dependent variable and baseline HbA_{1c} level and group as

Table 1 Baseline characteristics of participants with type 2 diabetes, by treatment allocation

	Treatment group $n = 50$	No-treatment group $n = 50$	P
Male/Female	22/28	26/24	NS
Age (years; mean ± SD)	51.82 ± 5.85	52.94 ± 6.03	NS
BMI (kg/m^2 mean ± SD)	26.41 ± 3.47	26.43 ± 3.41	NS
No. of remaining teeth (mean ± SD)	22.98 ± 4.59	24.30 ± 2.88	NS
Duration of diabetes (years; mean ± SD)	8.57 ± 6.39	7.05 ± 4.43	NS
OHA (n)	30	33	NS
Insulin (n)	20	17	NS
HbA_{1c} (%; mean ± SD)	8.17 ± 2.49	7.87 ± 2.56	NS
FPG (mmol/L; mean ± SD)	137.12 ± 59.71	120.74 ± 41.47	NS
PPG (mmol/L; mean ± SD)	185.70 ± 84.18	162.89 ± 68.99	NS

$n = 100$. All differences between groups at baseline were nonsignificant.
BMI: body mass index, OHA: oral hypoglycemic, HbA_{1c}: glycated hemoglobin, FPG: fasting plasma glucose, PPG: postprandial glucose, NS: not significant

Table 2 Baseline characteristics of participants, by study group

	Treatment/good glycemic control (TG) $n = 23$	Treatment/poor glycemic control $n = 27$	No treatment/good glycemic control (NTG) $n = 25$	No treatment/poor glycemic control $n = 25$	Treatment/ nondiabetic $n = 25$	P
Male/Female	10/13	12/15	14/11	12/13	15/10	NS
Age (years; mean ± SD)	52.83 ± 5.04	50.96 ± 6.43	54.28 ± 5.93	51.60 ± 5.93	51.56 ± 5.91	NS
BMI (kg/m^2; mean ± SD)	26.26 ± 3.82	26.26 ± 3.99	25.93 ± 3.17	26.93 ± 3.62	24.82 ± 2.75	NS
No. of remaining teeth (mean ± SD)	23.61 ± 3.75	22.44 ± 5.21	24.56 ± 2.16	24.04 ± 3.42	25.08 ± 3.23	NS
Duration of diabetes (years; mean ± SD)	8.76 ± 6.71	8.41 ± 6.25	6.40 ± 2.80	7.70 ± 5.60	NA	NS
HbA_{1c} (%; mean ± SD)	6.03 ± 0.47	9.99 ± 2.02*†	5.94 ± 0.75	9.81 ± 2.24*†	NA	<0.05
FPG (mmol/L; mean ± SD)	95.04 ± 20.14	172.95 ± 58.97*†	91.12 ± 15.30	150.35 ± 38.07*†	NA	<0.05
PPG (mmol/L; mean ± SD)	131.57 ± 35.71	231.81 ± 86.46*†	118.44 ± 24.18	207.33 ± 70.85*†	NA	<0.05

$n = 125$. BMI: body mass index, OHA: oral hypoglycemic, HbA_{1c}: glycated hemoglobin, FPG: fasting plasma glucose, PPG: postprandial glucose, NA: not applicable, NS: not significant
*Significant difference vs TG, †Significant difference vs NTG

independent variables to evaluate associations between these variables. All statistical analyses were two-tailed, with a significance level of 0.05, and were conducted using SPSS statistical software (version 19; Chicago, IL, USA).

Results

Tables 1 and 2 show the baseline demographic characteristics and laboratory results of the participants.

