Original Research Paper

University J Dent Scie 2025; Vol. 11, Issue 3

Evaluation of salivary cortisol level in type II diabetics and systemically healthy individuals with stage II and III slowly/moderately progressing periodontitis: a cross-sectional observational study

Abstract:

Background: Emerging evidence suggests a complex interplay between cortisol levels, type II diabetes mellitus, andperiodontal disease. This intricate relationship maybe influenced by hyperglycaemia in type 2 diabetes.

Aim: The aim of the current study was to assess salivary cortisol levels (SCL) in individuals with periodontitis and compare them to those in individuals with both periodontitis and type II diabetes with hyperglycaemia.

Materials and Methodology: A total of 102 individuals were evaluated and categorized into three groups: Group A(n=34) (n-sample size); periodontally and systemically healthy individuals; Group B(n=34); systemically healthy individuals with periodontitis; and Group C(n=34); individuals with both periodontitis and type II diabetes. Periodontal parameters and related indexes were recorded. Unstimulated whole saliva samples were procured and analysed for SCL.

Results: The mean SCL were 4.96 in Group A, 4.98 in Group B, and 5.03 in Group C, indicating a mild but not significant increase. A positive correlation was observed between SCL and the gingival index in Group A, whereas a negative correlation was found between SCL and periodontal probing depth in Group B.

Conclusions: SCL exhibited a mild increase from healthy individuals to those with periodontitis and further to hyperglycemic type II diabetic individuals with periodontitis, though these differences were not statistically significant. Future research should explore this area further to better understand the impact of periodontitis and type II diabetes on salivary cortisol secretion.

Key-words: Chronic periodontitis, 11-Epicortisol, Hydrocortisone,Hyperglycaemia, Type 2Diabetes Mellitus.

Introduction:

Cortisol is a potent, naturally occurring glucocorticoid hormone secreted by the adrenal cortex, accounting for approximately 95% of all glucocorticoid activity in the body. It plays an important role in resisting both physical and neurogenic stress, as well as in managing inflammation. Animal studies have demonstrated that cortisol secretion can increase sixfold within 4 to 20 minutes following any physical injury to the animal.[1] In recent years, salivary cortisol levels (SCL) have been routinely used as a biomarker for psychological stress and related mental or physical illnesses. It is considered one of the most reliable methods for measuring the hypothalamus-pituitary-adrenal axis response to stress coping.[2] The latest classification of periodontal and peri-implant disease and condition defines periodontitis as a condition characterized by microbially associated, host-mediated inflammation that results in loss of periodontal attachment.[3] A recent literature review based on 27 articles

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Received : 16 May, 2025, **Published :** 30 Sept., 2025

How to cite this article: Muthuraj, T. S., Angeline Deepthi, Polavan Mohammad Jumana, Meena Sri Muthuvel, Meena Devi, Meera Thomas, & Jomol Joby. (2025). Evaluation of salivary cortisol level in type II diabetics and systemically healthy individuals with stage II and III slowly/moderately progressing periodontitis – a cross-sectional observational study. UNIVERSITY JOURNAL OF DENTAL SCIENCES, 11(3).

Access this article online

Website: www.ujds.in

Quick Response Code

DOI: https://doi.org/10.21276/ujds.2025.v11.i3.5

published between 2017 and 2022 on the role of stress in periodontal disease and health concluded that chronic stress negatively affects periodontal tissues, both directly and indirectly.[4]

The relationship between periodontitis and type 2 diabetes is bidirectional and has been well established in dental literature through numerous systematic reviews and meta-analyses.[5,6,7,8] Chronic stress may lead to disturbed glucose homeostasis, which in turn results in chronic hyperglycemia, insulin resistance and type II diabetes.[9]Numerous studies in the past decade have reported a potential link between physiological and psychological stress and the development of type II diabetes, particularly in women.[10] However, the influence of type II diabetes and periodontitis on stress biomarkers, especially SCL, has not been thoroughly studied in the general population. Hence, the aim of the current study was to compare SCL among individuals with hyperglycemic type II diabetes and periodontitis, individuals with periodontitis without diabetes, and individuals who are both systemically and periodontally healthy.

