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Evaluation of Salivary Thrombospondin-1 levels in Healthy and Periodontitis patients with and without Type II Diabetes Mellitus – A Comparative Study

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KEYWORDS

Periodontitis; Thrombospondin-1; Type II diabetes mellitus; Periodontal Inflamed Surface Area

ABSTRACT:

Periodontitis, a multifactorial inflammatory disease is associated with dysbiotic plaque microbial flora and altered immune response. Thrombospondin-1 (TSP-1) is a multifunctional, extracellular matrix glycoprotein found in platelets, which is secreted during platelet activation. The aim of the present study was to compare and correlate salivary TSP-1 levels in periodontitis patients with and without type II diabetes mellitus and healthy subjects. A total of 90 patients, periodontally and systemically healthy subjects, periodontitis patients without diabetes and periodontitis patients with diabetes were selected. Periodontal parameters such as FMBS, FMPS, Probing Depth and CAL recorded. The overall comparison of TSP-1 levels and PISA score among groups shows a significant difference with higher values in group III (periodontitis with diabetes) when compared to other two groups. The individual intergroup pairwise comparison of TSP-1 levels shows statistically significant difference between Group I and II, Group I and III and Group II and III. The present study correlated TSP-1 levels with PISA score which shows a positive linear relationship in Group III. The results of present study showed that there is increase in TSP-1 level in periodontitis patients with diabetes mellitus as compared to healthy subjects. There exists a direct relationship between greater inflammatory burden as measured by PISA score and TSP-1 level. Hence findings of the present study support and extend the view that the evaluation of TSP-1 level can serve as possible inflammatory biomarker linking periodontal disease and type II Diabetes Mellitus.

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1. INTRODUCTION

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth supporting apparatus. Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss (CAL) and radiographically assessed alveolar bone loss with the presence of periodontal pocketing and gingival bleeding. Periodontitis is a major public health problem due to its high prevalence, as well as it may lead to tooth loss and disability which can negatively affect chewing function and aesthetics that could be a source of social inequality, and impair quality of life [1]. The bacterial biofilm formation initiates gingival inflammation; periodontitis initiation and progression depend on dysbiotic ecological changes in the microbiome in response to nutrients from gingival inflammatory and tissue breakdown products that enrich some species and anti- bacterial mechanisms that attempt to contain the microbial challenge within the gingival sulcus area once inflammation has initiated [2]. Bacterial stimuli induce an immune response that produces a variety of pro inflammatory cytokines and leads to destruction of periodontal supporting tissues and resorption of alveolar bone.

Number of diverse studies have indicated that periodontal diseases is a risk factor for a broad range of systemic diseases such as cardiovascular diseases, stroke, diabetes, pneumonia, and preterm low birth weight [3-5]. There is emerging evidence to support the existence of a two-way relationship between diabetes and periodontitis, with diabetes increasing the risk for periodontitis, and periodontal inflammation negatively affecting glycaemic control [6]. In the early 1990s periodontitis were considered as the sixth complication of diabetes [7].

Diabetes has been unequivocally confirmed as a major risk factor for periodontitis. The risk of periodontitis is increased by approximately threefold in diabetic individuals compared with non-diabetic individuals. The main influences of diabetes mellitus on periodontal disease appear to be related to alterations in host immuno - inflammatory reactions and tissue homeostasis and these include polymorphonuclear leukocyte dysfunction, dysregulated cytokine levels, vascular changes, altered collagen and glycosaminoglycan synthesis, and formation of Advanced Glycation end products (AGEs) [8].

Thrombospondin-1 (TSP-1) is a 420–450-kDa homotrimeric multifunctional extracellular matrix protein, which was first isolated from human blood platelets as a thrombin-sensitive protein. TSP-1 which is secreted from endothelial cells, fibroblasts, neutrophils, monocytes, and macrophages as a regulator of (TGF)-β activation, which mediates wound healing, proliferation, cell differentiation, and cytokine response. TSP-1 stimulates macrophage migration, neutrophil phagocytosis, and monocyte chemotaxis to modulate the inflammatory response. TSP-1 promotes T cell function by binding integrin CD47 to regulate immune response [9]. CD47-TSP-1 interaction is associated with nuclear factor- κB ligand (RANKL)-driven osteoclastogenesis and bone resorption. TSP-1 is abundantly expressed in damaged and inflamed tissues such as rheumatoid synovium, atherosclerotic lesions, and diabetes mellitus. Hyperglycemia potentially induces TSP-1 synthesis by vascular cells through pathways that may involve glucose mediated activation of hexosamine. TSP-1 deficiency decreases obesity-induced adipose tissue inflammation and also attenuates experimental autoimmune encephalomyelitis. The matricellular protein thrombospondin (TSP)- 1, a potent angiostatic mediator and activator of transforming growth factor (TGF)-β, is upregulated in diabetes and obesity which may be involved in the pathogenesis of metabolic dysregulation and organ dysfunction. TSP-1 may also be involved in the pathogenesis of diabetic nephropathy, atherosclerosis, with impaired angiogenesis in diabetic myocardium and the defective re-endothelialisation following vascular injury [10].

