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RESEARCH ARTICLE

Association of periodontal disease with glycemic control in patients with type 2 diabetes in Indian population

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Abstract **This study aims to investigate the link between glycated hemoglobin and diabetic complications with chronic periodontitis. A total of 207 patients with type 2 diabetes and chronic periodontitis (CP) were divided according to tertiles of mean PISA (periodontal inflamed surface area) scores as low, middle and high PISA groups. Simultaneously a group of 67 periodontally healthy individuals (PH) was recruited. Periodontal examinations, including full-mouth assessment of probing depths (PPD), bleeding on probing, clinical attachment level and plaque scores were determined. Blood analyses were carried out for glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), 2 h post parandial glucose (PPG). Individuals in PH group had significantly better glycemic control than CP group. Upon one-way analysis of variance, subjects with increased PISA had significantly higher HbA_{1c} levels, retinopathy and nephropathy ($P < 0.05$). After controlling for age, gender, body mass index (BMI), socioeconomic status (SES), family history of diabetes and periodontitis, duration of diabetes, the mean PISA in mm^2, PPD 4–6 mm (%) and PPD $\geqslant$ 7 mm (%) emerged as significant predictors for elevated HbA_{1c} in regression model ($P < 0.05$). Logistic regression analysis revealed that PISA was associated with higher risk of having retinopathy and neuropathy (odds ratio). In our study, the association between glycemic control and diabetic complications with periodontitis was observed.**

Keywords type 2 diabetes mellitus; hemoglobin A; glycated; chronic periodontitis

Introduction

Diabetes mellitus (DM) and periodontal disease are two chronic diseases that have long been believed to be biologically linked. Moreover, both are common and widespread enough to be considered as global epidemics. Diabetes is a pathological consequence of many physiological changes leading to metabolic imbalance, hyperglycaemia and chronic inflammation with potential influence on the tissue integrity and repair [1]. As a sequel to long standing metabolic derangement (poor glycemic control), blood vessels endure damage resulting in complications, namely, atherosclerosis, myocardial infarction, retinopathy, nephropathy, neuropathy, delayed wound healing and an increased risk of infections [2,3].

Periodontitis is a chronic multifactorial infectious disease of the supporting tissue of the teeth and is characterized by destruction of periodontal connective tissue and alveolar bone [4]. It is recognized as the sixth complication of diabetes [5].

There is increasing evidence suggesting periodontitis as risk factor for several systemic diseases such as cardiovascular diseases, preterm low-birthweight and diabetes [6,7]. A number of studies have been conducted to explore the association between diabetes and periodontal disease. Some studies have assessed the effects of diabetes on periodontal health [8–17]; whereas others have investigated the converse side of this relationship, i.e., the effect of periodontal disease on diabetic state and/or diabetes complications [18–31]. However, the most direct evidence can be derived from interventional studies and systematic reviews assessing the effect of treatment of periodontitis on glycemic control and reductions in HbA_{1c} [32–37].

The degree of association between periodontitis and type 2 diabetes mellitus (T2DM) appears to differ with the geographic distribution. The differences in the strength of association could be due to disparity in the cultural, genetic, socioeconomic factors among the ethnic groups; differences in study design, analysis, and measures to categorize periodontitis [38]. The criteria used to identify

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periodontitis are also believed to influence the strength of association between a particular systemic disease and periodontitis. Therefore the findings from one study can not be generalized to the overall population suffering from diabetes and periodontitis [38–41].

Most studies exploring the association between periodontitis and diabetes 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. As PPD and CAL are linear measures they do not quantify the amount of inflamed periodontal tissue. The measure periodontal inflamed surface area (PISA) expresses the surface area of bleeding pocket epithelium in square millimeters. By far it is believed to be better than currently used criteria's for classifying periodontitis. PISA was used in the present study as well to quantify periodontal inflammatory burden [42].

This study was conducted with the aim to assess the association of levels of glycemic control with periodontal disease in type 2 diabetic patients with periodontitis in north Indian population using several methods to classify periodontitis. The authors also seek to explore the association between periodontal inflamed surface area and diabetes related complications.

Materials and methods

Study population

This cross sectional study 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 1975 *Declaration of Helsinki*, as revised in 2000. A single examiner (R.K.S) screened 584 patients who had been receiving treatment for at least 1 year after a diagnosis of TD2M.

Criteria adopted for inclusion in the study were: (1) adults in the age group of 45 – 60 years having $\geqslant$ 12 natural teeth excluding third molars; (2) no periodontal intervention $\leqslant$ 6 months prior to study; (3) presence of chronic periodontitis (CP). Case definition for CP required presence of two or more interproximal sites with attachment loss $\geqslant$ 4 mm, not on the same tooth, or two or more interproximal sites with PPD $\geqslant$ 5 mm, not on the same tooth [36].

Following conditions made the case candidate for exclusion criteria: (1) indication for extraction at the time of entry in the study; (2) history of systemic disease which could influence course of periodontal disease or glucose metabolism such as cardiovascular diseases, rheumatoid arthritis, chronic respiratory, pregnancy or lactation, hormone replacement therapy at the time of study; (3) subjects aberrant lipid profile; (4) long-term treatment with non-steroidal anti-inflammatory drugs; (5) systemic infection or history of systemic antibiotic usage $\leqslant$ 3 months. Smokers as well as former smokers were also excluded from the study. Simultaneously a group of 67 periodontally healthy subjects (PH) with T2DM was also recruited (Fig. 1).

The American Diabetes Association (ADA) criteria were used to categorize the subjects into prediabetes and diabetes and microvascular complications [43].