Materials and Method:

The study was conducted at the Department of Periodontics and General Medicine unit of adental college between 2023 and 2024 and was approved by the institutional review board. This study followed the protocols outlined in the 1975 Helsinki Declaration of Experiments on Human Individuals (revised in 2013). The sample size was calculated using G*Power ver. 3.1.9.7 based on data obtained from a previous study by Vincent et al.[11]In that study, the mean and standard deviation of the gingival index score were reported as 1.37 ± 0.42 for chronic periodontitis patients and 1.62 ± 0.24 for periodontitis patients with diabetes. Using the above-mentioned values, (with α value equal to 0.05 and a power of 80%, Z score (Z)1-α/2= 1.96, and Z1-β = 0.84) the sample size was calculated to be 34 in each group, accounting for a total sample size of 102. More than 150 individuals who visited the outpatient unit of the Department of Periodontics and General Medicine were screened for this study. A modified version of the Self-Rating Depression Scale (SRDS), adjusted to reflect local cultural customs, was administered to all participants to assess participant's levels of stress and depression.[12] Based on SRDS scoring and the inclusion and exclusion criteria, 102 individuals were selected for the study (Figure 1), and informed consent forms were obtained from all participants.

Among the 102 individuals selected, 34 participants who were systemically and periodontally healthy were designated as Group A (GA). Groups B (GB) and C (GC) each consisted of 34 individuals diagnosed with mildly/moderately progressing stage II and III periodontitis, as defined by Tonetti et al.[3] The key difference between GB and GC is that the former included systemically healthy, while the latter consisted of participants diagnosed with type II diabetes and uncontrolled hyperglycemia, based on the glycated haemoglobin/haemoglobin A1C(HbA1c) values.[13] For GA, participants with clinically healthy periodontium, structurally and clinically intact with minimal or no inflammation, were included.[14] Inclusion criteria for GB were: (a) Clinical attachment loss (CAL) ≥ 4 mm and/or periodontal probing depth (PPD) ≥ 5 mm in two or more interdental region but not on the same tooth, (b)radiographic bone loss about 15% to 33% (approximately involving bone loss from coronal third to middle/apical third of the root length), (c) teeth lost due to periodontitis of 0 to 4 teeth, (d) mild to moderate rate of progression of periodontitis, (e) percentage of bone loss ranging from 0 to 1.0 (calculated directly or indirectly using the formula: radiographic bone loss/patient age),(f) periodontal destruction proportionate toplaque deposit, and (g)systemically healthy.Inclusion criteria for GC were identical to those for GB, except that participants were diagnosed with type II diabetes, with HbA1c values >8 (indicating uncontrolled hyperglycemia).

Exclusion criteria for the study include: (a) individuals unwilling to participate, (b) pregnant or lactating women, (c) smokers, (d) individuals taking medications affecting periodontal tissues,(e) history of periodontal surgery within six months,(f) systemic diseases or conditions (other than type II diabetes in GC) affecting salivary cortisol secretion or salivary flow rate,(g) rapidly progressing periodontitis, (h) periodontitis with stage I and IV (the former being mild form and the lattersevere), (i) individuals with fewer than 20 remaining teeth, and (j) individuals whose SRDS scoring was more than 33 (indicating depressive disorders). HbA1c was measured using a semi-automatic HbA1c analyzer (On Call A1c Hba1c Analysis system, ACON laboratories; San Diego, USA).Periodontal parameters, including gingival index (GI)[15] , plaque index (PI)[16], sulcular bleeding index (SBI)[17], PPD, and CAL were recorded for all the participats. PPD and CAL were measured using University of North Caroline-15 (UNC-15) probes (Hu-Friedy Group, USA) by a single experienced periodontist (kappa score 0.76 and 0.8 respectively) who was blinded. The radiographic examination and HbA1 were analyzed by a single experienced blinded oral radiologist (kappa score 0.78) and a single investigator (kappa score 0.82) respectively.

