

PROCALCITONIN LEVELS IN INDIVIDUALS WITH OR WITHOUT TYPE 2 DIABETES MELLITUS- A CROSS-SECTIONAL STUDY IN STAGE II PERIODONTITIS PATIENTS

Niveles de procalcitonina en individuos con o sin diabetes mellitus tipo 2: un estudio transversal en pacientes con periodontitis estadio II

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ABSTRACT

Aim: The objective of this current study is to evaluate and compare the concentrations of Procalcitonin (ProCT) in both serum and gingival crevicular fluid (GCF) of individuals with and without controlled Type II Diabetes Mellitus in relation to periodontal health and disease

Materials and Methods: In this study, 40 subjects were divided into four groups: 10 individuals with gingival health (Group 1), 10 with Type II Diabetes Mellitus (Group 2), 10 with Stage 2 Periodontitis and Type II Diabetes Mellitus (Group 3), and 10 with Stage 2 Periodontitis (Group 4). Baseline periodontal parameters such as gingival index, probing pocket depth, and clinical attachment level were recorded for each subject. Additionally, GCF and serum samples were collected, and ProCT levels were quantified using enzyme-linked immunosorbent assay (ELISA).

Results: Subjects with Stage 2 periodontitis and Type II Diabetes Mellitus were observed to have higher mean levels of GCF and serum ProCT compared to healthy patients and those with either periodontitis or diabetes mellitus alone. Additionally, ProCT levels were found to be higher in subjects with Type II Diabetes Mellitus compared to non-diabetics. Serum ProCT levels were also found to be higher than GCF levels.

Conclusion: The majority of edentulous patients both before and after prosthodontic rehabilitation had a lower calorie intake than recommended. There was no significant difference between calorie intake and physical status of patients after prosthodontic rehabilitation.

Keywords: Biomarkers; Procalcitonin; Periodontitis; Diabetes mellitus, type 2; Gingival crevicular fluid; Serum

RESUMEN

Objetivo: El objetivo de este estudio actual es evaluar y comparar las concentraciones de procalcitonina (ProCT) tanto en suero como en líquido crevicular gingival (GCF) de individuos con y sin diabetes mellitus tipo II controlada en relación con la salud y la enfermedad periodontal.

Materiales y métodos: En este estudio, 40 sujetos se dividieron en cuatro grupos: 10 individuos con salud gingival (Grupo 1), 10 con diabetes mellitus tipo II (Grupo 2), 10 con periodontitis en estadio 2 y diabetes mellitus tipo II (Grupo 3) y 10 con periodontitis en estadio 2 (Grupo 4). Se registraron los parámetros periodontales basales, como el índice gingival, la profundidad de la bolsa de sondaje y el nivel de inserción clínica, para cada sujeto. Además, se recogieron muestras de GCF y suero, y se cuantificaron los niveles de ProCT mediante un ensayo inmunoabsorbente ligado a enzimas (ELISA).

Resultado: Se observó que los sujetos con periodontitis en estadio 2 y diabetes mellitus tipo II tenían niveles medios más elevados de GCF y ProCT sérico en comparación con los pacientes sanos y aquellos con periodontitis o diabetes mellitus únicamente. Además, se encontró que los niveles de ProCT eran más elevados en sujetos con diabetes mellitus tipo II en comparación con los no diabéticos. Los niveles séricos de ProCT también fueron más elevados que los niveles de GCF.

Conclusión: Nuestros hallazgos sugieren que ProCT es un indicador fiable de la inflamación sistémica y local. Se observaron niveles elevados de ProCT en individuos con diabetes mellitus tipo II, tanto en suero como en GCF. Sin embargo, la inflamación local aumenta significativamente la concentración de esta proteína.