Following criteria were used for diagnosis of T2DM:

(1) $HbA_{1c} \geqslant 6.5\%$;

(2) FPG $\geqslant$ 126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h;

(3) 2-h plasma glucose $\geqslant$ 200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test was performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OGTT was done with 75 g anhydrous glucose powder dissolved in 250–300 ml water, which was to be consumed over 5 min. Time was counted from the start of the drink. Fasting plasma glucose and 2-h post glucose load were estimated by glucose oxidase method.

Detailed systemic examinations, rather than personal pronouncements, were relied upon to determine the individual's medical status via evaluation of plasma lipid profile, glucose level, liver enzymes, and thyroid tests. Of 584 patients referred from the Department of Medicine, 207 participants were included in the study on the basis of the inclusion and exclusion criteria. All patients were explained the procedure in detail and were given opportunity to ask questions, clear their doubts and were included in the study only after obtaining their written consent.

Clinical periodontal examination

After recruitment for the study, all patients underwent a full-mouth periodontal examination. All patients were examined in a standardized way using illumination by a dental light, a mouth mirror, tweezer, a manual calibrated periodontal probe (William's periodontal probe, Hu-Friedy, Chicago, IL, USA) and explorer. Recording of periodontal parameters throughout the study was done by a single examiner (S.C.N). Determination of the examiner reproducibility was done by carrying out double clinical periodontal data recording on 10 patients for PPD, location

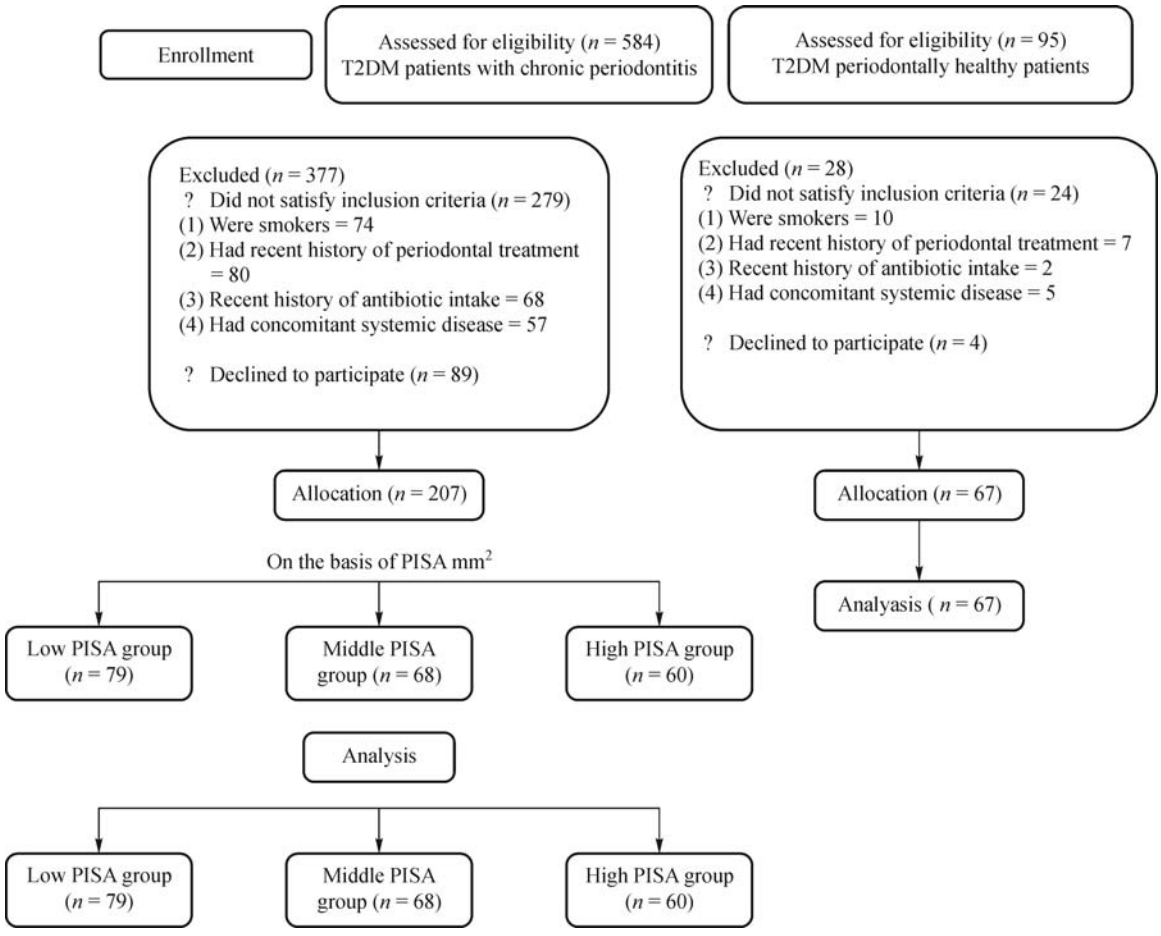

Fig. 1 Enrollment and participation of the study participants.

of gingival margin (LGM), and CAL on six sites per tooth. Each participant was assessed twice in one appointment, over a 3-h interval, and the repeat measurements were carried out blinded to the first measurement. Both sets of measurements had $k > 0.8$ for PPD, LGM, and CAL. Clinical parameters were recorded at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual/palatal, mid-lingual/palatal, disto-lingual/palatal) except third molars. Bleeding on probing (BOP) was recorded as present (score 1) if occurred within 30 s of probing and absent (score 0) in absence of bleeding. Periodontal probing depth (PPD) was measured as the distance from the gingival margin to the base of the clinical pocket. LGM was recorded with respect to the cementoenamel junction (CEJ). Clinical attachment level (CAL) was recorded as the distance from CEJ to the base of the clinical pocket. CAL and PPD were recorded in millimeters. A Microsoft Excel spreadsheet was used to facilitate periodontal inflamed surface area (PISA) determination following the procedure detailed on the website www.parsprototo.info. Plaque index (PI) [44] and gingival index (GI) [45] were recorded at 4 sites per tooth (mesio-buccal, midbuccal, disto-buccal, midlingual/palatal).