The study adheres to a previously established saliva collection protocol.[18] The unstimulated whole saliva (UWS) samples were collected 48 hours after recording the clinical and radiographic parameters.Participants were instructed to arrive at the dental college by 8:30 a.m. in a fasting state (without breakfast). They were asked to restin a quiet room (patient counseling room) without swallowing or moving their jaws or lips for a few minutes before UWS collection. UWS was allowed to accumulate in the oral cavity for 5 minutes, after which participants expectorated the UWS into disposable calibrated plastic tubes. A total of 5 ml of UWS was collected from each participant. Samples were immediately transferred to the central research laboratory (CRL) of the institute. Upon receipt, samples were centrifuged, and the resulting clear fluid was stored at -70° C untilcortisol analysis. Salivary cortisol levels were analysed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions. All analyses were conducted by an expert faculty member at the CRL, and data were collected.

Results:

The data collected were statistically analyzed by an expert statisticianusing Microsoft Excel (2020) and Statistical Package for the Social Sciences (SPSS®) software (IBM Corp. Released 2012 IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA: IBM Corp.). The normality of the data was assessed using the Shapiro-Wilk test/Kolmogorov-Smirnov test. Since the data were found to be normally distributed, parametric tests were applied. Descriptive statistics were used to calculate the mean values. A one-wayAnalysis of Variance(ANOVA) test was conducted to determine the difference between the groups while the Chi square test was applied for qualitative variables. Correlations between the factors were determined by Pearson correlation coefficient. All statistical tests were performed at a significance level of 5% (probability value (p value)< 0.05).

Demographic and periodontal parameters were analyzed using the One-way ANOVA test and the Chi-square test. A p value ≤ 0.05 was considered statistically significant (Table 1). Age and gender among the samples of all the three groups were analyzed, yielding p-values of 0.667 and 0.296 respectively, which were considered as non-significant. All the periodontal parameters (PI, GI, PPD, CAL and SBI) were analyzed and found to be statistically significant among GA, GB, and GC (Table 2). Mean values were also analyzed using the one-way ANOVA test and no significant difference was observed among the three groups (Figure 2). The SCL and SRDS scores were compared using the one-way ANOVA test and found to be non-significant (Table 3).Mean SCLs in GA, GB and GC were 4.96, 4.98 and 5.03, respectively. Although the mean value of SCL is a bit higher in GC (periodontitis with hyper glycemic type II diabetes), the difference was minimal and statistically not significant (Figure 2).The correlation between SCLs and various periodontal parameters was also analyzed using the Pearson's correlation coefficient (Table 2). A positive correlation was observed between SCL and GI in GA (healthy individuals), and a negative correlation was observed between SCL and PPD in GB (patients with periodontitis only). Bothcorrelations were found to be statistically significant (Figure 3, Table 4).

Table 1: Demographic characteristics and periodontal parameters of the study participants

Parameters		GA (n=34) (%)	GB (n=34) (%)	GB (n=34) (%)	p-value
Age (years)¥	Mean ± SD	40.82 ± 7.51	42.44 ± 7.77	41.21 ± 7.90	0.667
Gender¶	Male	21 (61.8 %)	16 (47.1%)	15 (44.1%)	0.296
	Female	13 (38.2%)	18 (52.9%)	19 (55.9%)	
PI¶	Good	25 (73.5%)	0 (0.0%)	0 (0.0%)	<0.001*
	Fair	9 (26.5%)	6 (17.6%)	0 (0.0%)	
	Poor	0 (0.0%)	28 (82.4%)	34 (100%)	
GI¶	Mild	31 (91.2%)	0 (0.0%)	0 (0.0%)	<0.001*
	Moderate	3 (8.8%)	9 (26.5%)	4 (11.8%)	
	Severe	0 (0.0%)	25 (73.5%)	30 (88.2%)	
PPD¶	Normal	34 (100%)	0 (0.0%)	0 (0.0%)	<0.001*
	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	34 (100%)	4 (11.8%)	
	Advanced	0 (0.0%)	0 (0.0%)	30 (88.2%)	
CAL¶	Normal	34 (100%)	0 (0.0%)	0 (0.0%)	<0.001*
	Slight	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Advanced	0 (0.0%)	34 (100%)	34 (100%)	
SRDS¶	CH	34 (100%)	34 (100%)	34 (100%)	NA
	DD	0 (0.0%)	0 (0.0%)	0 (0.0%)	

