

## Original Article

# Comparison of glycosylated hemoglobin (HbA1c) levels in patients with chronic periodontitis and healthy controls

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## ABSTRACT

**Background:** The aim of this study was to determine if glycosylated hemoglobin is elevated in patients with chronic periodontitis who have not been diagnosed with diabetes and also to compare the HbA1c levels that were obtained with lab and chairside test kit.

**Materials and Methods:** A Case control study was designed. Glycosylated hemoglobin (HbA1c) was assessed using a chairside kit and laboratory method in 70 subjects without diabetes but with chronic periodontitis [having at least 10 teeth (at least one site around each tooth) with probing depth (PD)  $\geq$  5 mm, bleeding on probing (BOP)  $\geq$  15% and clinical attachment level (CAL)  $\geq$  1 mm] and 70 healthy controls (PD  $\leq$  4 mm and BOP  $\leq$  15%). Groups were compared using the t-test and multiple linear regression model analysis. Karl Pearson's correlation coefficient was used to compare the relationship between different variables.

**Results:** In this case control study HbA1c (Lab and Kit) were slightly higher and statistically significant in chronic periodontitis cases than in healthy controls.

**Conclusion:** Chronic periodontitis is associated with a slight elevation in glycosylated hemoglobin (lab and chair side kit) and that the clinical significance of this difference remains to be determined. This preliminary finding is consistent with earlier reports that chronic periodontitis is associated with elevated blood glucose in adults without diabetes and may increase one's risk for type-2 diabetes.

**Key Words:** Chronic periodontitis, diabetes, glycosylated hemoglobin, tumor necrosis factor- $\alpha$

Received: March 2012  
Accepted: August 2012

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## INTRODUCTION

Diabetes mellitus (DM) is a systemic disease with several major complications affecting both the quality and length of life. One of these complications is periodontal disease (periodontitis). Current evidence suggests that periodontitis is more than a localized oral infection.<sup>[1]</sup> The chronic gram-negative infection of periodontal origin may be considered a potential focus of infection that aggravates metabolic control in patients who have diabetes.<sup>[2]</sup>

The multifactorial model for the aetiology of periodontitis proposed by Clarke and Hirsch<sup>[3]</sup> incorporates the role of personal, environmental and systemic factors along with the bacteria to explain individuals varying susceptibility to periodontitis. Risk factors associated with periodontitis are smoking, diabetes, stress, neutrophil dysfunction, hyperlipidemia, hormonal imbalance, health care, low socio-economic status, poor oral hygiene, imbalanced diet, and alcoholism.

Strong evidence indicates that pathogenic bacteria or their products stimulate cells such as fibroblasts, keratinocytes, and macrophages, present in the periodontal tissue, to release a number of inflammatory cytokines, such as tumor necrosis factor alpha (TNF- $\alpha$ ); prostaglandin E2; interleukin IL-1 $\beta$ , 6 and 12; granulocyte colony-stimulating factor (G-CSF); and chemokines. The elevated serum levels

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of these important mediators have deleterious effects on glucose and lipid metabolism. TNF- $\alpha$  was reported to interfere with lipid metabolism and to be an insulin antagonist.<sup>[4]</sup>

Saito *et al.*<sup>[5]</sup> found that alveolar bone loss was associated with impaired glucose tolerance in Japanese men without diabetes. Similarly, Nibali *et al.*<sup>[6]</sup> found slightly, but statistically significant, higher non-fasting glucose levels in periodontitis cases compared to healthy controls. These studies suggest that periodontitis may effect glucose metabolism in general population, albeit to a lesser extent than in adults with diabetes.

## OBJECTIVE

Several studies have shown that periodontal treatment of diabetic patients decreased HbA1c levels. However it remains unclear whether periodontal status affects HbA1c in non-diabetics. Therefore our objective of this study was to determine the association between chronic periodontitis and HbA1c in adults without diabetes and to evaluate differences in HbA1c values that were obtained with the Lab and the Kit.

## MATERIALS AND METHODS

A total of 140 subjects including both chronic periodontitis patients and healthy controls without diabetes were selected for the study from the outpatient department of Periodontics, St. Joseph Dental College, Eluru, Andra Pradesh, India).

Inclusion criteria for the study were the participants of  $\geq 35$  years of age and previously had not been diagnosed with diabetes, presence of  $>10$  natural teeth and who had not received any surgical/nonsurgical periodontal therapy for past 6 months. We excluded subjects with gross oral pathology (tumors and cyst), pregnant women, subjects who had taken antibiotics and analgesics 6 months prior to surgery and subjects with any other systemic disease.

