

## Evaluation of HbA1c in type-2 diabetes mellitus patients with periodontitis: preliminary findings of three-arm clinical trial

Ambrina Qureshi<sup>1</sup>, Zeba Haque<sup>2</sup>, Syed Akhtar Hussain Bokhari<sup>3</sup>, Akhtar Ali Baloch<sup>4</sup>

### Abstract

**Objective:** To assess a relationship and predict changes in glycaemic control due to chronic periodontitis in type-2 diabetic patients.

**Method:** Chronic periodontitis (CP) of a cross-section of 118 patients (age  $\geq$ 32 years) was determined using bleeding on probing (BOP), periodontal pocket depth (PPD) and clinical attachment loss (CAL). Their HbA1c, fasting blood glucose (FBG), fasting serum insulin (FSI) and homeostasis assessment model of insulin resistance (HOMA-IR) levels were also tested. Stata 11.0 was used to assess correlation between periodontal and glycaemic measures. Univariate analysis followed by multiple regression analysis through stepwise forward selection process was used to explore significant variables that may predict change in HbA1c. Multi-collinearity and heteroskedasticity were assessed at p-value  $>$  0.05.

**Results:** Results of participants (n=95) showed significantly positive correlations (r) between HbA1c and BOP [r = 0.34, p-value = 0.002], PPD [r = 0.36, p-value = 0.003] and CAL [r=0.42, p-value = 0.002]. However, FBG and HOMA-IR were not found correlated with any of the periodontal measures; except CAL with FBG [r=0.27, p-value=0.02]. In addition to healthy controlled diet, cultural background, education and FBG, CAL was found significant [coef. = 0.746, p-value = 0.001, CI = 0.339, 1.153] to predict change in HbA1c in the final model [R<sup>2</sup> = 0.549, p-value  $<$  0.001] with no multicollinearity [mean VIF=1.30] and heteroskedasticity [chi<sup>2</sup>=0.02, p-value=0.878] in final model.

**Conclusion:** Increased CAL is estimated to increase HbA1c level by 0.75% in T2DM patients after controlling other factors. It is suggested that periodontal prophylactic management may be planned with an aim to reduce HbA1c.

**Clinical Trial Registration No:** NCT03343366

**Keywords** (MeSH Terms): bleeding on probing; probing depth; clinical attachment loss; type 2 diabetes mellitus (JPMA 70: 1350; 2020). <https://doi.org/10.5455/JPMA.22016>

### Introduction

Research on systemic sequel of periodontitis has remained an area of particular interest. A recent systematic review has suggested that chronic periodontitis (CP) possibly has a causal relationship with diabetes mellitus (DM).<sup>1</sup> It is interesting to note that CP and DM are both common chronic conditions in many parts of the world.<sup>2</sup> Periodontitis is an anaerobic bacterial

infection of surrounding dental tissues which causes irreversible tissue destruction of periodontal collagen fibers and formation of periodontal pockets between gingiva and tooth.<sup>3</sup> By and large poor periodontal condition is common in all age groups in Pakistan; on severity scale CP is considered to be of moderate level with a prevalence of 25.9% (rural= 24.7%; urban= 27%).<sup>4</sup> Similarly, there is a high prevalence of type 2 diabetes mellitus (T2DM) throughout Pakistan with a reported level of 11.77%. Among them the males of Sind province show the highest level of 16.2%, considerably higher than other three provinces of Pakistan.<sup>5</sup> Uncontrolled DM is represented by high HbA1c levels depending on the availability of blood glucose levels monitored by insulin. In T2DM, patients suffer from insulin resistance

<sup>1</sup>Department of Community Dentistry, Dow University of Health Sciences, Karachi, Pakistan; <sup>2</sup>Department of Biochemistry, Dow University of Health Sciences, Karachi, Pakistan; <sup>3</sup>Department of Preventive Dentistry, Research & International Collaboration Committee, College of Dentistry, King Faisal University, Al-Ahsa Saudi Arabia; <sup>4</sup>National Institute of Diabetes & Endocrinology, Dow University of Health Sciences, Karachi, Pakistan.