Changes in periodontal parameters

Improvements in all periodontal parameters were significantly greater in the T group than in the NT group throughout the study ($P < 0.05$) (Table 3). SRP resulted in statistically significant improvements in all periodontal parameters in NoDM, individuals with good glycemic control (TG), and individuals with poor glycemic control (TP) at 3 months ($P < 0.05$) (Table 4). This trend continued until the end of the study. At baseline, the NoDM and TG groups had significantly higher percentages of sites with periodontal probing depth <3 (PPD <3) mm as compared with the TP group. In addition, the percentage of sites with a periodontal probing depth of 4-6 (PPD 4-6) mm was significantly lower in the TG group than in the TP group at baseline. At 3 months, there was a significant difference between the NoDM and TP groups in the percentage of sites with a periodontal probing depth ≥7mm (PPD ≥7) mm. Statistically significant differences in GI score ($P < 0.05$) and percentage of sites with BOP ($P < 0.05$) were observed between the NoDM and TP groups and between the TG and TP groups at 3 and 6 months. There was no significant difference between the TG and NoDM groups for any of the periodontal variables at any time point (Table 4). In the absence of periodontal treatment

Table 3 Periodontal and metabolic status in the treatment and no-treatment groups during the study period

Parameters		Treatment group		No-treatment group	
		n = 50	Δ	*n* = 50	Δ
PI	Baseline	1.64 ± 0.26		1.63 ± 0.26	
	3 months	0.29 ± 0.12*†	1.34 ± 0.30	1.65 ± 0.31	-0.02 ± 0.18
	6 months	0.28 ± 0.09*†	1.36 ± 0.26	1.68 ± 0.34	-0.05 ± 0.19
GI	Baseline	1.57 ± 0.28		1.63 ± 0.17	
	3 months	0.66 ± 0.27*†	0.92 ± 0.26	1.70 ± 0.30	-0.07 ± 0.22
	6 months	0.64 ± 0.26*†	0.94 ± 0.26	1.75 ± 0.32*	-0.12 ± 0.25
PPD (mm)	Baseline	2.96 ± 0.46		3.08 ± 0.55	
	3 months	2.17 ± 0.43*†	0.79 ± 0.28	3.10 ± 0.56	-0.03 ± 0.04
	6 months	2.15 ± 0.42*†	0.81 ± 0.28	3.13 ± 0.57*	-0.06 ± 0.08
PPD <3 mm (%)	Baseline	37.46 ± 8.67		35.97 ± 9.67	
	3 months	56.94 ± 12.32*†	-19.49 ± 9.37	33.84 ± 10.29*	2.14 ± 3.24
	6 months	58.94 ± 12.25*†	-21.48 ± 9.44	31.82 ± 11.44*	4.16 ± 5.62
PPD 4-6 mm (%)	Baseline	50.31 ± 8.37		52.20 ± 9.03	
	3 months	36.29 ± 10.8*†	14.01 ± 8.10	52.81 ± 9.12	-0.61 ± 1.91
	6 months	35.11 ± 10.81*†	15.19 ± 7.99	53.26 ± 9.72	-1.07 ± 3.35
PPD ≥7 mm (%)	Baseline	12.24 ± 3.52		11.82 ± 4.84	
	3 months	6.76 ± 2.91*†	5.47 ± 2.33	13.40 ± 6.59*	-1.58 ± 2.65
	6 months	5.94 ± 2.91*†	6.29 ± 2.70	14.98 ± 8.09*	-3.16 ± 4.41
CAL (mm)	Baseline	3.46 ± 0.53		3.37 ± 0.61	
	3 months	2.77 ± 0.62*†	0.69 ± 0.36	3.40 ± 0.62	-0.04 ± 0.04
	6 months	2.75 ± 0.62*†	0.71 ± 0.36	3.44 ± 0.64*	-0.07 ± 0.08
PESA (mm^2)	Baseline	1,513.73 ± 274.39		1,523.97 ± 323.59	
	3 months	1,082.03 ± 254.5*†	431.71 ± 116.21	1,544.59 ± 330.57	-20.61 ± 23.82
	6 months	1,067.94 ± 250.3*†	445.79 ± 116.87	1,558.88 ± 334.59*	-34.91 ± 38.19
PISA (mm^2)	Baseline	1,256.19 ± 339.98		1,289.92 ± 303.33	
	3 months	751.18 ± 270.94*†	505.01 ± 237.31	1,317.75 ± 307.84*	-27.84 ± 38.89
	6 months	729.22 ± 265.99*†	526.97 ± 239.41	1,337.37 ± 312.13*	-47.46 ± 53.76
BOP (%)	Baseline	73.68 ± 14.63		75.36 ± 10.49	
	3 months	39.07 ± 11.68*†	34.01 ± 14.81	76.99 ± 11.26	-1.63 ± 2.45
	6 months	38.96 ± 11.62*†	34.71 ± 14.78	78.88 ± 11.84*	-3.52 ± 4.43
HbA_{1c} (%)	Baseline	8.17 ± 2.49		7.87 ± 2.56	
	3 months	7.49 ± 1.83*†	0.69 ± 0.78	7.96 ± 2.65	-0.09 ± 0.31
	6 months	7.29 ± 1.61*†	0.88 ± 1.00	8.06 ± 2.72*	-0.18 ± 0.38
FPG (mmol/L)	Baseline	137.12 ± 59.71		120.74 ± 41.47	
	3 months	135.88 ± 59.54	1.24 ± 7.33	121.71 ± 42.39	-0.97 ± 3.69
	6 months	132.10 ± 56.91*†	5.02 ± 8.76	122.75 ± 42.67	-2.01 ± 3.72
PPG (mmol/L)	Baseline	185.70 ± 84.18		162.89 ± 68.99	
	3 months	179.18 ± 81.97*†	6.52 ± 9.91	164.58 ± 69.89	-1.69 ± 5.13
	6 months	174.60 ± 78.84*†	11.10 ± 13.17	166.00 ± 70.34*	-3.11 ± 5.47

