Original Article

Evaluation of Salivary Glycated Albumin in Periodontitis Patients with and without Type 2 Diabetes Mellitus and its Changes with Non-surgical Periodontal Therapy

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Abstract

Background: Bidirectional relationship exists between diabetes mellitus and periodontitis. Glycated albumin is an emerging biomarker to assess intermediate glycemic control. Salivary glycated albumin has not been evaluated in periodontitis. **Aim:** The aim of the study was to compare salivary glycated albumin in periodontitis patients with and without diabetes mellitus before and after periodontal therapy. **Materials and Methods:** This comparative cross-sectional study was conducted in the Department of Periodontics. Ninety subjects (mean age 41.8 ± 6.82) were categorized into three groups. Clinical examination and saliva sample collection were done at baseline and 4 weeks after scaling and root debridement. Salivary glycated albumin levels were estimated using an enzyme-linked immunosorbent assay. One-way analysis of variance with post hoc test and paired *t*-test was done for inter- and intra-group comparison. The optimal cut-off value was calculated using the receiver operating characteristic curve and by maximization of the Youden index. **Results:** Mean salivary glycated albumin was the highest in diabetic patients followed by non-diabetic periodontitis patients and least in healthy controls. All the intergroup comparisons were significant. A cut-off value of 72.19 ng/ml of salivary glycated albumin could predict diabetic status with a sensitivity and specificity of 75%. Salivary glycated albumin was significantly reduced in a similar manner in both groups after periodontal therapy (19.4% and 18.5%). **Conclusion:** Periodontitis patients with diabetes mellitus were presented with the highest salivary glycated albumin. Non-surgical periodontal therapy resulted in a similar reduction of salivary glycated albumin in periodontitis with and without diabetes mellitus.

Keywords: *Biomarker, diabetes mellitus, glycemic control, periodontitis, salivary glycated albumin*

Introduction

Type 2 diabetes mellitus (T2DM) and periodontitis are common chronic diseases that are highly prevalent worldwide.[1,2] Both diseases are multi-factorial, and periodontitis is recently categorized as a comorbidity rather than a complication of T2DM.[3] Patients with moderate-to-severe periodontitis are at increased risk of developing T2DM, and periodontal therapy is beneficial for improving glycemic control.[4,5]

The diagnostic criteria of T2DM proposed by the American Diabetes Association in 2020 include the evaluation of fasting plasma glucose or 2 h plasma glucose level or random plasma glucose or glycated hemoglobin A1c (HbA1c).[6] Among these biomarkers,

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glycemic control in diabetic patients can be better evaluated using HbA1c which provides an estimate of the average blood glucose level over the preceding 120 days corresponding to the lifespan of red blood cells.[7]

Hyperglycemia can glycate serum proteins other than hemoglobin, which can also be utilized for the assessment of glycemic control. Glycated albumin (GA) is a reliable marker to evaluate the serum glycemic status[8,9], and serum GA and HbA1c are positively correlated in individuals with and without T2DM.[10] Unlike HbA1c, GA shows short-term (2 to 3 weeks) glycemic control because the half-life of albumin is approximately 4 weeks.[9,10] GA was also found to have an association with chronic complications in type 1 and 2 diabetic patients.[11]

Current methods of assessing glycemic status require the drawing of blood, which is an invasive procedure. Salivary biomarker research is recently getting much popularity as a non-invasive and easy alternative to blood biomarkers. Most of the diagnostic biomarkers so far identified in plasma are also evaluated in saliva and found to be predictable. The presence of GA has been detected in saliva, and a correlation has been established between salivary GA and its serum counterpart.[12]

Since the prevalence of periodontitis in diabetic patients is extremely high, periodontist often gets a chance to use saliva for evaluating glycemic control. The effectiveness of non-surgical periodontal therapy is often evaluated after 4–6 weeks during which time we can also expect changes in salivary GA. To the best of our knowledge, we could not find any published reports of salivary GA estimation in periodontitis patients. In the present study, salivary GA is evaluated in periodontitis patients with and without T2DM as well as in periodontally healthy non-diabetic individuals. The impact of periodontal treatment on salivary GA level is another unexplored area. So, the study also aims to evaluate the change in salivary GA in diabetic and non-diabetic periodontitis patients after scaling and root debridement.