**Correspondence:** Ambrina Qureshi. e-mail: ambrina.qureshi@duhs.edu.pk

thereafter causing increased glucose levels in the body. Insulin resistance (IR) is said to be established as a result of low-grade inflammation.<sup>6</sup> Homeostasis Assessment Model of IR (HOMA-IR) has been used as a proxy assessment of insulin resistance.<sup>7</sup> All International associations of DM recognize an HbA1c level of 7% as optimal glycaemic control and 6.5% as a more stringent goal for selected individuals.<sup>8</sup>

Initially, the link between destructive CP and T2DM was thought to be unidirectional. However, currently there is increasing evidence that relationship between these entities may be bi-directional.<sup>2,3</sup> In the bi-directional relationship the evidence supports and establishes that diabetes adversely affects periodontal health and that CP adversely affects diabetes by worsening glycaemic control, possibly increasing the threat for complicated consequences of diabetes. A recent study conducted on Pakistani population report that uncontrolled DM patients are found at a larger risk of CP than individuals without diabetes.<sup>9</sup> Another study conducted among Chinese population suggests that persons with severe CP are found to have more than three times (OR=3.4) chances of suffering from DM as compared to those not having CP.<sup>10</sup> There is no research recorded so far on Pakistani population that suggests the chance of having DM in patients suffering from CP. In the absence of any conclusive data from Pakistan that could convincingly show a link between CP and T2DM, it was considered prudent to determine the status of glycaemic measures as an outcome of periodontitis in T2DM patients. The results would help in exploring options such as oral health prevention to improve diabetics' health and minimize disease prevalence as planned in the form of a three-arm "Diabetes (DIA) - Periodontitis (PER) Trial" [NCT03343366].<sup>11</sup>

The objectives to present these preliminary findings were to assess relationship between glycaemic control and chronic periodontitis and to predict changes in glycaemic control due to chronic periodontitis in diabetic patients. The rationale was to adequately describe the demographic profile, population diversity and possible presence of any confounding factors that may affect the actions of intervention as needed to carry out the proposed three-arm clinical trial. This would support in the generalizability of the trial results that is the external validity.<sup>12</sup>

## Material and Methods

Ethical approval for the trial was granted by Dow University of Health Sciences (IRB-900/DUHS/Approval/2017/146). This preliminary assessment was conducted on the cross-sectional study sample collected during the initial eight months period (November 2017 to June 2018) of Diabetes (DIA) - Periodontitis (PER) Trial before they were allocated into three arms. Minimum sample size required to conduct the trial was n=105 with 35 participants in each arm. This sample size was calculated using ANOVA method calculated on Power Analysis & Sample Size Software (PASS) V11.0. Reduction of 0.7%, 0.6% and no reduction of 0.06% in HbA1c level in T2DM patients with reference to periodontitis levels were used as reference readings according to previous study results.<sup>13</sup> Already diagnosed T2DM patients (age  $\geq$  32 years) were screened at the National Institute of Diabetes and Endocrinology (NIDE) of Dow University Hospital, Pakistan. Prior to recruitment a written informed consent was obtained from each patient. Patients already diagnosed as T2DM were selected whether they were on insulin therapy or oral hypoglycaemic drugs. Pregnant or nursing mothers, patients with gestational diabetes, undergoing dialysis therapy, alcoholics, those with any serious concurrent disease or with complications requiring emergency treatment were excluded. Patients under any anti-inflammatory or antibiotic drugs (daily for  $>7$  consecutive days) within the last two months of examination, other than low dose aspirin prescribed for cardio-vascular disease (CVD) were also excluded. Structured screening form was used to record patient information such as age (in years), gender (male/female), years of education, monthly income (in rupees), body-mass index (BMI) through height (in meter), weight (in kilogram), duration of T2DM ( $<$  and  $\geq$  1 year), diabetes management (oral hypoglycaemic, insulin or both), smoking (yes/ no) and cultural backgrounds (based on local mother languages). Patients were also inquired about their regular physical exercises (at least 30 minutes of jogging, walking or any other exercise) and their healthy controlled diet (completely avoiding sweetened, flavoured and processed items in daily meals or snacks). On the same day using sterilized instruments, their full-mouth periodontal examination was performed. Chronic periodontitis (CP) was assessed using standardized periodontal indices, bleeding on probing (BOP),