Values are mean ± SD.
*Significant intragroup difference vs baseline, †Significant intergroup difference at the same time point.
PI: plaque index, GI: gingival index, PPD: probing pocket depth (percentage of sites with <3 mm, 4-6 mm, or ≥7 mm), CAL: clinical attachment level, PESA: periodontal epithelial surface area, PISA: periodontal inflammatory surface area, BOP: percentage of sites with bleeding on probing, HbA_{1c}: glycated hemoglobin, FPG: fasting plasma glucose, PPG: postprandial glucose

those with poorly controlled diabetes (NTP) had greater deterioration in periodontal status than did those with good glycemic control (NTG) over a period of 6 months (Table 5).

Changes in metabolic markers

Improvement in HbA_{1c} was significant in the treatment group (T group) and was significantly greater in the treatment group than in the no-treatment group (NT group) ($P < 0.05$) (Table 3). Stratification of treatment group on the basis of HbA_{1c} revealed that the decrease in HbA_{1c} was significant for patients with poor glycemic control (TP group), with decreases of 11.8% and 14.9% at 3 and 6 months, respectively ($P < 0.05$) (Table 6). In addition, a statistically significant increase of 2.2% in HbA_{1c} was observed in the no-treatment group (NT group) at 6 months.

Partial correlations for the whole cohort showed that the reduction in HbA_{1c} at 6 months was significantly correlated with treatment (T group) (r = 0.547, $P < 0.05$)

Table 4 Periodontal clinical parameters in the treatment groups during the study period