Materials and Methods

The present study was conducted in the Department of Periodontics from December 2016 to September 2018 after obtaining clearance from the Institutional Ethics Committee.

Periodontitis patients with and without T2DM as well as systemically and periodontally healthy individuals in the age group 30–60 yrs were included in the study. Diagnosis of T2DM was done according to criteria by American Diabetes Association Diabetes Care 2010;[13] periodontitis/periodontal health was diagnosed according to criteria put forward by the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions in 2017.[14] The sample size was calculated using the formula $n = 2\ \sigma^2\ (Z_\alpha + Z_\beta)^2 \div \delta$. Type 1 error was kept as 0.05 and type 2 error as 0.20. Substituting the values and considering the chance of 10% dropouts during the study, the minimum sample size required was calculated as 30 in each group.

The participants were categorized into three groups based on periodontal and glycemic status.

- **GROUP A (*n* = 30)**—subjects diagnosed with T2DM and stage III–IV generalized periodontitis.
- **GROUP B (*n* = 30)**—subjects with stage III–IV generalized periodontitis, but without T2DM
- **GROUP C (*n* = 30)**—periodontally healthy non-diabetic individuals

In groups A and B, periodontitis patients with gingival index[15] [GI] ≥2 alone were selected. Patients with systemic diseases like hypertension, psychiatric problems, presence of life-threatening conditions like malignant tumors or radiotherapy either current or in the previous 6 months**,** bleeding disorders, and those who have taken antibiotics or anti-inflammatory drugs for the past 3 months, pregnant and lactating females, smokers and immuno-compromised patients were also excluded from the study. Participants who satisfy the criteria were selected using a consecutive sampling method till the required number of subjects is included. Written informed consent was obtained from every participant after explaining the study procedure in detail, and the study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Procedure

Sociodemographic data and periodontal findings [plaque index,[16] GI, pocket depth (PD), and clinical attachment loss (CAL)] were collected from all selected participants by a single examiner (SKM) using Williams graduated periodontal probe (Hu-Friedy, Chicago, IL) after verifying the intra-examiner agreement in a pilot study. Saliva samples were collected from all the participants before the clinical examination. One-stage, full-mouth scaling, and root debridement using an ultrasonic scaler (ACTEON SATELEC P5 Booster Scaler) and hand curettes were performed by the same investigator in periodontitis patients followed by oral hygiene instructions. They were recalled after 4 weeks for saliva collection and clinical examination.

Saliva collection and biomarker analysis

Saliva was collected as described previously.[17] 1.5 to 2 ml of the whole saliva was collected using a syringe into a polypropylene tube and was immediately placed in a cryo-box at -20°C and transported to the lab and

stored at -80°C until further evaluation. Samples were defrosted and analyzed within one month of the collection by a trained technician blinded to the study groups.

Each saliva sample was pipetted into a clean microcap tube, and centrifugation was done at 4,000 revolutions per minute (rpm) for 10 min at 4°C. The supernatant was transferred to clean microcap tubes and used immediately for assay. Concentrations of GA were determined using an enzyme-linked immunosorbent assay (Human GA ELISA Kit, Bioassay Technology Laboratory, cat No: E0029Hu Shanghai, China) according to the manufacturer's instructions. The standard curve range of the assay was 0.5 ng/ml → 200 ng/ml, and the sensitivity was 0.24 ng/ml. 40 µl sample, 10 µl GA antibodies, and 50 µl streptavidin-HRP were added to the precoated well with human GA antibody and then covered with a seal plate membrane. It was shaken gently to mix them up and incubated at 37°C for 60 min. After washing, chromogen solution was added and incubated for 10 min, and the absorbance (OD) of each well was measured under 450 nm. According to standards' concentrations and the corresponding OD values, a linear regression equation of the standard curve was derived to calculate the concentration GA in nanograms per milliliter.