The statistical test used: ¥ - One wayAnalysis of Variance(ANOVA) test and ¶ - Chi-square test.

Level of significance* - significant (p≤ 0.05 is considered statistically significant)

p value – probability value; SD - standard deviation; n - number of samples; GA - group A;

GB - group B; GC - Group C; PI - plaque index; GI - gingival index; PPD - periodontal probing depth;

CAL - clinical attachment level; SRDS - self-rating depression scale.

Table 2: Comparison of periodontal parameters among Group A, Group B and Group C.

Periodontal parameters		GA (*n*=34)	GB (*n*=34)	GC (*n*=34)	*F*-value	*p*-value
PI	Mean ± SD	0.84 ± 0.23	2.38 ± 0.31	2.71 ± 0.15	596.395	<0.001*
	95% CI	0.76 – 0.92	2.27 – 2.49	2.65 – 2.76		
GI	Mean ± SD	0.77 ± 0.20	2.33 ± 0.33	2.47 ± 0.28	394.636	<0.001*
	95% CI	0.70 – 0.84	2.21 – 2.45	2.37 – 2.57		
PPD	Mean ± SD	1.67 ± 0.30	5.70 ± 0.51	7.94 ± 0.80	1040.251	<0.001*
	95% CI	1.56 – 1.77	5.52 – 5.88	7.66 – 8.22		
CAL	Mean ± SD	0.00 ± 0.00	6.97 ± 0.51	9.31 ± 0.81	2620.985	<0.001*
	95% CI	0.00 – 0.00	6.79 – 7.15	9.03 – 9.59		
SBI	Mean ± SD	0.83 ± 0.32	3.61 ± 0.48	4.08 ± 0.49	550.415	<0.001*
	95% CI	0.72 – 0.94	3.44 – 3.78	3.91 – 4.25		

The statistical test used: One way Analysis of Variance (ANOVA)test. level of significance: * - significant ($p \leq 0.05$ is considered statistically significant). p value – probability value; *F*-value- F statistic (ANOVA test value); CI - confidence interval; SD - standard deviation; n-number of samples; GA, group A; GB - group B; GC - Group C; PI - plaque index; GI - gingival index; PPD - periodontal probing depth; CAL - clinical attachment level; SBI -sulcular bleeding index.

Table 3: Comparison of Salivary Cortisol levels and self-rating depression scale scoring among the three groups.

Parameter		GA*n*=34 (%)	GB *n*=34 (%)	GC *n*=34 (%)	*p*-value
SCL	Mean ± SD	4.96 ± 1.00	4.98 ± 0.38	5.03 ± 0.35	0.940
	95% CI	4.63 – 5.33	4.85 – 5.11	4.91 – 5.15	
SRDS	Mean ± SD	25.79 ± 2.61	25.85 ± 2.16	26.03 ± 2.15	0.910
	95% CI	24.88 – 26.71	25.10 – 26.61	25.28 – 26.78	

The statistical test used: One way Analysis of Variance (ANOVA) test. level of significance:* - significant ($p \leq 0.05$ is considered statistically significant) p value – probability value; CI - Confidence interval; SD - Standard deviation; n - number of samples; GA -Group A; GB -Group B; GC -Group C; SCL -Salivary cortisol level; SRDS -Self-Rating Depression Scale

Table:4 Correlation between periodontal parameters and salivary cortisol in healthy individuals, periodontitis patients, and periodontitis patients with uncontrolled diabetes.