Parameters		Nondiabetic control group		Treatment/good glycemic control group		Treatment/poor glycemic control group	
		n = 25	Δ	*n* = 23	Δ	*n* = 27	Δ
PI	Baseline	1.66 ± 0.41		1.64 ± 0.30		1.65 ± 0.23	
	3 months	0.28 ± 0.10*	1.38 ± 0.36	1.35 ± 0.28	0.29 ± 0.14*	0.31 ± 0.09*	1.34 ± 0.22
	6 months	0.27 ± 0.09*	1.39 ± 0.37	1.37 ± 0.29	0.27 ± 0.10*	0.29 ± 0.08*	1.36 ± 0.22
GI	Baseline	1.55 ± 0.28		1.56 ± 0.30		1.60 ± 0.25	
	3 months	0.46 ± 0.21*†	1.09 ± 0.41	0.52 ± 0.19*†	1.03 ± 0.21	0.78 ± 0.28*	0.82 ± 0.26
	6 months	0.42 ± 0.19*†	1.13 ± 0.4	0.50 ± 0.18*†	1.05 ± 0.22	0.76 ± 0.26*	0.84 ± 0.26
PPD (mm)	Baseline	2.77 ± 0.58		2.82 ± 0.44		3.08 ± 0.45	
	3 months	1.93 ± 0.44*	0.84 ± 0.29	2.00 ± 0.44*	0.82 ± 0.31	2.32 ± 0.37*	0.76 ± 0.26
	6 months	1.91 ± 0.44*	0.86 ± 0.29	1.98 ± 0.43*	0.84 ± 0.31	2.29 ± 0.37*	0.79 ± 0.26
PPD <3 mm (%)	Baseline	39.69 ± 9.23†		42.67 ± 9.06†		33.02 ± 5. 26	
	3 months	61.40 ± 9.56*	-21.72 ± 8.23	65.25 ± 10.89*	-22.58 ± 10.28	49.87 ± 8.51*	-16.85 ± 7.77
	6 months	62.94 ± 9.70*	-23.25 ± 8.4	66.87 ± 11.14*	-24.20 ± 10.30	52.19 ± 8.64*	-19.16 ± 8.11
PPD 4-6 mm (%)	Baseline	49.49 ± 8.00		46.06 ± 9.54†		53.92 ± 5.05	
	3 months	35.13 ± 9.27*	14.36 ± 6.01	29.60 ± 10.08*	16.45 ± 9.15	41.99 ± 7.79*	11.94 ± 6.57
	6 months	34.15 ± 9.48*	15.34 ± 6.71	28.49 ± 10.23*	17.56 ± 8.99	40.76 ± 7.72*	13.17 ± 6.55
PPD ≥7 mm (%)	Baseline	10.82 ± 4.09		11.27 ± 2.97		13.05 ± 3.78	
	3 months	3.47 ± 1.24*†	7.35 ± 3.67	5.14 ± 1.84*	6.13 ± 2.88	8.14 ± 3.16*	4.91 ± 1.59
	6 months	2.91 ± 1.30*	7.91 ± 3.64	4.63 ± 1.97*	6.64 ± 3. 25	7.05 ± 3.15*	5.99 ± 2.14
CAL (mm)	Baseline	3.14 ± 0.53		3.30 ± 0.52		3.59 ± 0.52	
	3 months	2.43 ± 0.55	0.71 ± 0.31	2.60 ± 0.43*	0.70 ± 0.34	2.91 ± 0.72*	0.68 ± 0.38
	6 months	2.41 ± 0.55*	0.73 ± 0.31	2.58 ± 0.43*	0.72 ± 0.34	2.90 ± 0.72*	0.71 ± 0.38
PESA (mm^2)	Baseline	1,407.51 ± 420.98		1,459.36 ± 309.83		1,560.65 ± 236.27	
	3 months	932.21 ± 329.91*	475.30 ± 210.64	995.30 ± 239.26*	464.06 ± 141.2	1,155.90 ± 247.61*	404.10 ± 82.86
	6 months	919.63 ± 324.48*	487.87 ± 212.3	981.67 ± 234.96*	477.68 ± 142.9	1,141.43 ± 243.25*	418.62 ± 82.3
PISA (mm^2)	Baseline	1,173.21 ± 335.42		1,230.70 ± 356.66		1,560.65 ± 236.27	
	3 months	592.81 ± 202.31*	580.40 ± 180.48	658.39 ± 150.25*	572.31 ± 324.5	1,155.90 ± 247.61*	404.10 ± 82.86
	6 months	573.15 ± 195.17*	600.08 ± 187.50	638.65 ± 148.29*	592.04 ± 329.5	1,141.43 ± 243.25*	418.62 ± 82.3
BOP (%)	Baseline	70.58 ± 16.62		71.95 ± 15.33		75.15 ± 14.15	
	3 months	29.16 ± 8.64*†	41.42 ± 15.28	31.91 ± 9.56*†	40.04 ± 15.65	45.17 ± 9.78*	29.98 ± 12.57
	6 months	29.10 ± 8.65*†	41.48 ± 15.27	31.85 ± 9.56*†	40.05 ± 15.63	45.03 ± 9.70*	30.11 ± 12.54