Statistical analysis

The Kolmogorov–Smirnov test was used to check the normality of the data. The variables obey the normality assumption, and hence, parametric statistical techniques have been employed in the present study. Patient characteristics are summarized in terms of mean, standard deviation (SD), and standard error (SE). Comparison of salivary GA levels in the three groups was done using one-way analysis of variance (ANOVA) with a post hoc test (Tukey's honestly significant difference (HSD)). Comparison of salivary GA levels in periodontitis patients before and after scaling and root debridement was done using paired *t*-test, and correlation was evaluated using Pearson correlation coefficient. Receiver operating characteristic (ROC) curve was constructed for GA concentration in diabetic and non-diabetic periodontitis patients, and the optimal cut-off values were determined by the maximization of the Youden index. Calculated *P*-value <0.05 was considered statistically significant in all the comparisons. The collected raw data were analyzed using commercially available software (SPSS software version 23.0, IBM, Chicago, IL).

Results

Ninety subjects (mean age 41.8 ± 6.82) consisting of 44 males and 46 females were included in the study, and they were categorized into groups A, B, and C based on their periodontal and diabetic status.

The three groups were similar in baseline characteristics like age and gender. Descriptive statistics are provided in Table 1. Clinical parameters at baseline evaluation were found to be significantly higher in groups A and B compared to group C (*P* <0.001) [Table 2]. There was no statistically significant difference between these parameters in groups A and B.

Statistically significant (*P*-value <0.001) difference in mean concentrations of salivary GA among three groups was observed, and it was higher in group A followed by group B and least in group C (79.86 ± 13.56, 62.94 ±16.74 and 25.13 ± 7.27, respectively) [Table 2]. All the intergroup comparisons were statistically significant (*P*-value <0.001) as per post hoc analysis.

Clinical parameters significantly reduced in both groups A and B when re-evaluated 4 weeks after non-surgical therapy [Table 3, *P* <0.0001]. A significant reduction of salivary GA was also noticed in both groups after scaling and root debridement (*P*-value <0.001) [Table 3]. But a similar reduction was noticed in both groups (19.4% in group A and 18.5% in group B). Salivary GA before and after non-surgical periodontal therapy was significantly correlated in both groups (r = 0.75 and 0.8, respectively).

ROC curves for the salivary GA concentration were plotted, and the cut-off value was determined to predict diabetic status [Figure 1]. The areas under the ROC curve (AUC) for salivary GA concentration were 0.79 (standard error 0.07, 95% confidence interval = 0.65 to 0.93, *P* <0.05). ROC analysis gave a cut-off value of 72.19 ng/ml of salivary GA concentration for the prediction of diabetes status with a sensitivity of 75% and a specificity of 75%. None of the periodontally and systemically healthy individuals had GA value above this cut-off point, and the maximum value reported was 37.41 ng/ml. The median salivary GA

Table 1: Demographic data at baseline

Study groups	Mean age (in years)	SD	F	*P*	Tukey HSD	Gender (M:F)	Chi-square value	*P*
Group A	46.65	9.94	4.11	0.05*	A Vs B*	2:3	0.63	0.73*
Group B	43.85	6.71			A Vs C*	7:8		
Group C	49.1	7.75			B Vs C*	1:1		

SD=Standard deviation, HSD=Honest significant difference. *Not significant

Table 2: Statistical analysis of clinical and biochemical parameters in three groups at baseline using one-way ANOVA and *post hoc* test