Parameters	Salivary Cortisol Level		
	GA	GB	GC
PI	0.12	0.319	0.18
GI	0.42*	-0.26	-0.11
PPD	0.12	-0.35*	0.08
CAL	---	-0.25	-0.04
SBI	0.26	0.35	-0.25
SRDS	0.13	-0.27	-0.10

The statistical test used: Pearson's correlation coefficient, *-Significant (probability value(p -value) ≤ 0.05 considered as statistically significant GA - group A; GB - group B; GC - group C; PI - plaque index; GI - gingival index, PPD - periodontal probing depth; CAL - clinical attachment level, SBI - sulcularbleeding index;SRDS - self-rating depression scale.

Discussion:

Salivary samples were collected from all individuals who participated in the study and cortisol levels were measured. The collected data were statistically analyzed to determine the correlation between cortisol levels and periodontal parameters. The demographic parameters of all 104 participants of the study were found to be non-significant. To avoid the influence of stress in the levels of salivary cortisol, a SRDS questionary was administered to the participants and participants with scores greater than 34 were excluded from the study. The mean SRDS scores were found to be non-significant across all three groups.

In a similar study conducted by Obulareddy et al. in 2018, individuals with periodontitis and stress were examined.[19] They reported an increase in SCL in individuals with periodontitis compared to periodontally healthy individuals, a finding consistent with our study. Obulareddy et al. reported a significant negative correlation between cortisol levels and both bleeding on probing and PPD in healthy individuals, as well as between PI and PPD in periodontitis patients. In contrast, our study observed a negative correlation between cortisol levels and PPD only in periodontitis patients and a positive correlation between cortisol levels and GI in healthy controls. These differences may be attributed to variations in methodology. For example, our study defined periodontal health and periodontitis using the latest classification of periodontal disease and conditions, whereas Obulareddy et al. employed different clinical definitions. Additionally, Obulareddy et al. utilized the Depression, Anxiety, and Stress Scale-21 items[20] for stress evaluation, whereas we used the Self-Rating Depression Scale.

In a related study, Lee et al. found that salivary cortisol levels were significantly higher in individuals with periodontitis compared to healthy controls, a result consistent with our findings.[21] However, in our study, the increase in salivary cortisol levels was mild and not statistically significant. A systematic review and meta-analysis reported that salivary cortisol levels are approximately 53% higher in aggressive periodontitis (rapidly progressing periodontitis) compared to chronic periodontitis (mild to moderately progressing periodontitis). In contrast, salivary cortisol levels in chronic periodontitis patients did not differ significantly from those in

periodontally healthy individuals.[22] This observation aligns the conclusion of our current study. A recent case-control study reported that salivary cortisol levels were higher in periodontitis patients with type 2 diabetes compared to non-diabetic periodontitis patients, a finding consistent with our observation that GC (periodontitis and diabetes) exhibited higher salivary cortisol levels compared to GA (healthy controls) and GB (periodontitis).[23]

The primary limitation of this study is its observational nature. Conducting an interventional study to examine the effects of treating periodontitis and diabetes on salivary cortisol levels would provide valuable insights into the underlying mechanisms of the pathogenesis of both conditions. Therefore, future research should prioritize interventional studies with long-term follow-ups. Additionally, this study did not examine the influence of psychological stress on periodontitis, diabetes, and salivary cortisol levels, which represents another avenue for future research.

Conclusion:

In this study, the levels of salivary cortisol were found to show a mild increase from healthy individuals to periodontitis patients, and further to hyperglycemic type II diabetes patients with periodontitis, although this increase was not statistically significant. Future studies should explore this area further to better understand the influence of periodontitis and type II diabetes on salivary cortisol secretion, which may subsequently contribute to psychological stress.

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