Palabras Clave: Biomarcadores; Polipéptido alfa relacionado con calcitonina; Periodontitis; Diabetes mellitus tipo 2; Líquido del surco gingival; Suero

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INTRODUCTION

Periodontal disease is a pathological condition that causes damage to the tissues by polymicrobial synergy and dysbiosis resulting in altered host response. The gram-negative bacteria primarily responsible for this condition release various in-inflammatory mediators such as cytokines and enzymes, which contribute to tissue destruction. The analysis of gingival crevicular fluid has been recognized as an effective method to diagnose the presence of periodontal disease since the levels of inflammatory biomarkers in this biological fluid can serve as useful indicators of ongoing inflammatory activity.¹

Procalcitonin (ProCT) gained attention in the early 1990s when it was identified as a protein with increased plasma levels in patients with sepsis and infection.² It is a precursor protein of calcitonin and consists of 116 amino acids, which plays a vital role in calcium balance in the body under normal physiological conditions. ProCT is synthesized in the C cells of the thyroid gland and neuroendocrine cells of the lungs.³

Previous research has shown that ProCT acts as a marker and potential mediator of systemic inflammation.⁴ During any inflammatory condition, ProCT can be generated through a pathway triggered by lipopolysaccharides or inflammatory mediators.⁵ Serum ProCT levels can assist in diagnosing infectious diseases, predicting their prognosis, and evaluating the progression of localized infections to systemic inflammation.

Moreover, a reduction in serum ProCT levels has been noted after the successful elimination of the infection focus through therapy, rendering it valuable for assessing infection severity and predicting treatment response outcomes.⁶

Elevated ProCT levels have been observed in the saliva and GCF of patients with chronic perio-

dontitis, a chronic inflammatory disease.⁵ These elevated levels may be due to either microbial toxin-induced production or inflammatory mediator-induced production of the protein.⁵ However, following non-surgical periodontal therapy, the ProCT levels significantly decreased, indicating its usefulness as a marker of disease activity and response to therapy.⁷

Research has shown that diabetes has an impact on the progression and severity of periodontitis.⁸ This is because when a local infection like periodontitis is present, it can trigger an upregulation of inflammatory processes, and if there is an additional comorbid condition like diabetes, it can lead to a low-grade systemic inflammation.

This relationship works both ways, and it has been observed that chronic periodontitis in the presence of diabetic complications can lead to an upregulation of ProCT levels in saliva.⁹ Based on this rationale, the purpose of the study was to assess the Procalcitonin levels in the serum and GCF of individuals with periodontal disease activity and to establish a correlation with their long-term glycemic status.

MATERIALS AND METHODS

Study population

Participants of both sexes, aged 29 to 50 years, were selected for this cross-sectional study from the Outpatient Department of Periodontology and Oral Implantology between February 2017 and November 2017. Each selected patient provided verbal and written consent prior to participation in the study. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013, and was approved by the institutional ethics committee.

The standard deviation of the primary outcome variable from a previous study⁹ was used to de-

termine the sample size of 40, calculated using the equation $(N = [(Z_{1-\alpha} - Z_{\beta}) \sigma / \delta]^2)$ with a 95% confidence interval and 80% power. The 40 recruited subjects were categorized into four groups, each comprising 10 individuals, based on the following inclusion criteria: Study participants with gingival health and Stage 2 periodontitis were included based on clinical and radiographic criteria.^{10,13}

Group 1 [Subjects with clinical gingival health on intact periodontium as described in the 2017 classification 11 with Bleeding on Probing(BOP) <10%, Probing depth (PD) <3 mm, Attachment loss – Nil];

Group 2 [Subjects with clinical gingival health on intact periodontium as described in the 2017 classification¹¹ with BOP <10%, PD <3 mm, Attachment loss – Nil; HbA1c levels >6.5 % and diagnosed with type 2 diabetes Mellitus (T2D);¹²

Group 3 [Subjects with Stage 2 periodontitis (3-4 mm interdental clinical attachment loss, Residual bone level(RBL)- coronal third [15-33%], Tooth loss-none, PD <5mm, Grade B or C; HbA1c levels > 6.5 % and diagnosed with type 2 diabetes Mellitus (T2D) 12);

Group 4 [Subjects with Stage II periodontitis (3-4 mm interdental clinical attachment loss, Residual bone level(RBL)- coronal third [15-33%], Tooth loss-none, PD <5mm).