Parameter	Groups	Mean	SD	*F*	*P*
PI	Group A	2.14†	0.2		
	Group B	2.15†	0.18	935.18	<0.001‖
	Group C	0.24‡	0.13		
GI	Group A	2.24†	0.15		
	Group B	2.25†	0.12	1201.72	<0.00001‖
	Group C	0.31‡	0.21		
PD	Group A	7.01†	0.48		
	Group B	6.81†	0.58	976.78	<0.00001‖
	Group C	2.24‡	0.14		
HbA1c	Group A	7.31†	0.53		
	Group B	6.05‡	0.25	198.59	<0.00001‖
	Group C	4.79§	0.36		
GA	Group A	79.86†	13.56		
	Group B	62.94‡	16.74	78.13	<0.05‖
	Group C	25.13§	7.27		

SD=Standard deviation, PI=Plaque index, GI=Gingival index, PD=Probing depth, GA=Glycated albumin in saliva. †,‡,§Means with different superscripts within each parameter differ from each other, ‖statistically significant

Table 3: Comparison of clinical parameters before and after scaling and root debridement in groups A and B using paired *t*-test

Parameter	Group A		Group B	
	Baseline	4 weeks	Baseline	4 weeks
PI				
Mean±SD	2.14±0.2	0.45±0.16	2.16±0.20	0.35±0.09
t	29.38		37.08	
P	<0.0001‖		<0.0001‖	
GI				
Mean±SD	2.24±0.16	0.44±0.15	2.25±0.12	0.63±1.27
t	35.66		5.7	
P	<0.0001‖		<0.0001‖	
PD				
Mean±SD	6.96±0.47	4.88±0.49	6.81±0.58	4.38±0.61
t	29.21		22.88	
P	<0.0001‖		<0.0001‖	
CAL				
Mean±SD	7.19±0.49	5.09±0.50	7.03±0.54	4.98±0.47
t	28.25		29.87	
P	<0.0001‖		<0.0001‖	
GA				
Mean±SD	79.86±13.56	64.32±9.22	61.94±18.36	49.47±11.78
t	7.72		4.42	
P	0.00001‖		0.0003‖	

SD=Standard deviation, PI=Plaque index, GI=Gingival index, PD=probing depth, CAL=clinical attachment level. ‖Significant

concentration in diabetic periodontitis and non-diabetic periodontitis groups was 75.73 ng/ml and 63.27 ng/ml, respectively. After periodontal therapy, it was decreased to 62.01 ng/ml and 50.60 ng/ml in the corresponding groups, both of which are less than the cut-off value. GA value of 25% of non-diabetic periodontitis was above the cut-off point before periodontal therapy which decreased to 10% after therapy. In the diabetic group, it was reduced from 75% to 15%.

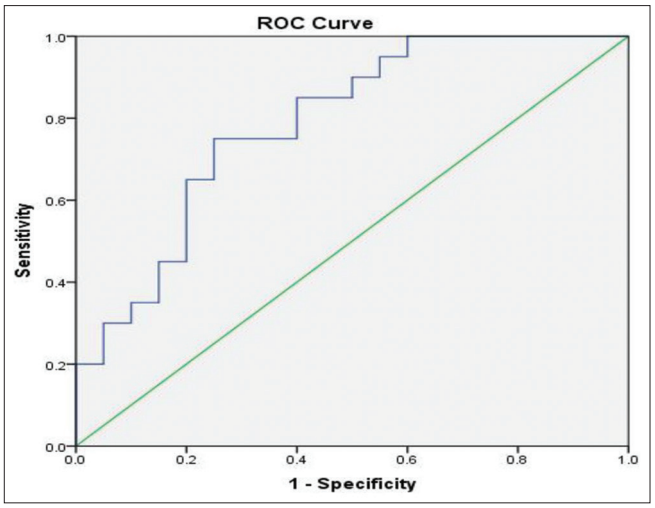

Figure 1: Receiver operator characteristic (ROC) curve analysis of salivary GA for the prediction of diabetic status

