

Periodontal Disease as a Potential Risk Factor for Prediabetes: A Case Control Study

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Abstract

Background: Periodontitis is associated with many systemic disorders, including diabetes and prediabetes. However, the information regarding role of periodontal inflammation and its effect on prediabetes is still not fully understood. The aim of the study was to assess the strength of association of periodontal disease as a risk factor for prediabetes.

Methods: A case-control study was conducted among 109 prediabetic cases and 109 normoglycemic controls to assess the periodontal health status and find its association with prediabetes. We identified the subjects from Department of Medicine and Endocrinology of Pt. B.D. Sharma, PGIMS, Rohtak, India with strict inclusion and exclusion criteria. We classified prediabetic cases and normoglycemic controls according to the guidelines of American Association of Diabetes diagnosed with periodontal illness according to guidelines of American Association of Periodontology. Periodontal condition was assessed among both the groups as per AAPD guidelines, along with a structured set of questionnaire.

Results: The study revealed a weak association of periodontitis with development of prediabetes (0.91). Cases with moderate periodontitis had 2.82 times more risk of developing diabetes when compared to no periodontitis. (2.82;95% CI 0.276-28.5).

Conclusion: The present findings show that there was weak or no association between periodontal disease and prediabetes. The strength and dose response relation does not support its occurrence. Therefore, further studies are needed to assess the influence of periodontal status on incidence of prediabetes.

Keywords: Periodontitis, Prediabetes, Dental Health, Plaque Index, Case Control Study

Introduction

Periodontitis is characterized as persistent inflammatory multifaceted condition associated with dysbiotic biofilm that results in irreversible destructive inflammatory responses, which advances through periodontal attachment and bone loss.¹⁻³ Periodontitis affects about 45% -50% of people in its mildest forms, rising to over 60% in people aged > 65 years.⁴ Some note that periodontal pathogens like *Porphyromonas gingivalis* are capable to invade gingival tissue and are able to gain access to systemic circulation.⁵ The pathogens of systemic inflammation via circulation in type 2 diabetes leads to reduced pancreatic b-cell function, apoptosis, and insulin resistance. The recent evidence supports that entry of periodontal pathogens and their virulence factors into circulation via oxidative-stress- mediated pathway and Advanced Glycation End products (AGE), RAGE (Receptor for AGEs) interactions results in an elevated systemic inflammation. These interactions provide possible mechanistic links for diabetes to periodontitis and vice versa.⁶ The second highest number of people with diabetes in the world is

reported in India, as per International Diabetes Federation (2017), with an estimated prevalence of 8.8%. The number of diabetics reported in the world is 425 million, with 82 million people within the South East Asian region, and by 2045 this may increase to 151 million.⁷ Because of an exponential increase in the number of cases of diabetics in the world, it is expected that by 2030, it would increase to 552 million.⁷ There is rapid increase in incidence of diabetes and is the forerunner of becoming a potential epidemic in India with over 62 million individuals currently being affected from diabetes and over 77 million suffering from Pre-diabetes.⁸ Recent studies have shown that around half of the diabetics in the world are undiagnosed,⁹ which has led to development of new classification by American Diabetes Association (ADA) for blood glucose levels, preceding the onset of diabetes, known as prediabetes.¹⁰ Prediabetes may be defined as a condition in which plasma glucose is higher than normal but does not reach up to the threshold level required for diagnosing diabetes.¹¹ Prediabetes is associated with an increased risk of developing overt