Patients with gross oral pathology, pregnant women, smokers, alcoholics, patients with anomalies of the immune system, and those who had taken medication affecting periodontal status or had received periodontal therapy in the preceding 6 months were excluded from the study.

Clinical examination

At baseline, all the selected individuals were examined to record the gingival index (GI), probing pocket depth (PD), and clinical attachment level

(CAL). Quantitative assessment of HbA1c in diabetic patients was assessed using the kit provided by Teco Diagnostics (U.S.A) and only those patients exhibiting HbA1c levels (> 6.5%) were selected in groups 2 and 3.¹⁴ All the measurements were performed by the same examiner.

Site selection and collection of gingival crevicular fluid

In Group 3 and 4 the site with the deepest probing depth was selected for GCF collection,¹⁵ while in Group 1 and 2, sites with PD ≤ 3 mm and no signs of inflammation, were chosen for obtaining GCF. The selected site was isolated and supragingival plaque was removed with a curette. GCF samples were collected using a calibrated volumetric microcapillary pipette (Sigma-Aldrich, St. Louis, USA) through the extra-crevicular (unstimulated) method, and a volume of 5 µL was obtained. Any contaminated pipettes were discarded, and the collected GCF was transferred to an Eppendorf tube containing 5ml of 7.4 pH Phosphate-buffered saline (PBS) at -80°C until assay.¹⁶

Serum collection

A total of 5cc of blood was collected from the antecubital fossa of each subject using a 20-gauge needle and a 2-mL syringe through venipuncture. The blood samples were then transferred to the laboratory immediately. After allowing the samples to clot for 1 hour at room temperature, they were centrifuged at 1200 rpm for 10 minutes. From each sample, 5 µL of serum was collected using a pre-calibrated pipette and transferred to an Eppendorf tube.¹⁷ The serum samples were then stored at -80°C until the time of assay.

Quantification of Procalcitonin in GCF and Serum

To determine the concentration of Procalcitonin, an enzyme-linked immunosorbent assay kit (Ray-Bio® Human Procalcitonin ELISA Kit) was used. This kit utilizes a specific antibody for human ProCT that is coated on a 96-well plate. Samples and

Figure 1. Procalcitonin (ProCT) levels (pg/ml) in gingival crevicular fluid and serum in all the groups.