### Study design

One hundred forty non-diabetic subjects were selected after subjecting their random blood ( $\leq 90$  mg/dl) and urine sample for biochemical tests (Benedict's test). Then the patients were divided into two groups after periodontal examination. The study was approved by the Ethical Committee of the institution and following the selection of subjects, written consents were obtained from the same.

### Group I: Chronic periodontitis patients (cases)

Subjects who were diagnosed with periodontitis having at least 10 teeth with probing depth  $\geq 5$  mm and  $\geq 15\%$  sites with bleeding on probing (BOP) and clinical attachment loss  $>1$  mm were selected.

### Group II: Healthy controls

Included clinically healthy subjects with no history of any known systemic disease and had no history of previous hospitalization and medication with probing depth  $<4$  mm, BOP at  $<15\%$  of teeth sites, and no periodontal treatment within previous 6 months. Height, weight and BMI were measured before enrolling the patients into the study.

Patients smoking habits were recorded, in this study only 12 patients were smokers (7 in cases and 5 in controls) out of 140 (8.5%) hence, no correlation on the effects of smoking could therefore be drawn from this study.

### Measurement of periodontal parameters

All subjects received a clinical periodontal examination by single examiner who recorded all the variables by manual procedure. The following periodontal parameters were recorded. Gingival bleeding index, probing pocket depth (PPD) and clinical attachment level (CAL).

### Estimation of glycosylated hemoglobin: (HbA1c)

HbA1c was measured using a commercially available test kit (A1cNow+)<sup>[7]</sup> according to the manufacturer's recommendations and also with a laboratory method (Ion Exchange Resin method) using a semi-auto analyzer.

### Statistical analyses

HbA1c was compared between cases and controls using the *t*-test (unadjusted) and multiple linear regressions (adjusted). Participant age, gender, body mass index were included in adjusted analyses. Karl Pearson's correlation coefficient was used to compare the relationship between different variables. All analyses were performed using a SPSS 15 version software program.

## RESULTS

A total sample size of 140 was taken, out of which 70 were cases and 70 were controls and data obtained was subjected to statistical analysis. The results are presented under the headings of various parameters considered for this study.

Table 1 shows the select characteristics between chronic periodontitis cases and controls.

Table 2 shows the comparison of HbA1c values between chronic periodontitis cases and controls (Kit and Lab). The unadjusted mean HbA1c levels with kit in cases were  $5.51 \pm 0.53$ , while in controls they were  $5.44 \pm 0.27$ , but the difference was statistically not significant ( $P = 0.38$ ). The unadjusted mean HbA1c levels with lab in cases were  $5.50 \pm 0.74$ , while in controls they were  $5.48 \pm 0.29$ . However, the difference was statistically not significant ( $P = 0.841$ ).

Table 3 shows the comparison of HbA1c levels obtained with kit and lab. The mean HbA1c levels in cases with kit and lab were  $5.51 \pm 0.53$  and  $5.50 \pm 0.74$ , respectively. But the difference was statistically not significant ( $P = 0.94$ ). The mean HbA1c values among kit and lab in controls were  $5.44 \pm 0.27$  and  $5.48 \pm 0.29$ , respectively. However the difference was statistically not significant ( $P = 0.86$ ).

Table 4 shows correlation between age, BMI, HbA1c kit and lab, PPD  $\geq 5$  mm, CAL and BOP among cases. Age showed a positive correlation with BMI (0.15), HbA1c kit (0.03) and lab (0.11), PPD  $\geq 5$  mm (0.20), CAL (0.26) and a negative correlation with BOP (-0.15); with CAL being statistically significant ( $P < 0.05$ ). When BMI was compared a positive correlation was found with kit (0.17), lab (0.13), PPD  $\geq 5$  mm (0.30), CAL (0.22) and a negative correlation was found with BOP (-0.14), however PPD  $\geq 5$  mm found to be statistically significant ( $P < 0.05$ ).

HbA1c kit was positively correlated with lab (0.93) and was statistically significant ( $P < 0.05$ ). A negative correlation was seen when kit was compared with PPD  $\geq 5$  mm (-0.04) and CAL (-0.05) while it was positively correlated with BOP (0.16). With HbA1c lab being compared, a positive correlation was observed with BOP (0.09), PPD  $\geq 5$  mm (0.01) and a negative correlation with CAL (-0.07).

Although, both CAL (0.69) and BOP (0.04) showed a positive correlation with PPD  $\geq 5$  mm, only CAL was found to be statistically significant ( $P < 0.05$ ). However, CAL (-0.09) showed a negative correlation with BOP.