periodontal pocket depth (PPD) and clinical attachment loss (CAL).<sup>14</sup>

Glycaemic control was assessed through assessing levels of HbA1c, fasting blood glucose (FBG) and fasting serum insulin (FSI). Fasting blood glucose was tested using standardized Accu Chek® Guide device by Roche, Germany. Whereas, HbA1c and serum insulin tests were performed at Dow Lab using standardized kits. HbA1c was tested on Cobas® C311 and its determination was based on the turbidimetric inhibition immunoassay (TINIA) for haemolyzed whole blood.<sup>15</sup> For quantitative determination of serum insulin, Chemiluminescent Microparticle Immuno-Assay (CMIA) was performed using kit from Abbott® ARCHITECT i2000 System.<sup>16</sup> Homeostasis Assessment Model of IR (HOMA-IR) was used as proxy assessment of insulin resistance, which was calculated as (fasting serum insulin in  $\mu\text{U}/\text{mL} \times$  fasting glucose in  $\text{mg}/\text{dl}$ )/ 405.<sup>7</sup>

Stata version 11.0 was used for all statistical management. Normality of data was assessed using Shapiro-wilk test at  $p$ -value  $>0.01$ . Linear relationship between periodontal variables and glycaemic variables were assessed using Pearson's ( $r$ ) correlation test. Simple regression analysis was performed to estimate each periodontal variable (BOP, PPD and CAL) by all explanatory variables individually. Multiple regression analysis was performed with variables those having  $p$ -value  $<0.25$  in simple regression models. Significant variables were added to find the best-fit model through a stepwise forward selection method keeping pre-set  $p$ -value  $=0.15$ . Multi-collinearity in the final model was checked by using Tolerance Test ( $1/\text{VIF}$ ) and Variance Inflation Factor (VIF), whereas Breusch-Pagan Test for Heteroskedasticity was used for potential homoskedasticity considering  $p$ -value  $>0.05$ .

## Results

Over a period of eight months 118 patients were screened, out of which only 95 fulfilled the inclusion criteria. Forty-one were males (44.2%) with mean age  $=49.51 \pm 7.13$  years and 53 (55.8%) were females with mean age  $53.35 \pm 9.94$  years. Table-1 shows the details of recruited participants suffering from T2DM since more than a year. Out of 90 participants whose co-morbidity status was found, 32.22% were found suffering from different co-morbidities. Most commonly found was hypertension and cardiac disease. Only one of them was

**Table-1:** Description of Study Sample.

Variables (No. of Observations)	Mean $\pm$ SD n (%)	Range (Min-Max)
Age (88)	51.73 $\pm$ 9.02 years	32 - 76 years
Education (68)	10.10 $\pm$ 5.09 years	0 - 18 years
Income (45)	36844.44 $\pm$ 22508.54 Rs.	3000 - 100000 Rs.
BMI (59)	26.31 $\pm$ 5.09 $\text{kg}/(\text{m})^2$	16.83 - 39.18 $\text{kg}/(\text{m})^2$
Gender (95)		
Male	41 (43.16)	
Female	54 (56.84)	
Cultural Background (90)		
Urdu	42 (46.67)	
Sindhi	22 (24.44)	
Punjabi	14 (15.56)	
Pashto	08 (8.88)	
Balochi	03 (3.33)	
Hindko	01 (1.11)	
Smoking (89)		
No	76 (85.39)	
Yes	13 (14.61)	
HbA1c (93)	9.16 $\pm$ 1.95 %	6.2 - 14.61 %
FBG (82)	173.25 $\pm$ 74.83 $\text{mg}/\text{dl}$	70 - 449 $\text{mg}/\text{dl}$
Serum Insulin (33)	21.65 $\pm$ 21.62 $\mu\text{m}/\text{l}$	4.2 - 98.6 $\mu\text{m}/\text{l}$
HOMA-IR (31)	10.97 $\pm$ 11.01	1.8 - 51.9
Co-morbidity (90)		
None	61 (67.78)	
Hypertension only	16 (17.78)	
CVD only	05 (5.56)	
Arthritis	05 (5.56)	
Gastric Ulcer	02 (2.21)	
Hypertension & CVD	01 (1.11)	
Duration of Diabetes (86)		
$< 1$ year	15 (17.44)	
$\geq 1$ year	71 (82.55)	
Current Diabetes Management (88)		
Hypoglycaemic drugs	51 (57.95)	
Insulin	25 (28.40)	
Both	12 (13.63)	
Regular Physical Exercise (86)		
No	49 (56.97)	
Yes	37 (43.02)	
Healthy Controlled Diet (83)		
No	23 (27.72)	
Yes	60 (72.28)	
Mean BOP sites	28.36 $\pm$ 19.06%	0.00 - 91.6%
Mean PPD	2.99 $\pm$ 1.09 mm	1.00 - 6.41 mm
Mean CAL	3.60 $\pm$ 1.54 mm	0.00 - 8.33 mm