diabetes, leading to greater occurrence of cardiovascular diseases, and there is also an accumulating evidence to suggest damage on kidney and nerves already at the prediabetic stage.¹² Patients with pre-diabetes are more likely to have periodontitis, whereas patients with moderate to-severe periodontitis are more likely to develop prediabetes than patients without periodontitis. These bidirectional relationships between the two conditions might be related to the common host immune response and related pathobiology, which have led to the indication for prediabetes screening in various parts of the world.¹³ Lot of research have showed that periodontitis significantly worsens the inception, development, and seriousness of prediabetes. The prevalence of periodontitis in people with prediabetics' issues is estimated to be twice and even three times greater than in an otherwise healthy population.¹³ Evidence suggests that periodontitis detrimentally affects glycaemic control and deteriorate the complications. Evidence-based studies lack the quality of data regarding the strength of the association of effect of periodontal disease on prediabetes and its therapeutic implications.¹³ To our best of knowledge there has been no study which has addressed the strength of association between periodontitis and development of prediabetes. Recent evidence suggests that prevalence of periodontitis is 33% higher in patients with prediabetes than healthy controls.¹⁴ Hence, we conducted this study based on the hypothesis that inflammation associated with periodontitis could be a risk factor and may worsen prediabetes. The aim of study was to examine whether periodontal diseases are associated with an increased risk of development of prediabetes.

Materials and Methods

Study Population: We conducted a case control study at Department of Endocrinology and Medicine of Pt. B.D. Sharma, PGIMS, Rohtak, which is a tertiary medical centre in the state of Haryana, India. The sample size was calculated based on the data from previous study¹⁵, we assumed that ratio of 1:1 would detect an odd of 2.5 with 95% CI and power of 80%, assuming a proportion of periodontal diseases among control group to be 50%. Therefore, 109 cases and 109 controls, aged between 20 years to 60 years, were recruited at Department of Endocrinology and Medicine of Pt. B.D. Sharma, PGIMS, Rohtak. The diabetic clinic was surveyed for 3 months from December 2019- February 2020, twice in a week until the required sample size of 218 was obtained (109 cases and 109 controls). Ethical clearance was sought from the Institution Ethics committee of "Post Graduate Institute Of Dental Sciences, Rohtak" explaining the aims & importance of the study via letter no PGIDS/IEC/2018/ 33 dated 30/11/18. To ensure comparability between cases and control and to avoid confounding bias variables like age, gender and SES was matched 1:1.

Definition of Cases and Controls: We defined cases as prediabetes based on the American Diabetes Association criteria of FPG (fasting plasma glucose) levels of 100 and 125mg/dl (5.6 to 6.9 mmol/L). Impaired glucose tolerance (IGT): 2 hour plasma glucose levels of 140 and 199mg/dl (7.8-11.0 mmol/L) after ingesting 75gm of glucose (OGTT); or a combination of both, or HbA1c levels of 5.7-6.4%. Those who were normal after passing the OGTT test were taken as controls. All the subjects were advised to fast overnight (at least 10 hrs.) For estimation of FPG (fasting plasma glucose), The participants were then subjected to OGTT with 75 gm of anhydrous glucose powder dissolved in 250-300 ml water, which was supposed to be consumed over 5 minutes. After the drink, 2 hours post glucose load, venous blood sample were taken for estimation of plasma glucose level by the Department of Endocrinology, PGIMS, Rohtak. While waiting after intake of 75 gm glucose, the subjects were asked to avoid physical activity.

Inclusion Criteria: Patients diagnosed with prediabetes, willingness of subject to take part in study, and presence of at least 8 teeth excluding 3rd molars or fully dentate patients. Exclusion criteria included those who did not give consent, Pregnant women or Lactating mothers, Chronic disorders requiring chronic or intermittent use of antibiotics, Diabetes, hypertension, blood disorders, coronary heart diseases, smokers, patient under immunosuppressive drugs, Patients who underwent periodontal therapy in last 6 months, medical or general health condition that may profoundly contribute to development of periodontitis. Participants were then classified as nondiabetics, prediabetics or diabetics as per ADA criteria. Diabetics were excluded from the study, while the participants who were diagnosed as prediabetes were assigned as "cases". The healthy age and sex matched normoglycemic were recruited as "controls". All the study participants were invited to take part in the study after signing the written informed consent.