Anthropometric and biochemical measurements

Information regarding age, gender, smoking status, physical activity, duration of diabetes, family history of diabetes, and type of medications used was obtained through interview. On the basis of education, income, and profession, patients were categorized into low, middle, and high socioeconomic status. Anthropometric evaluation included measurements of weight (kg) and height (m) for the determination of body mass index (kg/m^2).

Glycated hemoglobin (HbA_{1c}) determination was based on a latex agglutination inhibition assay using auto analyzer (Konelab clinical chemistry analyzers; Thermo scientific, Milan, Italy) and blood glucose level was determined using glucose oxidase–peroxidase method (Glucose *in vitro* diagnostic kit; Siemens, Vadodara,

Gujarat, India) at the Department of Biochemistry, PGIMS, Rohtak (laboratory staff was masked to the allocation group).

Statistical analysis

Post hoc power analysis was performed using statistical software (G power v.2.0, Bonn, Germany). With a sample size of 207, the significance level of two sided α 0.05, fixed-effect size was computed following the general rule of the standardized difference in a given output variable (HbA_{1c}). This came out to be 0.30. With these measurements, the statistical power of the study was found to be > 80%. Mean PI, GI, PPD, CAL, and PISA were calculated for each patient as well as group. For BOP the percentage of positive sites were obtained for each participant and thereafter a mean value was calculated for the group. The normality of distribution of data was tested using the Kolmogorov–Smirnov test. As data was normally distributed, independent sample *t* test was used to compare periodontally healthy group (PH) and chronic periodontitis (CP) group. For comparison, subjects in CP group were further divided into three groups according to tertiles of the mean PISA (low, ranging from 250 to 850 mm^2; middle, ranging from 851 to 1250 mm^2; and high, ranging from 1251 to 2500 mm^2). So subsequently according to their PISA scores patients were divided as low PISA (LP), middle PISA (MP) and high PISA (HP) groups. Differences between groups were assessed using one-way analysis of variance, with Tukey's *post-hoc* test for ordinal data and the chi-square test for dichotomous data. Partial correlations were carried out to calculate correlations among HbA_{1c} with various periodontal parameters, including the number of teeth, PI, mean PPD, mean PISA, percentage of sites with PPD 3 mm, percentage of sites with PPD 4–6 mm, percentage of sites with PPD ⩾ 7 mm, mean CAL, percentage of sites with BOP and diabetic complications after adjustment for potential confounders including age, gender, BMI, SES, family history of diabetes, family history of periodontitis, and the number of years since diagnosed with diabetes.

Multiple stepwise regression analyses were performed to explore the effect of each independent variable on the HbA_{1c}. All variables that had shown a significant association (mean PPD, PPD 3 mm (%), PPD 4–6 mm (%), PPD ⩾ 7 mm (%), mean PISA (mm^2), retinopathy, and neuropathy) were entered in regression model after controlling for confounders.

Binary logistic regression analyses were carried out to explore association between diabetic complications namely retinopathy, nephropathy, and neuropathy with PISA (median value) in three separate models. To compute the odds ratio (OR) and 95% confidence interval (CI), diabetic complications were set as dependent variables. The Hosmer–Lemeshow goodness-of-fit test statistic was applied to verify whether the present model fits well. Models were adjusted for covariates. All statistical analyses were two-tailed, with a significance level of 0.05, and were calculated using SPSS statistical software (SPSS, v.19.0 for Windows, SPSS, Chicago, IL, USA).

Results

Table 1 shows comparison between periodontally healthy (PH) group and chronic periodontitis (CP) group. Subjects with chronic periodontitis had significantly higher BMI, higher levels of HbA_{1c}, FPG, PPG, higher prevalence of diabetes related complications, and duration of diabetes as compared to periodontally healthy (PH) group.

Table 2 shows demographic parameters of study subjects by tertiles of mean PISA. Patients in all the groups were comparable in terms of age, gender, and BMI. Also no significant difference was observed between the groups in terms of modality to manage diabetes. Patients with family history of diabetes mellitus were significantly more in both middle PISA and high PISA groups than low PISA group ($P < 0.0001$ and $P < 0.0001$, respectively). High PISA group had significantly less number of patients with high socioeconomic status ($P < 0.0001$ and $P < 0.0001$, respectively). Diabetes associated complications were highest in high PISA group.

Table 3 depicts glycemic levels and plaque scores by PISA severity. HbA_{1c} in high PISA group was significantly higher than both low PISA and middle PISA groups ($P < 0.0001$ and $P < 0.0001$, respectively). Subjects in low PISA group had best control over glycemic control over time. FPG and PPG were significantly higher in high PISA group as compared to both low PISA and middle PISA groups.

In correlation analysis, HbA_{1c} had a significant and positive association with mean PPD ($r = 0.547$, $P < 0.0001$), PPD 4–6 mm (%) ($r = 0.543$, $P < 0.0001$), PPD ⩾ 7 mm (%) ($r = 0.678$, $P < 0.0001$), mean PISA (mm^2) ($r = 0.553$, $P < 0.0001$), retinopathy ($r = 0.162$, $P < 0.0001$), and neuropathy ($r = 0.192$, $P < 0.0001$) whereas HbA_{1c} shared a significant and negative association with PPD 3 mm (%) ($r = -0.722$, $P < 0.0001$) after controlling for confounders. Scatter plot between the level of HbA_{1c} in subjects with type 2 diabetes and periodontal parameters having positive association is depicted in Fig. 2.