BOP: Bleeding on Probing, PPD: Periodontal Pocket Depth, CAL: Clinical Attachment Loss. suffering from both hypertension and CVD. Approximately 9% of them suffered from other diseases that included arthritis (5.56%) and gastric ulcer (2.21%). Sample was normally distributed ( $p$ -value  $>0.01$ ) with reference to HbA1c.

An intermediate strength of significant and direct correlation ( $r$ ) was observed between HbA1c and BOP, PPD and CAL with  $r = 0.34$  ( $p$ -value  $=0.002$ ),  $r = 0.36$  ( $p$ -value  $<0.001$ ),  $r = 0.43$  ( $p$ -value  $<0.001$ ) respectively. Surprisingly, there was no significant correlation found between periodontal measures and FBG and HOMA-IR

**Table-2:** Simple Regression Analysis (unadjusted) between dependent (HbA1c) and Independent Variables.

Independent Variables	HbA1c (%)			
	Unadjusted		Adjusted	
	Coef.	p-value (95% CI)	Coef.	p-value (95% CI)
Age	-0.046	0.056 (-0.094, 0.001)*	-0.004	0.888 (-0.072, 0.063)
Gender				
Male	1.00	--	--	--
Female	0.432	0.292 (-0.378, 1.243)		
Education	-0.071	0.139 (-0.166, 0.023)*	0.145	0.032 (0.013, 0.277) ¥
Income	-4.360	0.765 (-0.000, 0.000)	--	--
BMI	0.011	0.825 (-0.089, 0.112)	--	--
Cultural Backgrounds				
Urdu	1.00	--	--	--
Sindhi	1.283	0.015 (0.255, 2.310)*	0.509	0.514 (-1.076, 2.094)
Punjabi	0.978	0.104 (-0.207, 2.163)*	2.341	0.009 (0.652, 4.030) ¥
Others	1.011	0.113 (-0.245, 2.268)*	1.654	0.045 (0.043, 3.264) ¥
Smoking				
No	1.00	--	--	--
Yes	0.689	0.251 (-0.497, 1.876)		
FBG	0.012	<0.001 (0.007, 0.017)*	0.007	0.063 (-0.000, 0.015)
Serum Insulin	-0.003	0.807 (-0.032, 0.025)	--	--
HOMA1R	0.008	0.784 (-0.051, 0.067)	--	--
Co-morbidity				
No	1.00	--	--	--
Yes	-0.104	0.563 (-0.461, 0.252)		
Duration of Diabetes				
< 1 year	1.00	--	--	--
≥ 1 year	-0.510	0.334 (-1.556, 0.535)		
Diabetes Management				
Hypoglycaemic	1.00	--	--	--
Insulin	0.329	0.487 (-0.610, 1.268)		
Both	0.371	0.565 (-0.906, 1.648)		
Regular Physical Exercise	-0.275	0.510 (-1.105, 0.553)	--	--
Healthy Controlled Diet	-0.693	0.147 (-1.636, 0.248)*	-1.201	0.047 (-2.387, -0.015) ¥
Mean BOP sites	0.034	0.002 (0.012, 0.056)*	-0.009	0.604 (-0.045, 0.027)
Mean PPD	0.659	<0.001 (0.312, 1.006)*	0.540	0.123 (-0.157, 1.237)
Mean CAL	0.542	<0.001 (0.265, 0.818)*	0.551	0.036 (0.038, 1.064) ¥

\*p-value < 0.25 was considered to highlight important exploratory variables; ¥ p-value < 0.05 was considered significant after adjusting for important variables. BOP: Bleeding on Probing, PPD: Periodontal Pocket Depth, CAL: Clinical Attachment Loss.