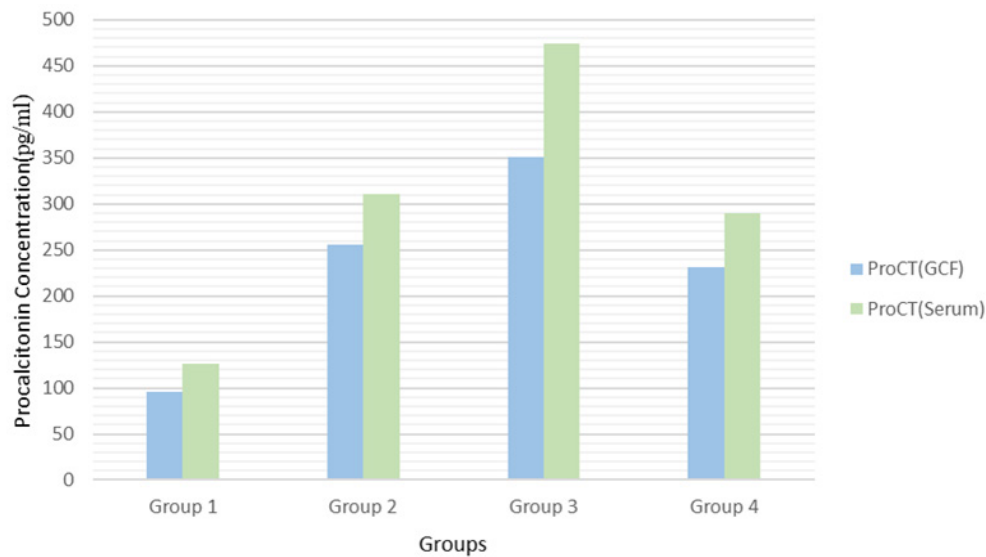


Table 1. Sociodemographic data of study patients.

Age- Group tabulation	N	Mean	Std. Deviation	F-Value	p-value
1	10	38.90	2.767		
2	10	39.90	5.915		
3	10	43.80	2.898	2.442	.080
4	10	40.80	4.709		
Total	40	40.85	4.510		

(I) group	(J) group	Mean	Std. Error Difference (I-J)	p-value	95% Confidence Interval Lower Bound	Upper Bound
1	2	-1.000	1.913	1.000	-6.34	4.34
	3	-4.900	1.913	0.089	-10.24	0.44
	4	-1.900	1.913	1.000	-7.24	3.44
2	3	-3.900	1.913	0.294	-9.24	1.44
	4	-0.900	1.913	1.000	-6.24	4.44
3	4	3.000	1.913	0.754	-2.34	8.34

	Group Cross Tabulation				Total	Chi-square	p-value
	Groups	1	2	3			
Gender	Count	6	3	6	5	20.0	
Female	% within group	60.0	30.0	60.0	50.0	50.0	
	Count	4	7	4	5	20.0	2.40
Male	% within group	40.0	70.0	40.0	50.0	50.0	0.494
Total	Count	10.0	10.0	10.0	10.0	40.0	
	% within group	100.0	100.0	100.0	100.0	100.0	

Diabetic medication status	No (%)	Yes(%)	Yes(%)	No (%)	N/A	N/A	N/A
Duration of Diabetes Mellitus	< 5 Years	-	30	30%	-	N/A	N/A
	5-10 Years	-	60	50%	-	N/A	N/A
	>10 years	-	10	20%	-	N/A	N/A

[Age Distribution- One-way analysis of variance (ANOVA), Boneferroni post hoc test, (p -value <0.001; significant)]; [Gender Distribution- Chi square test, (p -value <0.001; significant)]; NA- Not available.

standards were pipetted into the wells, and any ProCT present in the sample bound to the wells via the immobilized antibody. After washing the plate and adding substrates and a stop solution, the color changed from blue to yellow. The optical density values of the standards were used to plot a standard curve, from which the concentrations of Human ProCT in the samples were determined.

Statistical analysis

The statistical analysis was done using the Statistical Package for the Social science (SPSS) for Windows, version 19; SPSS Inc. Chicago,

IL, USA. All the periodontal parameters were described and reported as mean values (\pm SD). The distribution and comparison of clinical parameters and levels of ProCT in gingival crevicular fluid (GCF) and serum among all groups were evaluated using a one-way ANOVA test. Post Hoc Bonferroni test was used to compare the clinical parameters and the levels of ProCT in GCF and serum across the groups.

Pearson's correlation test was used to examine the correlation between the ProCT levels and clinical parameters in all four groups. A significance level of 0.05 was used for all analyses.

Table 2. Distribution and comparison of study parameters in the four different study groups.