Values are mean ± SD.
*Significant intragroup difference vs baseline, †Significant intergroup difference at the same time point.
PI: plaque index, GI: gingival index, PPD: probing pocket depth (percentage of sites with <3 mm, 4-6 mm, or ≥7 mm), CAL: clinical attachment level, PESA: periodontal epithelial surface area, PISA: periodontal inflammatory surface area, BOP: percentage of sites with bleeding on probing

and baseline HbA_{1c} level (r = 0.455, $P < 0.05$). Multivariate linear regression showed that being in a treatment group (β = 0.519, $P < 0.05$) and baseline HbA_{1c} level (β = 0.430, $P < 0.05$) were independently and significantly associated with improvement in glycemic control over 6 months.

Discussion

The present results show that nonsurgical periodontal treatment is associated with significant improvement in glycemic and periodontal status in individuals with T2DM and moderate-to-severe periodontitis. The improvement in periodontal status was independently associated with improvement in glycemic control in multiple linear regression. An independent effect of baseline HbA_{1c} level on change in HbA_{1c} was also observed. This suggests that the decrease in HbA_{1c} depends on baseline HbA_{1c}, i.e., the higher the baseline value the greater the decrease, irrespective of the type of antidiabetic treatment (39).

Inflamed periodontal tissue is highly vascular and thus may serve as an endocrine source for proinflammatory mediators, which, after entering systemic circulation, may alter lipid and glucose metabolism and induce insulin resistance (40,41). It is believed that resolution of periodontal inflammation after periodontal therapy reduces levels of inflammatory mediators, thereby improving glycemic control (1). Therefore, we studied patients with moderate-to-severe periodontitis for whom periodontal treatment was expected to substantially resolve periodontal inflammation.

To determine the influence of glycemic status on response to periodontal treatment, patients with diabetes were stratified on the basis of HbA_{1c} level as having good or poor glycemic control. Although such groups have been compared in cross-sectional studies, few intervention studies have stratified patients in this manner. Despite having similar plaque levels, both the percentage of sites with BOP and GI score were significantly higher at 3 and

Table 5 Clinical periodontal status in the no-treatment/good glycemic control and no-treatment/poor glycemic control groups at baseline, month 3, and month 6