**Table-3:** Final Model of Predicting Variables for HbA1c through Forward Selection Method (p-value=0.15).

HbA1c*	Coef. (S.E)	95% CI	p-value
Mean CAL	0.746 (0.199)	0.339, 1.153	0.001
Healthy Controlled Diet	-0.919 (0.548)	-2.041, 0.201	0.104
Cultural background	0.662 (0.237)	0.176, 1.147	0.009
Education	0.145 (0.062)	0.019, 0.271	0.025
FBG	0.007 (0.003)	0.000, 0.014	0.037

\*n= 35, R2= 0.5491, p-value< 0.001, intercept= 3.583; Mean VIF= 1.30

except for a weak correlation between CAL and FBG (r =0.25, p-value =0.039). Figure shows graphical representations of relationship between HbA1c and BOP (1a), PPD (1b) and CAL (1c) respectively. According to the coefficient of determination (R2) with increasing

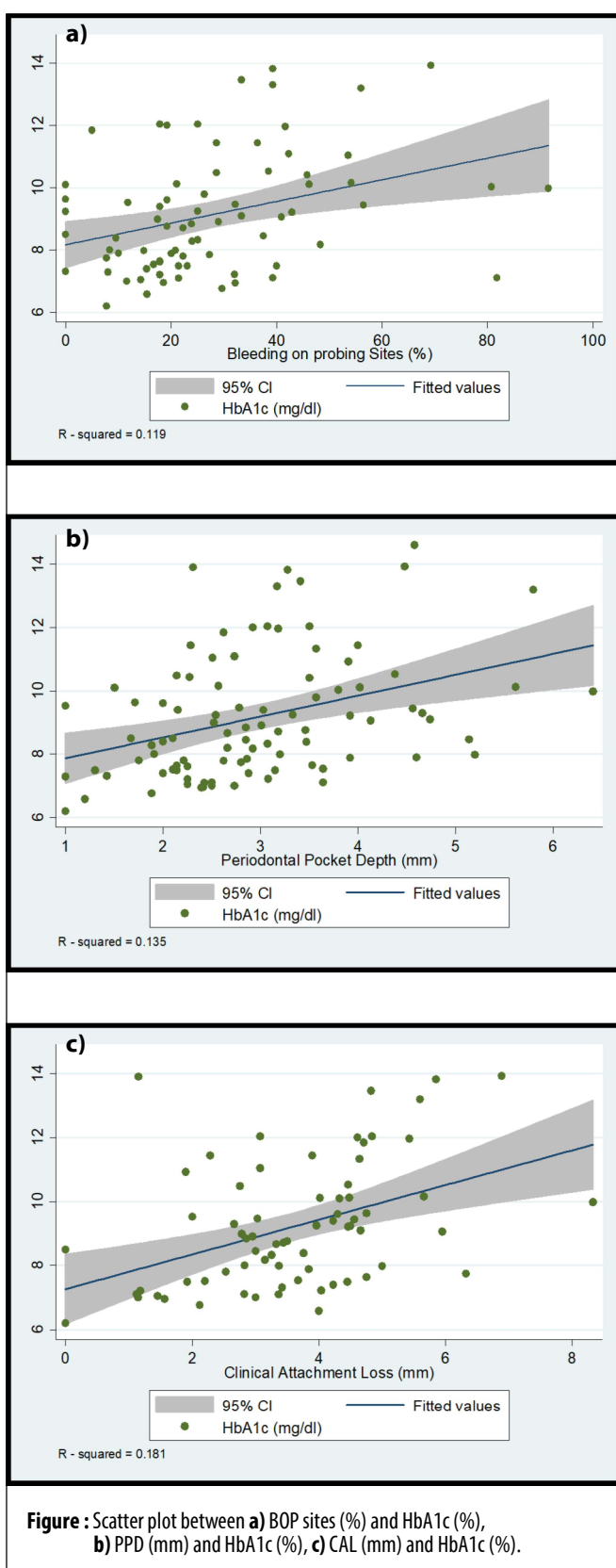
mean BOP sites, PPD (in mm) and CAL (in mm) a change in HbA1c was observed by approximately 12%, 13% and 19% respectively; where rest of the variations could be residing in the residuals. shows the univariate regression analysis according to which mean change in HbA1c may be predicted by unit change in a number of important variables (p <0.25) such as age, years of education, different cultural backgrounds, FBG, healthy controlled diet and periodontal measures (BOP, PPD, CAL). Multiple regression analysis was performed to assess how much variance was predicted by other important variables after adjusting for known confounders. According to the results BOP and PPD were rendered as not significant. Interestingly, Punjabi culture was found to significantly predict HbA1c levels by more than times.