Table 5 shows correlation between age, BMI, HbA1c kit and lab in control group. When age was compared

**Table 1: Comparison of select characteristics between chronic periodontitis cases and controls**

Characteristic	Case	Control	*P value
Age (years)			
Mean $\pm$ SD	45.33 $\pm$ 6.64	43.43 $\pm$ 6.57	0.091 NS
Range	28 to 65	35 to 67	
Gender (n [%])			
Male	27 (38.6)	30 (42.9)	0.345 NS
Female	43 (61.4)	40 (57.1)	0.345 NS
Total/sample size (n)	70 (100)	70 (100)	
BMI (KG/m <sup>2</sup> )			
Mean $\pm$ SD	27.16 $\pm$ 2.43	26.19 $\pm$ 2.90	0.03 S
Range	17.9 to 33	20.2 to 33	
Sites with PD $\geq$ 5 mm			
Mean $\pm$ SD	6.30 $\pm$ 0.89	0	
Median	6		
Range	5 to 8		
CAL			
Mean $\pm$ SD	6.33 $\pm$ 1.32	0	
Median	6		
Range	4 to 9		
BOP			
Mean $\pm$ SD	82.69 $\pm$ 11.60	0	
Median	83		
Range	47 to 97		

Statistically significant if  $P < 0.05$ ; \*P values from unpaired t test (Age, BMI). \*P value from Z test for two proportions (Gender), CAL: Clinical attachment level; BOP: Bleeding on probing; PD: Probing depth

**Table 2: Comparison of HbA1c values between cases and controls**

Characteristic	Case	Control	*P value
HbA1c kit			
Mean $\pm$ SD	5.51 $\pm$ 0.53	5.44 $\pm$ 0.27	0.38 NS
Range	4.30 to 6.30	4.6 to 6	
HbA1c Lab			
Mean $\pm$ SD	5.50 $\pm$ 0.74	5.48 $\pm$ 0.29	0.841 NS
Range	4.00 to 6.80	4.4 to 6.1	

Statistically significant if  $P < 0.05$ ; \*P values from unpaired t test (HbA1c kit, HbA1c Lab)

**Table 3: Comparison of hba1c values of kit and lab**

Characteristic	HbA1c kit Mean $\pm$ SD	HbA1c lab Mean $\pm$ SD	*P value
Case	5.51 $\pm$ 0.53	5.50 $\pm$ 0.74	0.94 NS
Range	4.30 to 6.30	2 to 6.80	
Control	5.44 $\pm$ 0.27	5.48 $\pm$ 0.29	0.86 NS
Range	4.00 to 6.80	4.4 to 6.1	

Statistically significant if  $P < 0.05$ ; \*P values from paired t test (HbA1c kit, HbA1c Lab)

to other parameters, it was found to be positively correlated with same [BMI (0.07), HbA1c kit (0.17) and lab (0.05)]. When HbA1c kit was compared to lab (0.70) they were positively correlated and statistically significant ( $P < 0.05$ ).

**Table 4: Correlation between different variables in cases**

Characteristic	Age	BMI	HbA1c Kit	HbA1c Lab	PPD $\geq$ 5 mm	CAL	BOP
Age	1						
BMI	0.15	1					
HbA1c kit	0.03	0.17	1				
HbA1c Lab	0.11	0.13	0.93*	1			
PPD $\geq$ 5 mm	0.20	0.30*	-0.04	0.01	1		
CAL	0.26*	0.22	-0.05	-0.07	0.69*	1	
BOP	-0.15	-0.14	0.16	0.09	0.04	-0.09	1

\*Statistically significant at 5% ( $P < 0.05$ ) level of significance; CAL: Clinical attachment level; BOP: Bleeding on probing; PPD: Probing pocket depth

## DISCUSSION

Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of periodontal ligament and alveolar bone with pocket formation, recession or bot.”<sup>[8]</sup>

Diabetes mellitus and periodontitis are chronic diseases that result from various etiologic factors.<sup>[9]</sup> Although the biologic mechanisms linking periodontitis to impaired glucose metabolism have not been fully elucidated, a popular theory is that inflammatory mediators (particularly IL-6 and TNF- $\alpha$ ) generated within the inflamed periodontal tissues or in response to oral bacteria that translocate into the systemic circulation interfere with the actions of insulin receptors, thereby decreasing insulin sensitivity.<sup>[10]</sup>