In multiple regression model using HbA_{1c} as the dependant variable, mean PISA in mm^2, PPD 4–6 mm (%) and PPD ⩾ 7 mm (%) became significant predictor variables for elevated HbA_{1c} levels (Table 4). The results of the logistic regression analysis (Table 5) revealed that

Table 1 Patients characteristics for periodontally healthy and chronic periodontitis groups

Variable	Periodontally healthy (PH) group (Total = 67)	Chronic periodontitis (CP) group (Total = 207)	*P*
Age (year; mean ± SD)	52.21±6.96	53.81±7.18	NS
Male/female (*n*)	34/33 (50.74%/49.25%)	102/105 (49.27%/50.72%)	NS
Duration of diabetes mellitus (year; mean ± SD)	4.95±2.03	7.59±5.49*	<0.0001
BMI (mean ± SD)	23.53±5.03	25.56±4.44*	<0.0001
Regular physical exercise (*n*)	51 (76.11%)	122 (58.93%)*	<0.0001
Family history of diabetes mellitus (*n*)	19 (28.35%)	104 (50.24%)*	<0.0001
Family history of periodontitis (*n*)	9 (13.43%)	94 (45.41%)*	<0.0001
Diabetes mellitus treatment (*n*)			
Diet control	35 (52.23%)	26 (12.56%)*	<0.0001
Oral medication	28 (41.79%)	154 (74.39%)*	<0.0001
Insulin	4 (5.97%)	27 (13.04%)*	<0.0001
Frequency of tooth brushing (*n*)			
⩾2 times/day	54 (80.59%)	172 (83.09%)	NS
Socioeconomic status			
Low	11 (16.41%)	103 (49.75%)*	<0.0001
Middle	35 (52.23%)	37 (17.87%)*	<0.0001
High	21 (31.34%)	67 (32.36%)*	<0.0001
Diabetic complications			
Retinopathy	14 (20.89%)	136 (65.7%)*	<0.0001
Nephropathy	10 (14.92%)	109 (52.65%)*	<0.0001
Neuropathy	6 (8.95%)	70 (33.81%)*	<0.0001
HbA_{1c} (%)	5.74±1.34	7.24±2.39*	<0.0001
FPG (mmol/L)	95.29±23.19	119.24±48.58*	<0.0001
PPG (mmol/L)	112.12±28.81	158.78±71.52*	<0.0001

n, number of subjects; mean±SD, mean±standard deviation; NS, not significant.
*indicates $P \leqslant 0.05$ significant difference between periodontally healthy and chronic periodontitis groups.

Table 2 Demographic parameters of study subjects (total = 207) by tertiles of mean PISA

Variable	Low PISA (LP) (*n* = 79)	Middle PISA (MP) (*n* = 68)	High PISA (HP) (*n* = 60)	*P* (LP/MP)	*P* (LP/HP)	*P* (MP/HP)
Age (year; mean±SD)	54.47±8.43	53.89±6.18	53.21±6.47	NS	NS	NS
Male/female (*n*)	39/40 (49.36%/50.63%)	33/35 (48.52%/51.47%)	32/28 (53.33%/46.66%)	NS	NS	NS
Duration of diabetes mellitus (year; mean±SD)	6.94±4.57	8.77±6.83	7.11±4.74	NS	NS	NS
BMI (mean±SD)	24.04±5.17	26.48±3.69*	28.51±3.62*†	<0.0001	0.002	0.002
Regular physical exercise (*n*)	41 (51.89%)	46 (67.64%)	35 (58.33%)	NS	NS	NS
Family history of diabetes mellitus (*n*)	24 (30.37%)	34 (50.00%)*	46 (76.66%)*†	0.000	0.000	<0.0001
Family history of periodontitis (*n*)	31 (39.24%)	26 (38.23%)	37 (61.66%)*	NS	NS	<0.0001
Diabetes mellitus treatment (*n*)						
Diet control	10 (12.65%)	8 (11.76%)	8 (13.33%)	NS	NS	NS
Oral medication	61 (77.21%)	51 (75.00%)	42 (70.00%)	NS	NS	NS
Insulin	8 (10.12%)	9 (13.23%)	10 (16.66%)	NS	NS	NS
Frequency of tooth brushing (*n*)						
⩾2 times/day	64 (81.81%)	57 (83.82%)	51 (85.00%)	NS	NS	NS
Socioeconomic status						
Low	37 (46.83%)	31 (45.58%)	35 (58.33%)	NS	NS	NS
Middle	9 (11.39%)	13 (19.11%)	15 (25.00%)	NS	NS	NS
High	33 (41.77%)	24 (35.29%)	10 (16.66%)*†	NS	<0.0001	<0.0001
Diabetic complications						
Retinopathy	38 (48.10%)	43 (63.23%)	55 (91.66%)*	NS	<0.0001	NS
Nephropathy	29 (36.70%)	37 (54.41%)	43 (71.66%)*	NS	<0.0001	NS
Neuropathy	21 (26.58%)	26 (38.23%)	23 (38.33%)	NS	NS	NS

n, number of subjects ; mean±SD, mean±standard deviation; NS, not significant.
* indicates $P \leqslant 0.05$ significant difference between low PISA with middle PISA and high PISA.
† indicates $P \leqslant 0.05$ significant difference between middle PISA and high PISA.