Table-3 shows the final models after applying step-wise forward selection method for variables that predict HbA1c with a pre-set p-value =0.15. According to this table CAL, cultural background, years of education and FBG were found significant (p-value <0.05) to predict HbA1c; whereas, healthy controlled diet was found significant with p-value =0.1. As per result in the final model HbA1c may significantly change by 0.74% (p-value =0.001) with each unit change in mean CAL in T2DM patients after adjusting for healthy controlled diet, cultural

background, education, and fasting blood glucose. This model significantly determines a variation in linear combination between HbA1c and significant independent variables by 55% (R2 =0.549, p-value <0.001) without any collinear effects having appropriate tolerance (mean VIF =1.30) and no evidence of heteroskedasticity (chi2 =0.02, p-value =0.891).

### Discussion

Although the current data was collected from single center, yet the participants belonged to diversified ethnic and cultural backgrounds representing all four provinces of Pakistan. This provided an opportunity to extrapolate the glycaemic and periodontal findings of the study



sample over the diverse Pakistani population. Less than half of our included participants were found with at least single co-morbidity. Higher prevalence (52%) of arthritis has been observed among diabetic adults;<sup>17</sup> however in the present study only few patients that is, approximately 6% were found suffering from arthritis. We included T2DM with arthritis as co-morbidity because they were not on regular anti-inflammatory drugs at the time of investigation as per inclusion criteria. As a number of covariates and mediating factors are responsible for the relationship between DM and CP it was considered necessary to understand the relatively complex relationship between both the diseases. Such factors include other co-morbidities (such as hypertension and CVD), diet, exercise, obesity, smoking, selective management through oral hypoglycaemic drugs and insulin.<sup>18</sup> All these factors were therefore considered and summarized while analyzing the preliminary data of the main trial. However, we found no association particularly between HbA1c and any of the co-morbid conditions that the participants were selected with.

It has been criticized by a team of reviewers that more than half of the included studies in their meta-analysis have used community periodontal index (CPI) to record mean periodontal pocket depth (PPD), which is considered as a serious limitation to assess CP.<sup>19</sup> Our study considered mean CAL in addition to mean PPD. It would be of an interest to mention that even in the absence of PPD in most of our study participants CAL was found higher with increased level of gingival recession apical to cement-enamel junction. Therefore, based on our findings we support the use of CAL for periodontal assessment<sup>20</sup> and suggested that PPD alone must not be considered to describe chronic periodontal status of any population or a group.

There was a weak level of statistically significant positive correlation found between measures of periodontitis (BOP, PPD and CAL) and HbA1c ( $p < 0.05$ ). Almost similar strength of significant correlation was found in observational study conducted on Asian Indian population groups; however, the Indian study participants were either pre-diabetic or diabetic with lower level of HbA1c as compared to a comparatively higher level of HbA1c of our study participants.<sup>21</sup> Authors have suggested that this weaker correlation may be because of confounding factors such as younger age, duration of diabetes, presence of calculus and smoking;

or may be smaller sample size.<sup>22</sup> Our analysis showed a correlation between HbA1c and CAL of more than 40% as compared to that found between HbA1c and PPD, and HbA1c and BOP. Moreover, majority of the participants were those with longer duration of diabetes denoting chronic destructive phase of periodontitis in the form of increased CAL as compared to active phase of periodontitis in the form of BOP and PPD. Although such chronic inflammatory condition is said to increase insulin resistance in diabetics but our results did not show any putative correlation between insulin resistance and periodontitis measures.