Periodontal Disease Measurement: A full-mouth periodontal examination was performed among all study participants, and measurements were taken at six sites on each tooth (mesio-buccal, mesio-lingual, disto-buccal, disto-lingual, mid-buccal and mid-lingual), using a standardized UNC-15 probe. The clinical parameters of periodontal conditions were probing depth (PD), gingival recession, clinical attachment loss (CAL), and bleeding on probing (BOP). PD was identified as the distance in millimeters from free gingival margin to the apical part of the pocket. Gingival recession was determined by measuring the distance from the Cemento-enamel junction to the gingival margin in millimeters. CAL was calculated from recession and probing depth (PD) measurements and represents the distance from the Cemento-enamel junction to the most apical portion

of the sulcus/pocket in millimeters. BOP was evaluated when probing to the base of the sulcus, six surface areas per tooth, and was expressed as the percent of bleeding sites over the total tooth surfaces. Third molars were not incorporated in the analysis.

Training and Calibration: A single examiner conducted the examination to eliminate inter examiner variability. The training and calibration of investigator was done among 10 volunteers for recording all periodontal parameters in the Department of Public Health Dentistry under the supervision of the Head of Department of Public Health Dentistry. The investigator was calibrated on 10 volunteers by the experienced periodontist as the standard examiner. To minimize intra-examiner variability, 10 subjects were randomly called on different days and the same trained expert did recalibration of the investigator. The kappa coefficient value for intra examiner reliability regarding periodontal health status was 0.83, which suggests high conformity. Periodontal status was defined according to the American Academy of Periodontology (AAP): These parameters were examined on six sites per tooth using a graduated periodontal probe. Cases and controls were classified as: Healthy, No bleeding upon probing, Gingivitis with bleeding on probing, Slight chronic periodontitis (at least one periodontal site with 1-2 mm AL and= 4 mm PD), Moderate chronic periodontitis (at least two teeth with 3-4 mm AL or at least 2 teeth with= 4 mm PD), Severe chronic periodontitis (at least two teeth with= 5 mm AL and one tooth with =5 mm PD).¹⁶

The information regarding sociodemographic characteristics, oral hygiene practices, and patterns of medications was assessed through personal interview from both cases and controls before the dental examination. Initial evaluation included detailed history and clinical examination of each study participant to exclude any systemic diseases. Personal and family history was assessed regarding diabetes, hypertension, and cerebrovascular disease / coronary artery diseases. Personal history of smoking/ alcohol consumption/ dietary intake was also recorded. Anthropometric measurements such as height, weight body mass index Waist Circumference and hip Circumference were recorded. Waist/hip ratio (WHR) and waist/height ratio (WHtR) was calculated, and a WHR ratio of 0.9 in men and 0.8 in women was taken as a cut-off for WHR and a WHtR of 0.5 as a cut-off for WHtR. Voluntary informed consent was obtained from all study participants, after explaining the study which was presented in both English and local language for easy understanding and convenience for the study participants.

Statistical Analysis

Various statistical tests were applied using SPSS v 21 (SPPS, Inc. Chicago). Chi-square test was used to

examine the difference in proportions and t-test was used to assess the difference in means of various anthropometric measures and periodontal parameters among cases and controls. Binary logistic regression analysis was used to examine the association between periodontal status and prediabetes and was further adjusted for various potential confounders including age, gender, education, income, family history of diabetes, smoking, alcohol.

Binary logistic regression analysis depicted the adjusted odds (OR) and the 95% upper and lower bound confidence interval were derived from the coefficients of the logistic models and standard error. The dose response relationship was calculated for periodontitis and prediabetes to assess whether adjusted OR (95% CI) of periodontitis (PD and CAL) increased with its severity. The strength of association was determined using OR for the presence or absence of periodontitis among both the groups.

Results

Demographic details revealed that most of the study subjects belonged to urban area of Rohtak and were married. The study subjects comprising adults male (56.4%) with the majority in the age group of 41-50 years. The mean height among normoglycemic controls was 162 ± 13.23 while in prediabetic cases, it was 161.88 ± 10.35 , which was statistically significant ($p<0.05$). There was a significant difference in mean body fat among prediabetic cases (31.03 ± 06.05) and normoglycemic controls (26.19 ± 05.97) at $p<0.05$ (Table 1).