Study Parameters	Groups	N	Mean	Standard Deviation	F-Value	p-value
HbA1C(%)	Group 1	10	5.2000	0.27080	79.092	<0.001*
	Group 2	10	7.6600	0.66866		
	Group 3	10	7.5900	0.57822		
	Group 4	10	5.2700	0.33015		
		40	6.4300	1.29935		
Gingival Index	Group 1	10	0.0291	0.06210	44.090	<0.001*
	Group 2	10	0.1829	0.24863		
	Group 3	10	1.5752	0.39962		
	Group 4	10	1.4095	0.60298		
		40	0.7992	0.79704		
ProCT(GCF) (pg/ml)	Group 1	10	95.3100	4.29456	527.945	<0.001*
	Group 2	10	256.2300	18.17116		
	Group 3	10	350.4100	20.58022		
	Group 4	10	230.9500	8.27624		
		40	233.2250	93.43020		
ProCT(Serum) (pg/ml)	Group 1	10	126.2000	4.92883	1141.635	<0.001*
	Group 2	10	310.1300	17.21673		
	Group 3	10	474.4900	19.23997		
	Group 4	10	290.1200	4.45291		
		40	300.2350	125.56830		
Probing Depth	Group 3	10	9.0000	2.00000		0.083
	Group 4	10	10.4000	1.34990		
Clinical Attachment Level	Group 3	10	10.0000	1.94365		0.101
	Group 4	10	11.9000	2.88483		

(One-way analysis of variance [ANOVA]; *. $p < 0.05$; significant).

Table 3. Comparison of the study parameters in the four groups.

Parameter	(I) grp	(J) grp	Mean Difference (I-J)	Std. Error	p-value
HbA1C (%)	Group 1	Group 2	-2.46000*	0.21952	<.001*
		Group 3	-2.39000*	0.21952	<.001*
		Group 4	-0.07000	0.21952	1.000
	Group 2	Group1	2.46000*	0.21952	<.001*
		Group3	0.07000	0.21952	1.000
		Group 4	2.39000*	0.21952	<.001*
	Group 3	Group 1	2.39000*	0.21952	<.001*
		Group 2	-0.07000	0.21952	1.000
		Group 4	2.32000*	0.21952	<.001*
	Group 4	Group 1	0.07000	0.21952	1.000
		Group 2	-2.39000*	0.21952	<.001*
		Group 3	-2.32000*	0.21952	<.001*
Gingival Index	Group 1	Group 2	-0.15380	0.17160	1.000
		Group 3	-1.54610*	0.17160	<.001*
		Group 4	-1.38040*	0.17160	<.001*
	Group 2	Group 1	0.15380	0.17160	1.000
		Group 3	-1.39230*	0.17160	<.001*
		Group 4	-1.22660*	0.17160	<.001*
	Group 3	Group 1	1.54610*	0.17160	<.001*
		Group 2	1.39230*	0.17160	<.001*
		Group 4	0.16570	0.17160	1.000
	Group 4	Group 1	1.38040*	0.17160	<.001*
		Group 2	1.22660*	0.17160	<.001*
		Group 3	-0.16570	0.17160	1.000
ProCT (GCF)(pg/ml)	Group 1	Group 2	-160.92000*	6.48335	<.001*
		Group 3	-255.10000*	6.48335	<.001*
		Group 4	-135.64000*	6.48335	<.001*
	Group 2	Group 1	160.92000*	6.48335	<.001*
		Group 3	-94.18000*	6.48335	<.001*
		Group 4	25.28000*	6.48335	0.002
	Group 3	Group 1	255.10000*	6.48335	<.001*
		Group 2	94.18000*	6.48335	<.001*
		Group 4	119.46000*	6.48335	<.001*
	Group 4	Group 1	135.64000*	6.48335	<.001*
		Group 2	-25.28000*	6.48335	0.002
		Group 3	-119.46000*	6.48335	<.001*
ProCT (Serum) (pg/ml)	Group 1	Group2	-183.93000*	5.96118	<.001*
		Group 3	-348.29000*	5.96118	<.001*
		Group 4	-163.92000*	5.96118	<.001*
	Group 2	Group1	183.93000*	5.96118	<.001*
		Group3	-164.36000*	5.96118	<.001*
		Group4	20.01000*	5.96118	0.011
	Group 3	Group 1	348.29000*	5.96118	<.001*
		Group 2	164.36000*	5.96118	<.001*
		Group 4	184.37000*	5.96118	<.001*
	Group 4	Group 1	163.92000*	5.96118	<.001*
		Group 2	-20.01000*	5.96118	0.011
		Group 3	-184.37000*	5.96118	<.001*