Our study found no significant correlation between other glycaemic measures (FSI, FBG, HOMA-IR) with any of the periodontitis measures (p-value >0.05). This may be due to reduced number of fasting blood samples as most of the patients were visiting during random hours. However, concordant result was found in a study conducted on T2DM patients where HOMA-IR was not found correlated with any periodontal examination result.<sup>23</sup> Yet, conflicting results have been observed in other studies conducted among non-diabetic Spanish and Korean population groups.<sup>24,25</sup>

In order to predict variables that may have impact on the HbA1c levels a purposeful selection process began with univariate analysis of each variable in this study. Variables were selected as a candidate for the multivariate analysis on the basis of p-value cut off of 0.25 because the more traditional levels such as 0.05 could fail in identifying variables known to be important.<sup>26</sup> Based on this assumption participants' age, years of education, cultural backgrounds (Sindhi, Punjabi and others including Pushto, Balochi and Hindko), FBG, healthy controlled diet and all measures of periodontitis (BOP, PPD and CAL) were considered as important factors to be explored that could predict change in HbA1c levels of the study participants. On the other hand, gender, income, BMI, smoking, comorbidity, diabetes duration, its management and regular physical exercise were not considered as statistically important factors. Even the FSI and HOMA-IR were not considered important in predicting HbA1c levels, which may suggest that HbA1c levels are not affected by change in insulin resistance (HOMA-IR).

Furthermore, adjusted analysis of our study revealed attenuation of associations between BOP - HbA1c and PPD - HbA1c. This may suggest an "underestimation" of

the adjusted relative risks due to negative confounding effect. This may be due to convenience sampling method applied during collection of baseline study participants, which is common in observational study method. This limitation shall be overcome during trial recruitment and this problem will be addressed through random allocation of the participants in groups.

Standards for inclusion of a variable in the adjusted model vary with problem to problem and with discipline to discipline. We chose the common approach to statistical model building by minimizing variables through forward selection method with an aim to numerically stabilize and generalize the result. Here, statistically the specified level of entry was considered as p-value <0.15,<sup>26</sup> where mean CAL, healthy controlled diet, cultural background, years of education and FBG were retained as variables to predict change in HbA1c level in the final model. This method helped us not only in predicting the level of HbA1c due to CAL but also in risk factor modeling where other factors were also retained as a significant factor for change in HbA1c level in T2DM patients. Although jointly significant variables could cause multi-collinearity but interestingly there was no multi-collinearity found between CAL and healthy controlled diet in the final model. Moreover, there was no heteroscedasticity found as well suggesting that there was no problem in the sample homogeneity.

## Conclusion

The preliminary findings show that increased CAL is estimated to raise HbA1c level in T2DM patients even if other factors are controlled. It is predicted that prophylactic management of CAL may reduce HbA1c by 0.75% in T2DM patients.

**Disclaimer:** The manuscript is part of PhD thesis project of Dow University of Health Sciences, Karachi Pakistan

**Conflict of interest:** The authors declare that there is no conflict of interest.

**Sources of Funding:** The research project title: Glycaemic control in type-2 diabetes mellitus patients through non-surgical periodontal therapy - a randomized controlled trial has successfully won HEC-NRPU (2017-2018) Research Grant (No. 7143/Sindh/NRPU/R&D/HEC/2017)