The mean values of fasting oral glucose tolerance test, fasting plasma glucose and HbA1c were found to be statistically significant ($p<0.05$) (Table 2). The mean probing depth among prediabetic cases (2.46 ± 0.57) was slightly higher than normoglycemic controls (2.37 ± 0.58) which was statistically non-significant ($p = 0.690$). In the present study, mean clinical attachment loss among prediabetic cases was higher (1.63 ± 1.42) than normoglycemic subjects (1.15 ± 1.54) which was also statistically non-significant ($p= 0.592$) (Table 3). Dose relation relationship revealed that subjects with moderate periodontitis have 2.82 odds of developing prediabetes when compared to no periodontitis (95% CI; 0.276-28.5) (Table 4). The strength of association revealed that subjects with periodontitis have 0.91 odds of developing prediabetes when compared to no periodontitis (95% CI; 0.51-1.63).

(Table 5). Pearson correlation of different independent variables like age, gender, smoking habit, alcohol habit, periodontal status, waist circumference/hip circumference ratio, BMI with HbA1c showed that only smoking habit (0.181) and BMI (0.311) were correlated significantly ($p<0.05$). (Table 6).

Table 1: Distribution of cases and control on the basis various anthropometric measurements (Height, Weight, Hip circumference, Waist to hip ratio, BMI and Body fat percentage)

Anthropometric Measurements	Case group N=109	Control group N=109	<i>p</i> value
	MEAN±S.D.	MEAN±S.D.	
Height (cms)	161.88 ± 10.35	162.58 ± 13.23	0.00
Weight (kgs)	74.82 ± 13.42	67.41 ± 14.53	0.19
Waist Circumference (cms)	97.97 ± 11.12	70.82 ± 9.98	0.00
Hip Circumference (cms)	106.27 ± 10.92	96.17 ± 08.34	0.08
Waist to Hip Ratio	0.93 ± 0.073	0.94 ± 0.0622	0.10
BMI (kg/m²)	28.57 ± 04.15	25.45 ± 3.84	0.13
Body Fat (%)	31.03 ± 06.05	26.19 ± 05.97	0.00

Table 2: Distribution of cases and control on the basis various laboratory parameters (fasting blood sugar, oral glucose tolerance test and HbA1c)

Laboratory Parameters	Case group N=109	Control group N=109	<i>t</i> value	<i>p</i> value
	MEAN±S.D.	MEAN±S.D.		
Fasting Plasma Glucose (mg/dl)	113± 9.51	87 ± 9.14	92.98	0.00
75 gm Oral Glucose Tolerance Test (mg/dl)	153± 19.45	115 ± 12.58	79.2	0.00
HbA1c (%)	5.91± 0.20	5.01± 0.321	153.89	0.00

Table 3: Mean probing depth and mean attachment loss in cases and control group

	Case group N=109	Control group=109	<i>p</i> VALUE
Mean Probing Depth	2.46±0.57	2.37±0.57	0.69
Mean Clinical Attachment Loss	1.63±1.42	1.15±1.54	0.59

Table 4: Dose response relationship between degree of periodontitis and Prediabetes (HbA1C) in cases and control group

Variable	β coefficient	Wald	P value	Odd's ratio	95% C.I. for odd's ratio	
					Lower	Upper
No Periodontitis		1.389	.708	1		
Mild Periodontitis	-.466	.455	.500	.627	.162	2.430
Moderate Periodontitis	1.038	.773	.379	2.824	.279	28.562
Severe Periodontitis	-.090	.090	.765	.914	.508	1.644

Table 5: Strength of association between periodontitis and prediabetes

	Prediabetes (Cases)		Normoglycemic (Control)		Odd's Ratio Value (95% Confidence Interval)	
	N	%	N	%		
Periodontitis Present	101	64.6	52	35.4		
Periodontitis Absent	8	11.7	57	88.3	0.91 (0.51-1.63)	

Table 6: Pearson correlation of different independent variables among study subjects