(Group 1- Healthy control; Group 2-Type 2 Diabetes mellitus with healthy gingiva; Group 3- Stage 2 periodontitis + Type 2 Diabetes mellitus; Group 4 –Stage 2 Periodontitis.Bonferroni post hoc test; * $p < 0.05$; significant).

Table 4. Correlation between GCF and serum levels of procalcitonin (ProCT) and HbA1c in all the four groups.

	Healthy controls (Group 1)		Type II Diabetes (Group 2)		Stage 2 Periodontitis and Type II Diabetes Mellitus group (Group 3)			Stage 2 Periodontitis group (Group 4)				
	HbA1c (r)		HbA1c (r)		HbA1c (r)	PD (r)	CAL(r)	HbA1c(r)	PD (r)	CAL(r)		
ProCT - GCF	0.930**	0.910**	0.907**	0.974**	0.956**	0.714*	14**	0.978**	0.297	0.274	0.546	0.714
ProCT- SERUM	0.971**		0.938**		0.991**	0.710*	0.862**	0.327		0.570	0.723*	

[Pearson's correlation coefficient - r; **. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2- tailed)].

RESULTS

A total of 40 patients aged 29-50 years, who met the required eligibility criteria mentioned above, were included in the study. Sociodemographic data such as age, gender, diabetic medication status and the duration of Diabetes Mellitus (Table.1)

Clinical Analysis

Periodontal parameters of the study groups, Table 2. Groups 2 and 3 showed statistically significant differences in HbA1c levels when compared to groups 1 and 4. The gingival indices (GI) of all four groups exhibited a statistically significant difference ($p < 0.05$). However, the p -values for the probing depths and Clinical attachment level between groups 3 and 4 were 0.083 and 0.101 respectively, indicating that there was no significant difference between these groups. (Table.2)

GCF ProCT levels

The GCF ProCT levels (in pg/ml) in groups 1, 2, 3 and 4 were 95.3 + 4.29, (T2 256.2 + 18.17, 350.4 + 20.58, and 230.95 + 8.28 respectively. The pair-wise comparison revealed statistically significant differences in the GCF ProCT levels between all the groups (Table 3 and Figure 1).

Serum ProCT levels

The serum ProCT levels (in pg/ml) in groups 1, 2, 3 and 4 were 126.2 + 4.93; 310.1 + 17.22; 474.5 + 19.24; 290.1 + 4.45 respectively. Pair-wise comparison revealed statistically significant differences in the serum ProCT levels between all the groups (Table 3 and Figure 1).

HbA1c levels

The HbA1c levels (%) in groups 1, 2, 3 and 4 were 5.2 + 0.27; 7.7 + 0.67; 7.6 + 0.58; 5.3 + 0.33. A statistically significant difference of $p = 0.001$ was obtained between the groups (Table.3).

Pair-wise comparison of the groups showed a statistically significant difference in the HbA1c levels between the groups (Table 2 and Table 3).

Correlations

In all groups, a significant positive correlation ($p < 0.01$) existed between ProCT Serum and GCF levels. Groups 1, 2, and 3 showed a positive correlation between ProCT serum/GCF levels and HbA1c levels. However, in group 4, no significant positive correlation was found. Group 2 and Group 3 demonstrated a strong positive correlation between the Serum and GCF ProCT levels ($p < 0.01$), (Table.4).