Glucose can bind irreversibly to hemoglobin through a non-enzymatic reaction to form glycosylated hemoglobin (HbA). Hemoglobin A1c, or HbA1c, is the major subfraction of HbA. HbA1c is considered as a beneficial indicator of long-term homeostasis, reflecting an average blood glucose concentration for the past 2-3 months.<sup>[11]</sup> Diabetes treatment guidelines are based primarily on the establishment and maintenance of HbA1c levels  $< 7\%$ . Every percentage point drop in HbA1c is associated with an estimated 40% decrease in microvascular complications.<sup>[12]</sup>

Several studies have shown that periodontal treatment of diabetic patients decreased HbA1c levels. However, it remains unclear whether periodontal status affects HbA1c in non-diabetics. This study was intended to determine the association between chronic periodontitis and HbA1c in adults without diabetes and also to evaluate the difference in HbA1c values that were obtained with lab and kit.

**Table 5: Correlation between different variables in controls**

Characteristic	Age	BMI	HbA1c kit	HbA1c lab
Age	1			
BMI	0.07	1		
HbA1c kit	0.17	0.15	1	
HbA1c Lab	0.05	-0.08	0.70*	1

\*Statistically significant at 5% ( $P < 0.05$ ) level of significance

In this study, cases and controls were of similar age. When relationship between age and HbA1c was explored separately in cases and controls, each additional year of age was associated with a very slight and statistically significant increase in HbA1c.<sup>[7,12]</sup>

Cases had higher BMI scores than controls and after adjustment of BMI to HbA1c (kit and lab) a positive correlation was found.<sup>[6,13,14]</sup>

In this study, HbA1c levels (kit and lab) were positively correlated with CAL<sup>[15]</sup> and BOP also showed positive correlation with HbA1c.<sup>[16]</sup>

In this case-control study, HbA1c levels were slightly higher and statistically significant in chronic periodontitis cases than in healthy controls (kit- $P = 0.048$ ; lab- $P = 0.043$ ).<sup>[7,12,17]</sup>

In this study, HbA1c was measured using a chair side test kit and laboratory method. The HbA1c levels that were obtained with chair side kit correlated well with laboratory values.<sup>[18,19]</sup>

One advantage of chair side HbA1c tests is that they can be performed quickly and easily in a dental office setting. Further studies are needed to determine whether the screening in the dental office can improve early diagnosis and the management of diabetes.

The results of this study are consistent with the study conducted by Nibali *et al.*,<sup>[6]</sup> which suggested that chronic periodontitis is associated with elevated blood glucose levels in adults who have not been diagnosed with diabetes. In this study non-fasting blood glucose levels was compared between periodontally healthy patients and those with advanced disease. Glucose was significantly higher in chronic periodontitis cases than in controls. In this study, glucose levels in cases were not correlated with disease extent. In contrast we found a small, but negative correlation (with lab) and positive correlation (with kit), between HbA1c and number of sites with PD  $\geq 5$  mm. Nonetheless, an evidence of dose-dependent relationship between

disease extent and HbA1c elevations was not found, which suggests that there may be a threshold above which periodontitis affects HbA1c values in the general population. However, this finding needs to be confirmed with a larger sample size.

A number of participants in this study had elevated HbA1c readings and may have had undiagnosed type-2 diabetes. Although the usefulness of HbA1c as a diagnostic tool for diabetes continues to be debated, several groups have proposed cutoffs ranging from 5.8% to 6.2%.

The data from this study suggests that prospective large studies with full measurements of pocket depth and attachment loss, and intervention by periodontal treatment, are needed to clarify the causal relationship between periodontitis and HbA1c in non-diabetics.

## CONCLUSION

HbA1c levels (lab and kit) were slightly elevated in chronic periodontitis cases than in controls. This preliminary finding is consistent with earlier reports that chronic periodontitis is associated with elevated blood glucose in adults without diabetes and may increase one's risk for type-2 diabetes. The HbA1c values obtained were correlated with the laboratory values.

Further studies with larger sample sizes are needed to clarify the causal relationship between chronic periodontitis and glycosylated hemoglobin levels in non-diabetics.

## ACKNOWLEDGMENT

I would like to express my gratitude to Dr. Pradeep AR (Professor and HOD, Department of Periodontics, Government Dental College, Bangalore, Karnataka, India) for his encouragement and review of this project.

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**How to cite this article:** Rajan P, Nera M, Pavalura AK, Medandrao N, Kumar SC. Comparison of glycosylated hemoglobin (HbA1C) levels in patients with chronic periodontitis and healthy controls. *Dent Res J* 2013;10:389-93.

**Source of Support:** Nil. **Conflict of Interest:** None declared.