Table 3 Glycemic levels and plaque scores by PISA severity (mean±SD)

Variable	Low PISA ($n = 79$) (LP)	Middle PISA ($n = 68$) (MP)	High PISA ($n = 60$) (HP)	P (LP/MP)	P (LP/HP)	P (MP/HP)
HbA_{1c} (%)	6.06±1.59	7.03±1.77*	9.05±2.79*†	0.006	<0.0001	<0.0001
FPG (mmol/L)	101.04±28.81	121.98±48.86*	140.11±59.47*	0.014	<0.0001	0.066
PPG (mmol/L)	129.68±38.08	166.93±82.09*	187.85±78.87*	0.003	<0.0001	0.170
PI	1.48±0.31	1.43±0.37	1.51±0. 24	NS	NS	NS

mean±SD, mean±standard deviation; NS, not significant.
* indicates $P \leqslant 0.05$ significant difference between low PISA with middle PISA and high PISA.

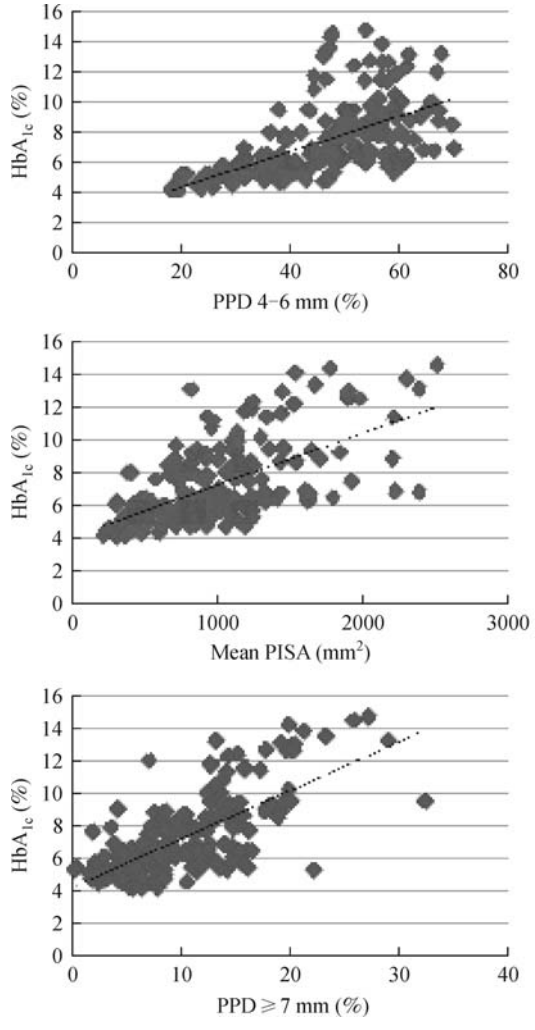

Fig. 2 Scatter plot of subjects with type 2 diabetes showing, after controlling for age, gender, BMI, SES (high/middle versus low), family history of diabetes, family history of periodontitis, the number of years since diagnosed with diabetes, a positive relationship between the level of HbA_{1c} and PPD 4–6 mm (%) (r = 0.543, $P < 0.0001$) in partial correlation analysis. There was also a significant positive correlation between the levels of HbA_{1c} with PPD ⩾ 7 mm (%) (r = 0.678, $P < 0.0001$) and mean PISA (mm^2) (r = 0.553, $P < 0.0001$).

there was a significant association between retinopathy and neuropathy with PISA (median).

Discussion

The results of the present study show association between glycemic control (HbA_{1c}) over time with chronic periodontitis. This relationship was found to be independent of age, gender, BMI, SES, family history of diabetes or periodontitis, and duration of diabetes in regression analysis model. Further, higher odds of retinopathy and neuropathy with high periodontal inflamed surface area after applying logistic regression suggests that periodontal inflammation may contribute to diabetic complications.

Our results are in agreement with the study by Nesse *et al.* [21] who observed a dose–response relationship between PISA and HbA_{1c} in T2DM patients. It is imperative to note that their study had a relatively small sample size of 40 patients having T2DM. Moreover, 90% of their study population was either overweight or obese, with more than 80% of female participants. Consequently results of their study can be mainly confined to obese women of mixed black origin from the Netherlands Antilles [21].

Our results confirm those of Chen *et al.* [23], who observed that subjects with an increased mean PPD had significantly higher levels of HbA_{1c} and CRP (C-reactive proteins). In their study mean PPD emerged as a significant predictor variable for elevated HbA_{1c} levels [23].

In contrast to our findings, in the study [26] on Indonesian population no association was observed between any measure for periodontitis severity and HbA_{1c} in patients with diabetes. Authors in the study [26] believed that this could be due to the influence of oral hypoglycemic agents used by the patients in their study which may have veiled the effect of periodontitis on the HbA_{1c} level. They also advocated that since diabetic patients follow dietary restrictions (e.g., avoiding sugar rich foods), such a diet may impact blood glucose levels and consequently mask the influence of periodontitis on HbA_{1c} level. They also concluded that relatively controlled BMI (average 25) could be the reason for no observed association. A rather relaxed inclusion criteria in terms of age (stated as ⩾ 18 years) of the participants in their study might have also influenced their results [26]. As both diabetes and periodontitis are chronic inflammatory states,

Table 4 Results from multiple linear regression analyses (models to predict HbA_{1c})