Discussion

Periodontitis and T2DM are comorbidities, and the incidence of periodontitis in patients with T2DM is higher than that in the general population.[18] Hyperglycemia in T2DM induces the production of accumulated glycation end products (AGEs) and results in diabetic complications like vascular abnormalities, altered collagen metabolism, and dysfunction of immune cells and regulates the expression of inflammatory cytokines and chemokines in periodontal tissues.[19] Excess AGEs accumulate in the periodontal tissues of patients with T2DM and aggravate periodontal diseases.[20]

Long-term glycemic control is often assessed with HbA1c, but it is not recommendable in patients with rapid changes in glucose homeostasis and larger glycemic excursions. The reliability of HbA1c is also questionable in diseases and conditions which may interfere with the metabolism of hemoglobin, such as in hemolytic, secondary, or iron deficiency anemia, hemoglobinopathies, pregnancy, and uremia.[21,22] Genetic factors, ethnicity, and age are also recognized as factors that influence HbA1c levels.[23] HbA1c ≥ 6.5% (48 mmol/mol) diagnoses only 30% of the diabetes cases identified collectively using HbA1c, FPG, and/or 2 h PG.[24] So, there is a need for an alternate biomarker for the diagnosis of diabetes and to assess glycemic status.

GA is an emerging biomarker that reflects glycemic control in the short term (2 to 3 weeks) and has been used to evaluate the postprandial glycemic status in diabetic patients after treatment. Extracellular proteins, like albumin, are more susceptible to the glycation process than intracellular proteins like Hb, and 9–10 times greater glycation in albumin is observed compared to Hb.[11] Moreover, rapid detection of variation in glycemic control is possible with GA, and reagent cost is also less compared to HbA1c. A recent meta-analysis has reported good diagnostic accuracy for GA.[25]

Saliva is an alternate source of a biomarker that offers a non-invasive and easy diagnosis for many systemic and oral diseases.[26] Albumin is the most osmotically active and abundant serum protein.[27] It is regarded as a serum ultra-filtrate to the oral cavity, and it may diffuse into the mucosal secretions due to disturbances in the mucosal integrity of salivary glands and oral mucous membranes.[28,29] Under hyperglycemic condition, albumin undergoes glycosylation and forms glycated albumin. GA can be detected in saliva, unlike HbA1c which can be detected only in blood. Rao *et al.* demonstrated that salivary protein glycosylation is a potential alternative biomarker for recent hyperglycemia, as it has a better ability to predict 7- to 21-day blood glucose measures.[30]

In the present study, the highest mean concentration of salivary GA was found in diabetic patients with periodontitis. Significantly, higher levels of GA were noticed in non-diabetic periodontitis patients compared to periodontally healthy individuals which suggest periodontitis is a factor influencing glycemic status.

Since there are no previous reports of salivary glycated albumin estimation in periodontitis patients, a direct comparison of our results with previous literature was not possible. We could find a published report of GA in GCF samples of patients with and without periodontitis and T2DM.[31] They have found increased concentrations of GA in diabetic patients with periodontitis compared to non-diabetic individuals which is like our observation. They have also established a positive correlation between GA levels in GCF with blood levels of GA and HbA1c. When they compared non-diabetic periodontitis patients with the healthy group, the amount of GA was higher in the periodontitis group, and on the contrary, a higher concentration was noticed in the healthy group. The increased flow rate of GCF in periodontitis might have resulted in this dilution. But when we evaluated salivary GA instead of GCF, higher concentration was seen in the non-diabetic periodontitis group compared to the healthy. Salivary diagnostics offer advantages over GCF in terms of ease of collection and the number of samples obtained. We have collected unstimulated saliva samples because stimulated saliva samples may cause dilution of the proteins like glycated albumin.[32]

Following scaling and root debridement, a statistically significant decrease was observed in plaque index, gingival index and probing pocket depth from baseline to 4 weeks in diabetic and non-diabetic periodontitis patients. Corresponding to the improvement in periodontal parameters, we could observe a significant reduction in salivary GA levels in both groups. In group A, the mean concentration was reduced from 79.863 ± 13.56 ng/ml to 64.32 ± 9.2 ng/ml and in group B from 61.94 ± 18.36 ng/ml to 49.47 ±11.78 ng/ml. Even though we could see a significant reduction in GA in the diabetic group, it was still higher than the baseline value of the non-diabetic group. We could also find that the salivary GA in the diabetic and non-diabetic periodontitis group at baseline and during re-evaluation was positively correlated (r = 0.75 and 0.8, respectively).