Parameters		No-treatment/good glycemic control group		No-treatment/poor glycemic control group	
		n = 25	Δ	*n* = 25	Δ
PI	Baseline	1.59 ± 0.26		1.68 ± 0.26	
	3 months	1.61 ± 0.33	-0.02 ± 0.19	1.70 ± 0.29	-0.02 ± 0.16
	6 months	1.63 ± 0.3	-0.04 ± 0.24	1.73 ± 0.34	-0.05 ± 0.19
GI	Baseline	1.62 ± 0.17		1.65 ± 0.17	
	3 months	1.67 ± 0.22	-0.05 ± 0.19	1.74 ± 0.36†	-0.09 ± 0.25
	6 months	1.71 ± 0.25	-0.09 ± 0.22	1.79 ± 0.39*†	-0.14 ± 0.28
PPD (mm)	Baseline	2.92 ± 0.58		3.23 ± 0.48	
	3 months	2.93 ± 0.58	-0.01 ± 0.04	3.28 ± 0.48*†	-0.05 ± 0.03
	6 months	2.94 ± 0.57	-0.02 ± 0.07	3.33 ± 0.50*†	-0.09 ± 0.06
PPD <3 mm (%)	Baseline	38.03 ± 10.84		33.92 ± 8.05	
	3 months	37.24 ± 10.72	0.79 ± 3.34	30.44 ± 8.78*†	3.48 ± 2.53
	6 months	36.51 ± 11.03	1.52 ± 5.51	27.13 ± 9.99*†	6.79 ± 4.41
PPD 4-6 mm (%)	Baseline	52.51 ± 10.15		51.90 ± 7.96	
	3 months	53.10 ± 10.04	-1.59 ± 1.96	52.52 ± 8.30	-0.63 ± 1.89
	6 months	53.52 ± 10.14	-1.01 ± 3.44	53.02 ± 9.47	-1.12 ± 3.34
PPD ≥7 mm (%)	Baseline	9.47 ± 2.76		14.18 ± 5.34	
	3 months	9.65 ± 2.76	-0.19 ± 1.54	17.15 ± 7.21*†	-2.97 ± 2.81
	6 months	9.98 ± 2.99	-0.51 ± 2.37	19.99 ± 8.53*†	-5.81 ± 4.41
CAL (mm)	Baseline	3.19 ± 0.62		3.54 ± 0.55	
	3 months	3.21 ± 0.62	-0.12 ± 0.04	3.60 ± 0.56*†	-0.05 ± 0.03
	6 months	3.23 ± 0.63	-0.04 ± 0.09	3.65 ± 0.58*†	-0.11 ± 0.07
PESA (mm^2)	Baseline	1,485.23 ± 262.14		1,562.72 ± 376.77	
	3 months	1,496.81 ± 262.09	-11.58 ± 25.16	1,592.37 ± 386.86*†	-29.65 ± 18.84
	6 months	1,503.31 ± 260.25	-18.08 ± 40.21	1,614.46 ± 392.96*†	-51.74 ± 27.77
PISA (mm^2)	Baseline	1,255.29 ± 265.79		1,324.54 ± 338.70	
	3 months	1,270.90 ± 256.87	-15.61 ± 45.24	1,364.61 ± 350.60*†	-40.06 ± 24.6
	6 months	1,279.42 ± 252.99	-24.14 ± 60.59	1,395.32 ± 357.63*†	-70.77 ± 33.10
BOP (%)	Baseline	73.60 ± 6.97		77.13 ± 13.02	
	3 months	74.36 ± 7.36	-0.77 ± 21.3	79.63 ± 13.79*†	-2.5 ± 2.48
	6 months	75.67 ± 7.62*	-2.06 ± 3.08	82.09 ± 14.37*†	-4.97 ± 5.11

Values are mean ± SD.
*Significant intragroup difference vs baseline, †Significant intergroup difference at the same time point.
PI: plaque index, GI: gingival index, PPD: probing pocket depth (percentage of sites with <3 mm, 4-6 mm, or ≥7 mm), CAL: clinical attachment level, PESA: periodontal epithelial surface area, PISA: periodontal inflammatory surface area, BOP: percentage of sites with bleeding on probing

Table 6 Glucose markers in participants with type 2 diabetes at baseline, 3 months, and 6 months, by study group