## References

- Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes: An update of the EFP-AAP review. *J Clin Periodontol* 2018; 45:167-87.
- Lalla, E., Papapanou, P. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nat Rev Endocrinol* 2011; 7: 738-48.
- Llambes F, Arias-Herrera S, Caffesse R. Relationship between diabetes and periodontal infection. *World J Diabetes*. 2015; 6:927-35.
- Khan AA, Ijaz S, Syed A, Qureshi A, Padhiar I, Sufia S et al. Oral Health in Pakistan- A situation analysis. *Dev Dent* 2004; 5: 35- 44.
- Meo SA, Zia I, Bukhari IA, Arain SA. Type 2 diabetes mellitus in Pakistan: current prevalence and future forecast (Systematic Review). *J Pak Med Assoc* 2016; 66: 1637-42.
- Ding Y, Li S, Ma RL, Guo H, Zhang J, Zhang M, et al. Association of homeostasis model assessment of insulin resistance, adiponectin, and low-grade inflammation with the course of the metabolic syndrome. *Clin Biochem* 2015; 48: 503-7.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28:412-9.
- Diabetes Care: Standards of medical care in, diabetes - 2018. *Diab Care J Clin App Res Edu* 2018;41:1-150.
- Tanveer F, Tariq A. Effect of glycemic control on periodontal status. *J Coll Physician Surg Pak* 2012; 22:371-4.
- Awuti G, Younusi K, Li L, Upur H, Ren J. Epidemiological Survey on the Prevalence of Periodontitis and Diabetes Mellitus in Uyghur Adults from Rural Hotan Area in Xinjiang. *Experiment Diabetes Res* 2012; Article ID 758921.
- ClinicalTrials.gov [Internet]. National Library of Medicine (US). (2000 Feb 29 - ). Identifier NCT03343366. Glycemic Control in T2DM through Non-Surgical Periodontal Therapy. Retrieved in August, 2018 from: <https://clinicaltrials.gov/ct2/show/NCT03343366>.
- Burgess DC, GebSKI VJ, Keech AC. Baseline data in clinical trials. *Med J Aust* 2003; 179: 105-7.
- Singh S, Kumar V, Kumar S, Subbappa A. The effect of periodontal therapy on the improvement of glycaemic control in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. *Int J Dia Dev Count* 2008; 28:38-44.
- Glavind L, Loe H. Errors in the clinical assessment of periodontal destruction, *J Periodont Res* 1967; 2:180-64.
- Tina-quant® HbA1c Gen. 3 Turbidimetric inhibition immunoassay (TINIA) for the in vitro determination of hemoglobin A1c in whole blood or hemolysate. [online][cited 2018 Aug 11]. Available from:URL: [http://www.roche-diagnostics.ch/content/dam/corporate/roche-dia\\_ch/documents/broschueren/professional\\_diagnostics/serumarbeitsplatz/klinische\\_chemie/03HbA1c/EN\\_Tina-quant%20HbA1c%20Gen%203.pdf](http://www.roche-diagnostics.ch/content/dam/corporate/roche-dia_ch/documents/broschueren/professional_diagnostics/serumarbeitsplatz/klinische_chemie/03HbA1c/EN_Tina-quant%20HbA1c%20Gen%203.pdf)
- Diagnostics, ARCHITECT ci System Specification. [online][cited 2018 Aug 11]. Available from:URL: [https://www.corelaboratory.abbott/sal/specSheet/ADD-00058823-R1\\_ARCHITECT%20Specifications.pdf](https://www.corelaboratory.abbott/sal/specSheet/ADD-00058823-R1_ARCHITECT%20Specifications.pdf)
- Centers for Disease C, Prevention. Arthritis as a potential barrier to physical activity among adults with diabetes-- United States, 2005 and 2007. *MMWR Morb Mortal Wkly Rep*. 2008; 57: 486-9.
- Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2 diabetes mellitus. *J Clin Periodontol* 2001; 28: 306-310
- Nascimento GG, Leite FRM, Vestergaard P, Scheutz F, Lopez R. Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies. *Acta Diabetol* 2018; 55: 653.
- Mdala I, Olsen I, Haffajee AD, Socransky SS, Thoresen M, de Blasio BF. Comparing clinical attachment level and pocket depth for predicting periodontal disease progression in healthy sites of patients with chronic periodontitis using multi-state Markov models. *J Clin Periodontol* 2014; 41:837-45.
- Karthik SJ, Anoop S, Kumar RS, Usha Rani MV. Predictors for Gingival Index in Middle-Aged Asian Indians with Type 2 Diabetes from South India: A Cross-Sectional Observational Study. *Scientific World Journal* 2018; 2018: 9081572.
- Santos T, Foss-Freitas MC, Nogueira-Filho GR. Impact of periodontitis on the diabetes-related inflammatory status. *J Can Dent Assoc* 2010; 76:a35.
- Sugihara K. Periodontal study on patients with type 2 diabetes. *Jpn Periodontal Soc J* 2005; 47: 178-85.
- Moran MP, Bullon P, Morillo JM, Battino M, Quiles JL, Ramirez-Tortosa MC. The relationship between insulin resistance and periodontitis is not affected by Mediterranean diet in a Spanish population. *Arch Oral Biol* 2017;77: 62-7.
- Islam SK, Seo M, Lee YS, Moon SS. Association of periodontitis with insulin resistance, β-cell function, and impaired fasting glucose before onset of diabetes. *Endocr J* 2015; 62:981-9.
- Zhang Z. Model building strategy for logistic regression: purposeful selection. *Ann Transl Med* 2016; 4(6):111.