Model	Unstandardized coefficients		Standardized coefficients	t	Sig.	95% confidence interval for B	
	B	Std. Error	Beta			Lower bound	Upper bound
(Constant)	1.070	1.246		0.859	0.391	−1.387	3.527
PPD mm	−0.092	0.444	−0.031	−0.208	0.836	−0.969	0.784
PPD 4–6 mm (%)	0.058	0.011	0.303	5.440	<0.0001*	0.037	0.079
PPD⩾7mm (%)	0.223	0.019	0.521	11.687	<0.0001*	0.186	0.261
CAL mm	0.174	0.338	0.061	0.513	0.608	−0.495	0.842
PISA mm^2	0.001	0.000	0.194	2.066	0.040*	0.000	0.002
BOP (%)	−0.003	0.007	−0.023	−0.421	0.674	−0.015	0.012
Retinopathy	−0.080	0.245	−0.017	−0.329	0.743	−0.563	0.403
Nephropathy	0.155	0.247	0.032	0.627	0.531	−0.330	0.643
Neuropathy	0.180	0.208	0.037	0.863	0.389	−0.231	0.590

Dependent variable, $HbA_{1c.}$ Confounders: age, gender, BMI, SES, family history of diabetes, family history of periodontitis, the number of years since diagnosed with diabetes.
* $P \leqslant 0.05$ indicates significance.

Table 5 Logistic regression analyses of the association between diabetic complications with PISA (median value)

Variable	Model 1			Model 2			Model 3		
	95% CI	P*	SE	95% CI	P*	SE	95%CI	P*	SE
PISA median	1.010–1.568	0.04	0.298	0.965–1.491	NS	0.021	1.084–1.674	0.007	0.301

* indicates $P \leqslant 0.05$ significance. NS, not significant. Model 1 dependent variable, retinopathy. Model 2 dependent variable, nephropathy. Model 3 dependent variable, neuropathy.

any proven effect of such diseases takes time to manifest [46–48]. Therefore, there is possibility of underlying derangement which may not be large enough to be of clear clinical or statistical relevance at initial stages of these chronic diseases. In our study we restricted the age of the participants to 45–60 years. Also when measures to control diabetes were included in the linear regression model in our study, the association of periodontitis and HbA_{1c} was not influenced by it.

We grouped the patients based on their PISA scores unlike the previous studies. It is noteworthy that out of the several methods to operationalize periodontitis severity, the PISA, PPD 4–6 mm (%) and PPD ⩾ 7mm (%) emerged as significant predictors of HbA_{1c}. The possible reason for this observation may be that as PISA reflects the amount of inflamed periodontal tissue, therefore it possibly predicts both infectious and inflammatory burden more accurately than conventional methods used to operationalize periodontitis [21,42]. Also as periodontal destruction is site-specific therefore taking into account overall mean values often leads healthy sites to obscure sites of destruction, thereby leading to loss of important observations and probable associations with systemic health [49]. We believe that this might have been a reason for observation of lack of association between periodontitis and metabolic control in some studies in contrast to our study where association between PPD 4–6 mm (%) and PPD ⩾ 7 mm (%) with HbA_{1c} was observed [26,50]. Patients in high PISA group had highest HbA_{1c} values followed by middle PISA group while patients with diabetes in low PISA group had least HbA_{1c}. A dose response relationship was observed between control of blood glucose level over time (HbA_{1c}) and PISA.

In the study by Wolff *et al.* [50] glucose levels in patients with periodontitis who have not been diagnosed with diabetes were not found to be correlated with periodontal disease extent suggesting there may be a threshold above which periodontitis influences HbA_{1c} values. In another study, subjects with periodontitis but otherwise healthy individuals exhibited higher levels of systemic inflammation, dyslipidemia, and increased non-fasting serum glucose levels compared with those with good oral health [51].

We found that periodontally healthy subjects (PH group) had significantly lower levels of HbA_{1c} and diabetic complications as compared to periodontitis group (CP group) (Table 1).

Furthermore higher prevalence of diabetic related complications namely retinopathy and nephropathy was observed in patients with high periodontal inflamed surface as compared to low and middle PISA groups (Table 2). The logistic regression outcomes of our study revealed that PISA (median) became a significant predictor variable for retinopathy and neuropathy (Table 5). Our results are in agreement with previous studies which found an association between periodontal diseases and diabetic complications [19–24,30].

Chronic dysregulation of the cytokine pool is hallmark

of prediabetic conditions as well as type 1 diabetes mellitus (T1DM) and T2DM [52]. The presence of a chronic inflammatory condition, such as periodontitis, is believed to induce an increase of circulating mediators such as CRP, tumor necrosis factor-α (TNFα), interleukin (IL)-6 and IL-1 and this could be the biological basis of its influence on the diabetic state [53,54]. Furthermore, once periodontitis is established, its lingering character may contribute to worsening of diabetic status leading to more severe diabetes linked complications [55,56].

The strength of the present study is that, despite the consequent reduction in sample size, stringent inclusion criteria were followed to minimize potential confounding factors. Subjects within a range of age 45–60 years were included to minimise the confounding effect of age. The fact that participants had at least 12 teeth reduced heterogeneity in the study group, thereby minimizing confounding. The authors ensured that the patients included in the study were never smokers as despite good adjustment for smoking, residual confounding effect of smoking can lead to biased estimates [57].

The observations of the present study should be interpreted with caution in light of certain limitations. The participants for the study were recruited at a single center, thus limiting the validity and generalizability of the findings of this study to overall patients with T2DM and periodontitis. The inbuilt formulas translating CAL and recession to surface area used in the PISA assessment software use population-based average mean values of root surface areas and root lengths, which limits its accountability for individual variation in root surface area and root length [42]. UNC-15 probe would have been a more superior and reliable probe over Williams probe to assess periodontal parameters. Systemic markers of inflammation such as TNFα, IL-6 and IL- 1 are believed to correlate best with the indicators of glycemic control. As none of the inflammatory markers were assessed in the present study, future studies should aim to do the same.