Variables	Age	Gender	Smoking Habit	Alcohol Habit	Periodontal status	WC/HC ratio	BMI	HbA1c
Age	1	-0.248	0.077	0.162	0.137	0.259	0.076	-0.02
Gender	-0.248	1	-0.171	-0.249	-0.009	-0.434	-0.73	-0.018
Smoking Habit	0.077	-0.171	1	0.582	0.119	0.115	-0.067	-0.181**
Alcohol Habit	0.162	-0.249	0.582	1	0.258	0.171	-0.054	-0.067
Periodontal status	0.137	-0.009	0.119	0.258	1	-0.048	-0.098	0.215
WC/HC ratio	0.259	-0.434	0.115	0.171	-0.048	1	0.081	-0.067
BMI	0.076	-0.073	-0.067	-0.054	-0.098	0.081	1	0.311**
HbA1c	-0.02	-0.018	-0.181	-0.067	0.015	-0.061	0.311	1

Discussion

The result of our study did not find a consistent association between different parameters of periodontitis and prediabetes respectively, but there is substantial evidence in the literature¹⁷ that periodontitis may play a role in increasing the incidence of diabetes and prediabetes along with other risk factors like increased BMI, unhealthy diet, lack of physical activity and familial history. Findings were reported by Andriankaja O et.al.¹⁸ where subjects with high BOP often had higher odds of IFG (odds ratio 5.5, 95% confidence interval CI 1.2- 25.3) and prediabetic condition (OR 3.6, 95% CI 1.0-13.2) than those with a low percentage of BOP after adjusting for age, sex, smoking, alcohol consumption, waist circumference and number of missing teeth. Our study also revealed a dose response relationship, which depicted that association of prediabetes with periodontitis was weaker than expected (no significant associations). Dose response relationship with periodontitis and prediabetes showed that subjects with moderate periodontitis have 2.824 odds of developing prediabetes when compared to no periodontitis at 95% CI (0.27-28.56). There is substantial evidence that the severity of periodontitis increases with age, but because the study participants in our study were younger (21-40 years), and they are less prone to progressing towards developing severe periodontitis, which reflected the higher odds of developing prediabetes in moderate periodontitis than in severe periodontitis. Results of our case control study agrees with the findings of cohort study by Joshipura KJ et al.¹⁹ There is substantial evidence that the severity of periodontitis increases with age, but because the study participants in our study were younger (21-40 years), and they are less prone to progressing towards developing severe periodontitis, which reflected the higher odds of developing prediabetes in moderate periodontitis than in severe periodontitis.³³ which revealed that greater mean pocket depth and mean attachment loss at baseline were associated with lower risk of developing prediabetes/diabetes over the follow-up (IRR = 0.81; and IRR = 0.86; respectively). Increase in periodontal attachment loss from baseline to follow-up was associated with higher prediabetes/diabetes risk (multivariate IRR = 1.25; 95% CI: 1.09-1.42), and increase in pocket depth was associated with > 20% fasting glucose increase (multivariate IRR = 1.43). The indicators of a periodontal disease like bleeding on probing, pocket depth and clinical attachment loss were often correlated with IFG, HbA1c, oral GTT to find out the association with periodontal diseases and prediabetes/diabetes. Our results revealed that the mean probing pocket depth among prediabetic was higher than controls, which was statistically non-significant (p= 0.690). In our study, mean clinical attachment loss among prediabetic was higher than normoglycemic subjects, which was also statistically non significant (p= 0.59). These results agree with