DISCUSSION

Procalcitonin (ProCT) is a soluble protein that functions as a prohormone or precursor to calcitonin, with diverse induction and functional properties. During elevated serum calcium levels, the thyroid gland's C-cells secrete ProCT.¹⁸ However, "inflammatory" ProCT production is unrelated to hypercalcemia.¹⁹ Several studies have reported increased ProCT production during bacterial infections.^{19,29} Prolonged elevated ProCT levels can indicate a systemic inflammatory burden.^{20,21} Abbasi *et al.*,²² concluded that ProCT plays a role in insulin resistance and serves as a proinflammatory marker¹⁰ to predict the occurrence of Type 2 Diabetes Mellitus.

In this study, we hypothesized that periodontitis influences ProCT production in diabetic individuals. We speculate that the local bacterial challenge from periodontitis could increase ProCT expression in both the oral environment and systemic circulation, leading to elevated serum levels.

Healthy subjects were included to establish baseline ProCT levels in a healthy periodontium and compare them to levels observed during inflammatory periodontal disease.

Studies by Bassim *et al.*,⁹ and Abbasi *et al.*,¹⁰ have shown increased levels of ProCT in diabetic individuals; likewise, diabetics were also included in this study. Our results indicate that serum and GCF ProCT levels were higher in patients with Stage 2 Periodontitis and Type 2 Diabetes Mellitus, consistent with the findings reported by Bassim *et al.*⁹

Our study also revealed that the ProCT serum and GCF levels in healthy controls positively correlated with normal HbA1c levels, indicating very low expression of the protein in healthy individuals without any systemic or local factors

contributing to inflammation.²³ Furthermore, we found a moderately significant positive correlation in the ProCT serum/GCF levels of stage 2 periodontitis patients similar to a previous study report.⁷

In our study, we observed that individuals with coexisting diabetes and periodontitis exhibited the highest levels of ProCT, suggesting the presence of bacteremia. The elevation in ProCT levels noted in Group 3 can be attributed to the worsening of both diabetic and periodontal conditions. This is supported by the positive correlation between ProCT levels and probing depth and clinical attachment level.

These findings align with previous research associating ProCT levels in saliva and serum with periodontitis in diabetic patients.^{6,7,9,10} Additionally, we noted a positive correlation between ProCT levels in GCF and serum across all the groups studied, consistent with published research demonstrating a positive correlation between serum and salivary levels of ProCT.²⁴

Therefore, ProCT can be considered a reliable marker of disease severity. Indeed, further research is needed to understand the mechanisms underlying the production of ProCT in periodontal tissues and its effect on disease progression and immune status. Additionally, a larger sample size and longitudinal studies would be useful to determine the temporal relationship between ProCT levels and disease severity. Some limitations of our study include the cross-sectional data collection, which lacked post-treatment follow-ups. Additionally, the study had a limited number of groups, and gingivitis patients were not included. Furthermore, the medication history of diabetic participants may have indirectly influenced the outcome.

CONCLUSION

The current study provides valuable insights of procalcitonin levels among individuals with diabetes, with or without periodontitis. Our findings highlight that ProCT, as an inflammatory marker, is produced in elevated quantities in individuals affected by Stage 2 periodontitis and type 2 Diabetes Mellitus, evident in both serum and gingival crevicular fluid (GCF).

Moreover, the results suggest that effectively managing an individual's diabetic condition significantly alleviates the overall inflammatory load, both systemically and in the oral cavity. Additionally, our findings imply that addressing periodontitis can lead to improvements in the diabetic status of affected individuals.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS APPROVAL

Patients provided verbal and written consent prior to participation in the study. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013, and was approved by the institutional ethics committee.

FUNDING

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AUTHORS' CONTRIBUTIONS

Soniya Dharmadhikari: Conceptualization, Data curation, Formal analysis, Investigation, Formal analysis, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review and editing.

Gopalakrishnan Dharmarajan: Conceptualization, Data curation, Formal analysis, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

Sangamithra Sidharthan: Conceptualization, Formal analysis, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

Santosh Martande: Conceptualization, Data curation, Formal analysis, Investigation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft.


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