The improvement in glycemic control after non-surgical periodontal therapy was also reported using different biomarkers and was supported by many systematic reviews and meta-analyses.[5,33] Even though the changes in salivary GA after periodontal therapy were not monitored previously, blood GA changes after non-surgical periodontal therapy were evaluated in a previous study in patients with controlled and uncontrolled T2DM and periodontitis.[34] They reported that the level of GA was higher in the uncontrolled diabetic group and following periodontal therapy, there was a modest improvement in GA levels in both groups, and improvement was more pronounced in controlled diabetic groups. But there are contradictory reports also. Mizuno *et al.* 2017 conducted a randomized controlled clinical trial, and they could find no improvement in glycated albumin and HbA1c levels in the blood following non-surgical periodontal therapy in periodontitis patients with T2 DM.[35] This may be due to the small sample size of the study, and clinical trials with large samples are required in the future to draw a proper conclusion.

In our study, we could notice a reduction in salivary GA even in non-diabetic periodontitis patients following non-surgical periodontal therapy consistent with the results of a previous study where they compared serum HbA1c levels.[36] The possible reason for decreased levels of GA may be due to the close links between inflammatory factors and insulin resistance.[37] By effective periodontal treatment, the pathogenic microorganisms were eliminated from periodontal pockets, which reduced the inflammation. This might have decreased inflammatory

mediators like tumor necrosis factor α (TNF-α) leading to an improvement in insulin resistance and an increased sensitivity to insulin which further resulted in the reduction in GA concentration.[38,39] The decrease in gingival inflammation may be another contributing factor to reducing the seepage of GA from blood to saliva through GCF. Future studies evaluating the GA concentration in blood, as well as saliva after periodontal therapy, will provide more information in this regard.

We could find a cut-off value of salivary GA (72.19 ng/ml) to predict T2DM with a sensitivity and specificity of 75%. AUC of 0.79 gives a high predictability of the test to be employed for assessing diabetic status. When we analyzed our post-treatment salivary GA values, 90% fell under the cut-off value in the non-diabetic group, and surprisingly 85% in the diabetic group indicating a 15% improvement in glycemic control in the non-diabetic group and 60% in the diabetic group. This clearly demonstrates the usefulness of GA as a biomarker for glycemic control and the beneficial effects of periodontal therapy in improving glycemic control.

The major drawbacks to using GA for assessing glycemic index in the conditions affecting the albumin metabolism like nephrotic syndrome, hyperthyroidism, obesity, non-alcoholic fatty liver disease, hypertriglyceridemia, and hyperuricemia during which GA levels will be higher than blood glucose level. In such conditions, the GA should be used with caution to assess glycemic status. Future studies with larger sample sizes are required to find the effect of confounding factors as well as to correlate the serum HbA1c level with salivary glycated albumin level.

Conclusion

The present study shows the possibility of utilizing GA for predicting glycemic control in patients with T2DM and periodontitis. Since changes in GA occur after 2–3 weeks, the influence of non-surgical therapy on glycemic control can be better evaluated using GA than HbA1C. Chairside salivary diagnostic equipment can be developed in the future for the rapid and easy assessment of glycemic control in diabetic patients, and we can prevent long-term diabetes complications. Moreover, salivary chairside diagnostics offer an excellent opportunity for the patients to non-invasively self-monitor their glycemic status. It can also be used as a potential biomarker of glycemic control for screening large populations at the community level, health care programs, and in epidemiological studies.

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Conflicts of interest

There are no conflicts of interest.

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