findings of Arora N et al.,²⁰ who reported that mean PD was 1.63 ± 0.58 mm and mean AL was 1.59 ± 1.05 mm was higher among prediabetic/ diabetic than controls. Another study by Choi YH et al.,²¹ reported that participants in the top quintile category of CAL had higher odds of IFG (OR= 1.55) and diabetes (OR=4.77) after adjustment for related confounders. Anthropometric measurements are indicator of nutritional status of an individual. Increased height, weight, TBF, BMI is often associated with cardiovascular disease and diabetes and maintaining of ideal weight and BMI is vital in prevention of prediabetes/ diabetes. The mean body fat percent among prediabetes and normoglycemic showed a statistically significant difference (p=0.00). In spite of being overweight in both the groups, the study subjects in prediabetes showed significantly higher body fat percent when compared to normoglycemic. The results are in accordance with findings of National Health and Nutrition Examination Survey, 1999-2006, conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention which revealed that 13.5% of those with normal BMI and high body fat percentage progressed into prediabetes of type 2 diabetes, compared with only 10.5% of those overweight by their BMI but who had low body fat.²² The mean fasting oral glucose tolerance test (OGTT) values reported among cases were 153 ± 19.45 , while healthy controls had 115 ± 12.58 (p< 0.05). The mean HbA1c showed a significant difference among case group (6 ± 0.20) and control groups (5 ± 0.321) at p=0.00 which were in lines with study reported among prediabetes patients in Iran (mean HbA1c = 5.928 ± 0.09).²³ In a systematic review by Borgnakke WS et al.,²³ it was concluded that compared to periodontally healthy individuals, people with poor periodontal health have greater risk of developing poorer glycemic control and have greater risk of diabetes-related complications which explains the increase in glycemic parameters such as HbA1c and oral glucose tolerance test because of periodontal infections. Many researchers have focused to find out the biologically plausible reasons between the periodontal pathogens and increased insulin resistance. The findings of the Oral Infections, Glucose Intolerance, and Insulin Resistance Study (ORIGINS STUDY)² have revealed that periodontal pathogens are responsible for incidence of prediabetes. Periodontal pathogens such as *A. actionomycetemcomitans*, *P. gingivalis*, *T. denticola*, *T. forsythia*, *A. naeslundii*, were associated with prediabetes among participants and the risk of prediabetes was increased by 1.47 times in individuals with moderate/severe vs. no/mild periodontitis (OR= 1.47 (0.78, 2.74), P = 0.23. The "Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology"³ shows that there was a strong evidence that people with periodontitis have elevated

risk for impaired glucose tolerance and insulin resistance (precursor of diabetes). There is a strong evidence to suggest that periodontitis increases the risk for dysglycaemia and insulin resistance.²⁴ Salmeron D et al.,²⁵ have found a significant linear correlation between the gingival risk score and prediabetes risk score providing evidence regarding the association (Finnish Diabetes Risk Score (FINDRISC). Hence, periodontitis can be considered as an important risk factor for prediabetes/diabetes. The results of the study conducted by Torrungruang K et al.,²⁶ supports the evidence regarding the role of systemic inflammation as mediators for the associations between periodontitis and Impaired Fasting Glucose (IFG) or diabetes. Because of the dynamic nature of the inflamed periodontium, the tissue may serve as an endocrine-like source of inflammatory mediators. Amongst the inflammatory biomarkers examined, CRP and IL-6 seem to be promising, because of their plausible biological mechanisms, as revealed in studies of links between periodontal disease and cardiovascular disease. This case control study was done to assess the association of periodontal diseases as a risk factor for prediabetes, which included periodontal parameters, anthropometric parameters, and laboratory parameters. The results depicted periodontal parameters exhibited weak association with prediabetes, though it can be still considered as a potential risk factor. Chronic periodontitis as assessed by CAL was associated in a dose response way with increased prevalence of odds of HbA1c and prediabetes in a representative sample. The increased blood glycemic level in prediabetic patients can be reduced or controlled by maintaining the periodontal health. Henceforth, dentist can play a significant role in early diagnosis and prevention of periodontal diseases which could further control blood glycemic level. Strength of the study: It's the first case control study to date, large sample size, the present study included extensive data of diagnosis of prediabetes including HbA1c, OGTT, fasting glucose level and various anthropometric measurement. Matching was done to reduce the effect of potential confounding factors and incorporation of maximum factors affecting the periodontal status.

Limitations of the Study

It is possible that this study suffered from some sampling bias as prediabetes patient have more visits than healthy controls, Although adjustment was done for major confounders like age, gender and socioeconomic status other factors were not assessed which may also contribute to development of prediabetes. As this was case control study assessment of causality cannot be done, only strength of association can be determined, the observational nature of case control study can lead to bias inherent to these types of study. It will require further investigation using a cohort study design to establish a

temporality and biological plausibility between disease and risk factors.

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