	HbA_{1c} (%)	Δ	FPG (mmol/L)	Δ	PPG (mmol/L)	Δ
Treatment/good glycemic control group *n* = 23						
Baseline	6.03 ± 0.47		95.04 ± 20.14		131.57 ± 35.71	
3 months	5.94 ± 0.48	0.10 ± 0.28	94.70 ± 19.98	0.35 ± 2.44	129.96 ± 35.94	1.61 ± 4.31
6 months	5.89 ± 0.41	0.16 ± 0.32	93.91 ± 19.60	1.13 ± 3.07	128.83 ± 34.95*	2.73 ± 5.01
Treatment/poor glycemic control group *n* = 27						
Baseline	9.99 ± 2.01		172.96 ± 58.97		231.81 ± 86.46	
3 months	8.81 ± 1.47*	1.19 ± 0.72	170.96 ± 59.71	1.99 ± 9.74	221.11 ± 87.19*	10.70 ± 11.39
6 months	8.50 ± 1.21*	1.49 ± 0.98	164.63 ± 58.22*	8.33 ± 10.57	213.59 ± 85.14*	18.22 ± 13.8
No-treatment/good glycemic control group *n* = 25						
Baseline	5.94 ± 0.75		91.12 ± 15.30		118.44 ± 24.18	
3 months	6.01 ± 0.82	-0.06 ± 0.35	91.20 ± 14.70	-0.08 ± 2.04	119.16 ± 24.69	-0.72 ± 2.45
6 months	6.08 ± 0.89	-0.15 ± 0.41	92.12 ± 14.88	-1.00 ± 2.12	120.52 ± 24.80*	-2.08 ± 2.76
No-treatment/poor glycemic control group *n* = 25						
Baseline	9.81 ± 2.24		150.35 ± 38.07		207.33 ± 70.85	
3 months	9.92 ± 2.37	-0.11 ± 0.28	152.22 ± 38.91	-1.86 ± 4.68	210.00 ± 71.17	-2.67 ± 6.76
6 months	10.03 ± 2.49*	-0.22 ± 0.35	153.38 ± 39.26*	-3.03 ± 4.64	211.48 ± 71.95*	-4.15 ± 7.16

n = 100, Values are mean ± SD.
*Significant intragroup difference vs baseline.
FPG: fasting plasma glucose, PPG: postprandial glucose, HbA_{1c}: glycated hemoglobin

6 months for patients with poor glycemic control (TP group) than for those without diabetes (NoDM group) and those with good glycemic control (TG group). These differences might be due to a hyperinflammatory gingival response caused by vascular alterations and poor healing in patients with poorly controlled diabetes. We hypothesize that the level of glycemic control affects gingival response to bacterial plaque in diabetic individuals.

A statistically significant increase in periodontal variables was observed in patients who did not receive periodontal treatment over 6 months (NT group). However, the change was not large enough to be of clear clinical relevance (42). Periodontal disease progression was seen in both the no-treatment groups (NTG and NTP groups) but was significantly greater among those with poorly controlled diabetes (NTP group). This indicates that diabetes is a risk factor for periodontal disease, as the level of glycemic control appears to be an important determinant of this relationship (43). There was a statistically significant decrease in a PPD <3 mm (%) and a statistically significant increase in a PPD ≥7 mm (%) in the NTP group at 3 and 6 months, which indicates a significant decrease in healthy sites and an increase in diseased sites (Table 4). We believe that the underlying mechanism is impaired immune cell function leading to inhibition of bactericidal activity in periodontal pockets, which affects periodontal disease severity and progression (1).

Our results confirm those of Kiran et al. (11) and Koromantozos et al. (17), who reported significant improvements in HbA_{1c} after SRP. In this study we observed that a decrease of 526.97 mm^2 in periodontal inflammatory surface area was associated with a 10.8% improvement in HbA_{1c}. Our results are consistent with those of a study of Asians (18), which found significant improvement at 3 months after periodontal therapy in serum levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) , interleukin-6 (IL-6), fasting plasma glucose (FPG), HbA_{1c}, fasting insulin, homeostasis model assessment of insulin resistance, and triglycerides.

In contrast to our findings, a recent study did not observe a significant improvement in HbA_{1c} with SRP even after 1 year (23). That study enrolled participants with well-controlled baseline HbA_{1c} levels, which left little room for improvement. Patients with mild periodontitis were also included, and this might have limited the potential for improvement after treatment. Their study also had a rather high dropout rate, which is a potential source of bias.

Similarly, in a recent trial (24) periodontal treatment did not significantly improve metabolic status because the enrolled patients did not have severe periodontal disease. In contrast, only patients with moderate-to-severe periodontitis were included in our study.