Saliva has great potential as a diagnostic fluid and offers advantage over serum and other biological fluids by its non-invasive method of collection. Saliva, like blood, contains an abundance of protein and nucleic acid molecules that reflects physiological status; hence, unlike other bodily fluids, salivary diagnostics offer an easy, inexpensive, safe, and non-invasive approach for disease detection. Salivary biomarkers are potentially important for determining the initiation, risk, and progression of periodontal disease [11].

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2. MATERIALS AND METHODS

STUDY SETTING:

Tertiary care setting

The study was conducted in the Department of Periodontics, PMS College of Dental Science and Research, Vattappara, Thiruvananthapuram. Clinical and radiographic evaluation was done in the Department of Periodontics. Detection of salivary Thrombospondin-1 level was analysed by Enzyme-Linked Immunosorbent Assay (ELISA) technique at Central Research Laboratory (CRL), PMS College of Dental Science and Research, Vattappara, Thiruvananthapuram.

STUDY DESIGN:

Comparative study

STUDY SUBJECTS

90 subjects were selected from the outpatient section of the Department of Periodontics, PMS College of Dental Science and Research, Vattappara, Thiruvananthapuram for a period of one and half years. All the subjects belonging to age group 30-60 years including both sexes were selected including healthy volunteers and are categorized into 3 groups based on periodontal health status and glycemic levels as Group I: Systemically and Periodontally Healthy Subjects, Group II: Periodontitis without Type II Diabetes Mellitus and Group III: Periodontitis with Type II Diabetes Mellitus. The participants were recruited based on World workshop 2017 Classification of Periodontal and Peri-implant diseases and Conditions[1] - European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP), criteria for diagnosis of Diabetes by American Diabetes Association (ADA); Standards of Care -2023 [12].

CLINICAL EXAMINATION:

The protocol was summarized and approved by the institutional ethics committee (PMS/IEC/2022/REGULAR/APR/18). All the patients were briefly informed about the procedure before the start of experiment and informed and written consent was taken. Clinical examination includes full mouth plaque score (FMPS) [13], full mouth bleeding score (FMBS) [14], Periodontal Inflamed Surface Area (PISA) Score [15] and full mouth periodontal status evaluation on six sites per tooth including probing pocket depth (PPD), clinical attachment level (CAL) and recession/enlargement using (Michigan O probe with Williams marking, Hu Friedy IL Chicago) and recorded at six sites (buccal, lingual, mesio-lingual, mesio-buccal, disto-lingual, and disto-buccal). Mobility and furcation involvement was also noted. Intra oral periapical radiographs were taken in relation to the relevant sites for periodontal diagnosis.

SALIVA COLLECTION PROCEDURE:

Unstimulated whole expectorated saliva (2 ml), samples were collected prior to clinical measurements, between 9 am and 11 am. Subjects were instructed not to consume any food or liquids 2hrs before sample collection. Subjects were asked to rinse their mouth thoroughly with distilled water, to remove any food debris and then to spit into sterile vial. The subjects were instructed not to spit forcefully so as to avoid blood contamination. Samples were then transported to laboratory for biochemical analysis and the collected whole saliva was stored in -200C deep freezer. The analysis was performed in Central Research Laboratory (CRL), PMS College of Dental Science and Research, Vattappara, Thiruvananthapuram.