Clinical significance

The results of present study demonstrate that a dose response relationship between HbA_{1c} and periodontal inflammatory surface area. Also periodontitis was seen to be associated with diabetic complications. Therefore, periodontal treatment might benefit diabetic patients to achieve better glycemic control.

Conclusions

The results of this study suggest a strong association between periodontal inflamed surface area and sites with greater periodontal destruction (severity of periodontitis) with glycemic control. Also periodontal inflammation was observed to be associated with diabetic complications. Considering that periodontal diseases can be managed effectively with the available inhand treatment modalities, it becomes pertinent to determine if periodontitis indeed plays a role in the development of diabetes and its potentially hazardous complications. If a causal relation indeed exists between these two chronic diseases, a new paradigm in dental and medical standard of care for screening, prevention, and management of diabetes could be developed in the future for the benefit of population worldwide.

Compliance with ethics guidelines

Palka Kaur Khanuja, Satish Chander Narula, Rajesh Rajput, Rajinder Kumar Sharma, and Shikha Tewari declare that there are no conflicts of interest in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

References

1. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Clin Periodontol 2013; 40(Suppl 14): S113–S134
2. King GL. The role of inflammatory cytokines in diabetes and its complications. J Periodontol 2008; 79(8Suppl): 1527–1534
3. Graves DT, Kayal RA. Diabetic complications and dysregulated innate immunity. Front Biosci 2008; 13(13): 1227–1239
4. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005; 366(9499): 1809–1820
5. Löe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care 1993; 16(1): 329–334
6. Garcia RI, Henshaw MM, Krall EA. Relationship between periodontal disease and systemic health. Periodontol 2000 2001; 25(1): 21–36
7. Amar S, Han X. The impact of periodontal infection on systemic diseases. Med Sci Monit 2003; 9(12): RA291–RA299
8. Lu HK, Yang PC. Cross-sectional analysis of different variables of patients with non-insulin dependent diabetes and their periodontal status. Int J Periodontics Restorative Dent 2004; 24(1): 71–79
9. Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G. Diabetes and periodontal disease: a case-control study. J Periodontol 2005; 76(3): 418–425
10. Lu HK, Yang PC. Cross-sectional analysis of different variables of patients with non-insulin dependent diabetes and their periodontal status. Int J Periodontics Restorative Dent 2004; 24(1): 71–79
11. Novak KF, Taylor GW, Dawson DR, Ferguson JE 2nd, Novak MJ. Periodontitis and gestational diabetes mellitus: exploring the link in NHANES III. J Public Health Dent 2006; 66(3): 163–168
12. Novak MJ, Potter RM, Blodgett J, Ebersole JL. Periodontal disease in Hispanic Americans with type 2 diabetes. J Periodontol 2008; 79