In a recent multicenter trial (22) the authors claimed a significant improvement in periodontal health; however, although the 19% improvement was statistically significant, it had no clinical relevance and therefore would not likely affect HbA_{1c}. In addition, no significant effect of periodontal treatment would be expected, as baseline HbA_{1c} levels were already consistent with good glycemic control. In fact, the results showed decreased glycemic control 6 months after therapy. This might be linked to the limited improvement in PI and GI scores, which are closely linked to patient compliance. This finding raises concerns about patient commitment to diabetes management. Another significant problem with this study was the chronic low-grade inflammatory state elicited by the frank obesity in the treatment group (mean ± standard deviation (SD) BMI, 34.7 ± 7.5 kg/m^2), which might have masked any anti-inflammatory effect of successful periodontal treatment. In contrast (22), a study of Japanese patients (19) found a significant improvement in HbA_{1c} levels after 3 months of combination therapy comprising topical antibiotics combined with conventional mechanical debridement. Baseline hs-CRP level was significantly independently associated with the rate of HbA_{1c} reduction, and the greatest reduction in HbA_{1c} level was seen in the group with the highest reduction in hs-CRP after periodontal treatment. Interestingly, the participants in the Hiroshima study (19) were non-obese adults with T2DM, unlike the participants in the recent multicenter trial (22), in which the level of obesity in the treatment group might have obscured the effect of periodontal treatment.

A strength of the present study is that, despite the consequent reduction in sample size, stringent inclusion criteria were used to minimize confounding factors. The fact that all participants had at least 12 teeth reduced heterogeneity in the study sample, thereby minimizing confounding. Effective periodontal treatment was administered in the treatment group. The resultant significant improvement in periodontal status was independently associated with improvement in glycemic status. To our knowledge, PISA sheets have never been used to evaluate the effect of periodontal treatment in individuals with type 2 diabetes. PISA quantifies the amount of inflamed periodontal tissue (in mm^2); thus, it clearly represents the inflammatory burden posed by periodontal tissues. Current or past smokers were excluded from our study because the residual confounding effect of smoking can

bias estimates. Individuals of the same ethnicity were included in the various groups in our study; therefore, the effects of differences in genetic background on the present results are likely to be minimal.

The present study has some limitations. The sample size is small and the participants were recruited at a single center. Thus, the validity and generalizability of the findings to all patients with T2DM and periodontitis are limited. Although PISA is believed to be the best tool for assessing the amount of inflamed periodontal tissue, it might not precisely quantify the amount of inflamed tissue. Calculation of CAL, recession, and BOP, which are used to estimate PISA, is subject to measurement errors related to the observer, instrument, and patient. In addition, the formulas transforming CAL and recession to surface area use population-based mean values of root surface areas and root lengths, which limits the ability to account for individual variation in root surface area and root length when calculating PISA. PISA quantifies the amount of inflamed periodontal tissue in two dimensions, whereas periodontitis is a three-dimensional inflammatory process, i.e., it extends into the connective tissue around the roots of teeth. For these reasons, PISA may not precisely quantify the amount of inflammatory periodontal tissue (29). Systemic markers of inflammation, such as tumor necrosis factor-α, interleukin-6, and interleukin-1, are believed to correlate closely with indicators of glycemic control and would thus have helped to better explain our observations. No inflammatory markers were assessed in the present study; thus, future studies should investigate these markers.

Nonsurgical periodontal treatment was an independent factor in improving glycemic control in patients with T2DM and moderate or severe chronic periodontitis. Clinically and statistically significant improvement in periodontal status was observed after periodontal therapy. Our results indicate that individuals with good glycemic control respond to scaling and root planing as well as systemically healthy individuals, and that patients with poorer glycemic control had a less favorable periodontal response. Periodontal disease progression was observed in the no-treatment group (NT group) and was greater in those with poorly controlled diabetes. The present study was not designed to investigate the underlying biologic mechanisms that contribute to changes in metabolic control. Large-scale multicenter trials that include measurements of inflammatory markers and long-term observation are necessary in order to confirm the present findings.

Conflict of interest and source of funding statement
The authors have no conflicts of interest to declare.

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