(4): 629–636
13. Wang TT, Chen TH, Wang PE, Lai H, Lo MT, Chen PY, Chiu SY. A population-based study on the association between type 2 diabetes and periodontal disease in 12,123 middle-aged Taiwanese (KCIS No. 21). J Clin Periodontol 2009; 36(5): 372–379
14. Rajhans NS, Kohad RM, Chaudhari VG, Mhaske NH. A clinical study of the relationship between diabetes mellitus and periodontal disease. J Indian Soc Periodontol 2011; 15(4): 388–392
15. Pathak AK, Shakya VK, Chandra A, Goel K. Association between diabetes mellitus and periodontal status in north Indian adults. European J Gen Dent 2013; 2(1): 58–61
16. Kalra N, Pradeep AR, Priyanka N, Kumari M. Association of stem cell factor and high-sensitivity C reactive protein concentrations in crevicular fluid and serum in patients with chronic periodontitis with and without type 2 diabetes. J Oral Sci 2013; 55(1): 57–62
17. Tandon V, Tangade P, Lingesha RT, Tirth A, Pal SK, Yadav V. Glycemic control and periodontal disease in type 2 diabetes mellitus patients: a cross-sectional study. J Indian Assoc Public Health Dent 2015; 13(3): 297–301
18. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontol 1996; 67(10 Suppl): 1085–1093
19. Noma H, Sakamoto I, Mochizuki H, Tsukamoto H, Minamoto A, Funatsu H, Yamashita H, Nakamura S, Kiriyama K, Kurihara H, Mishima HK. Relationship between periodontal disease and diabetic retinopathy. Diabetes Care 2004; 27(2): 615
20. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. Oral Dis 2008; 14(3): 191–203
21. Nesse W, Linde A, Abbas F, Spijkervet FK, Dijkstra PU, de Brabander EC, Gerstenbluth I, Vissink A. Dose-response relationship between periodontal inflamed surface area and HbA1c in type 2 diabetics. J Clin Periodontol 2009; 36(4): 295–300
22. Abrao L, Chagas JK, Schmid H. Periodontal disease and risk for neuropathic foot ulceration in type 2 diabetes. Diabetes Res Clin Pract 2010; 90(1): 34–39
23. Chen L, Wei B, Li J, Liu F, Xuan D, Xie B, Zhang J. Association of periodontal parameters with metabolic level and systemic inflammatory markers in patients with type 2 diabetes. J Periodontol 2010; 81(3): 364–371
24. Morita T, Yamazaki Y, Mita A, Takada K, Seto M, Nishinoue N, Sasaki Y, Motohashi M, Maeno M. A cohort study on the association between periodontal disease and the development of metabolic syndrome. J Periodontol 2010; 81(4): 512–519
25. Demmer RT, Desvarieux M, Holtfreter B, Jacobs DR Jr, Wallaschofski H, Nauck M, Völzke H, Kocher T. Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP). Diabetes Care 2010; 33(5): 1037–1043
26. Susanto H, Nesse W, Dijkstra PU, Hoedemaker E, van Reenen YH, Agustina D, Vissink A, Abbas F. Periodontal inflamed surface area and C-reactive protein as predictors of HbA1c: a study in Indonesia. Clin Oral Investig 2012; 16(4): 1237–1242
27. Southerland JH, Moss K, Taylor GW, Beck JD, Pankow J, Gangula PR, Offenbacher S. Periodontitis and diabetes associations with measures of atherosclerosis and CHD. Atherosclerosis 2012; 222 (1): 196–201
28. Kim EK, Lee SG, Choi YH, Won KC, Moon JS, Merchant AT, Lee HK. Association between diabetes-related factors and clinical periodontal parameters in type-2 diabetes mellitus. BMC Oral Health 2013; 13: 64
29. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. Br Dent J 2014; 217(8): 433–437
30. Amiri AA, Maboudi A, Bahar A, Farokhfar A, Daneshvar F, Khoshgoeian HR, Nasohi M, Khalilian A. Relationship between type 2 diabetic retinopathy and periodontal disease in Iranian adults. N Am J Med Sci 2014; 6(3): 139–144
31. Gokhale NH, Acharya AB, Patil VS, Trivedi DJ, Setty S, Thakur SL. Resistin levels in gingival crevicular fluid of patients with chronic periodontitis and type 2 diabetes mellitus. J Periodontol 2014; 85(4): 610–617
32. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev 2015; 11(11): CD004714
33. Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care 2010; 33(2): 421–427
34. Liew AK, Punnanithinont N, Lee YC, Yang J. Effect of non-surgical periodontal treatment on HbA1c: a meta-analysis of randomized controlled trials. Aust Dent J 2013; 58(3): 350–357
35. Engebretson S, Kocher T. Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. J Periodontol 2013; 84(4 Suppl): S153–S169
36. Sgolastra F, Severino M, Pietropaoli D, Gatto R, Monaco A. Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials. J Periodontol 2013; 84(7): 958–973
37. Mohan M, Jhingran R, Bains VK, Gupta V, Madan R, Rizvi I, Mani K. Impact of scaling and root planing on C-reactive protein levels in gingival crevicular fluid and serum in chronic periodontitis patients with or without diabetes mellitus. J Periodontal Implant Sci 2014; 44 (4): 158–168
38. Bhopal R, Rankin J. Concepts and terminology in ethnicity, race and health: be aware of the ongoing debate. Br Dent J 1999; 186(10): 483–484
39. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol 2007; 78(7 Suppl): 1387–1399
40. Costa FO, Guimarães AN, Cota LO, Pataro AL, Segundo TK, Cortelli SC, Costa JE. Impact of different periodontitis case definitions on periodontal research. J Oral Sci 2009; 51(2): 199–206
41. Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ. Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. J Clin Periodontol 2008; 35(5): 385–397
42. Nesse W, Abbas F, van der Ploeg I, Spijkervet FKL, Dijkstra PU, Vissink A. Periodontal inflamed surface area: quantifying inflammatory burden. J Clin Periodontol 2008; 35(8): 668–673
43. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(Suppl 1): S62–S69
44. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol

Scand 1964; 22(1): 121–135
45. Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand 1963; 21(6): 533–551
46. Genco RJ. Current view of risk factors for periodontal diseases. J Periodontol 1996; 67(10 Suppl): 1041–1049
47. Torrungruang K, Tamsailom S, Rojanasomsith K, Sutdhibhisal S, Nisapakultorn K, Vanichjakvong O, Prapakamol S, Premsirinirund T, Pusiri T, Jaratkulangkoon O, Unkurapinun N, Sritara P. Risk indicators of periodontal disease in older Thai adults. J Periodontol 2005; 76(4): 558–565
48. Choi BC, Shi F. Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey. Diabetologia 2001; 44(10): 1221–1231
49. Imrey PB. Considerations in the statistical analysis of clinical trials in periodontitis. J Clin Periodontol 1986; 13(5): 517–528
50. Wolff RE, Wolff LF, Michalowicz BS. A pilot study of glycosylated hemoglobin levels in periodontitis cases and healthy controls. J Periodontol 2009; 80(7): 1057–1061
51. Nibali L, D'Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS. Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. J Clin Periodontol 2007; 34(11): 931–937
52. Kolb H, Mandrup-Poulsen T. The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. Diabetologia 2010; 53(1): 10–20
53. Engebretson S, Chertog R, Nichols A, Hey-Hadavi J, Celenti R, Grbic J. Plasma levels of tumour necrosis factor-α in patients with chronic periodontitis and type 2 diabetes. J Clin Periodontol 2007; 34(1): 18–24
54. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008; 35(4): 277–290
55. Ebrahimi A, Nabipour I, Vahdat K, Jafari SM, Fouladvand M, Assadi M, Movahed A, Obeidi N, Sanjdideh Z. High sensitivity C-reactive protein is associated with the metabolic syndrome independent to viral and bacterial pathogen burden. Diabetes Res Clin Pract 2009; 84(3): 296–302
56. Hung CH, Lee CM, Chen CH, Hu TH, Jiang SR, Wang JH, Lu SN, Wang PW. Association of inflammatory and anti-inflammatory cytokines with insulin resistance in chronic hepatitis C. Liver Int 2009; 29(7): 1086–1093
57. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontitis-systemic disease associations in the presence of smoking—causal or coincidental? Periodontol 2000 2002; 30(1): 51–60