BIOMARKER ANALYSIS:

Each saliva sample was pipetted into a clean microcap tube and centrifugation was done at 1,000×g at 2-8°C for 15 minutes. The supernatant was transferred to clean microcap tubes and were used immediately for assay. Concentrations of Thrombospondin were determined using an enzyme-linked immunosorbent assay ELISA kit according to the manufacturer's instructions. The results of Thrombospondin assay were expressed as picograms per milliliter for concentrations. All laboratory tests were performed in Central Research Laboratory (CRL), PMS College of Dental Science and Research, Vattappara, Thiruvananthapuram.

PRINCIPLE:

The enzyme-linked immunosorbent Assay (ELISA) kit used was ImmunoTag. The test principle applied was Sandwich enzyme immunoassay. The microtiter plate had been pre-coated with an antibody specific to Thrombospondin-1 (TSP-1). Standards or samples were added to the appropriate microtiter plate wells then with a biotin-conjugated antibody specific to Thrombospondin-1(TSP-1). Next, Avidin conjugated to

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Horseradish Peroxidase (HRP) was added to each microplate well and incubated. After TMB substrate solution was added, only those wells that contain Thrombospondin-1 (TSP-1), biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in colour. The enzyme-substrate reaction was terminated by the addition of sulphuric acid solution and the colour change was measured spectrophotometrically at a wavelength of 450nm ± 10nm. The concentration of Thrombospondin-1 (TSP-1) in the samples were then determined by comparing the OD of the samples to the standard curve.

ASSAY PROCEDURE

1) DILUTION OF STANDARD SOLUTIONS

Dilution method: prepare 7 tubes containing 0.5mL Standard Diluent and use the diluted standard to produce a double dilution series. Mix each tube thoroughly before the next transfer. Set up 7 points of diluted standard such as 8000 pg/mL, 4000 pg/mL, 2000 pg/mL, 1000 pg/mL, 500 pg/mL, 250 pg/mL, 125 pg/mL, and the last EP tubes with Standard Diluent was the blank as 0 pg/mL.

2) NUMBER OF STRIPS NEEDED:

The number of stripes needed was determined by the number of samples to be tested. Each standard solution and each blank well should be arranged with three or more wells as much as possible. The required strips were inserted into the frames.

3) SAMPLE INJECTION

The required strips were inserted into the frames. Add 100µL of standard working Buffer (gradually diluted according to the instructions) or 100µL of sample to each well, incubate at 37°C for 80 minutes.

4) WASHING

Discard the liquid in the plate, add 200µL of Wash Buffer to each well, and wash the plate 3 times. After spin-drying, add 100µL Biotinylated Antibody working solution to each well, incubate at 37°C for 50 minutes. Discard the liquid in the plate, add 200µL Wash Buffer to each well, and wash the plate 3 times. After drying, add 100µL Streptavdin-HRP working solution to each well, incubate at 37°C for 50 minutes.

5) COLOR DEVELOPMENT

Discard the liquid in the plate, add 200µL Wash Buffer to each well, and wash the plate 5 times. After spin-drying, add 90µL TMB to each well. Cover with a new Plate sealer. Incubate at 37°C for 20min.

6) STOP

After incubation, add 50µL stop solution to each well, which leads the colour change from blue to yellow.

7) ASSAY:

Considering blank well as zero, absorbance (OD) of each well was measured one by one under 450nm wavelength, immediately.

8) CONCENTRATION OF SAMPLE

According to standards concentration and the corresponding OD values, a linear regression equation of the standard curve was calculated. Then according to the OD value of the samples, the concentration of the corresponding samples was calculated. Special software was employed to calculate as well. The Thrombospondin-1 concentration in each well was reported as picograms/milliliter (pg/ml).

STATISTICAL ANALYSIS:

Descriptive part

Categorical and quantitative variables were expressed as frequency (percentage), mean value, and standard deviation respectively.

Inferential part

• One way ANOVA test and Bonferroni test adjusted for multiple comparisons (post- hoc analysis) were used to compare quantitative parameters among the groups.

• Pearson Correlation Coefficient was used to find out the relationship of salivary Thrombospondin-1 and PISA score.

• For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance and statistical analysis was performed by using a statistical software SPSS Version 22, IBM Statistics, USA.

3. RESULTS

The comparison of age between all the three groups were done using ANOVA (Analysis of variance) (Table 1).

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Table 2: Comparison of salivary Thrombospondin -1 level in Group I (Healthy), Group II (Periodontitis without type II Diabetes Mellitus) and Group III (Periodontitis with type II Diabetes Mellitus)

		N	Mean	Standard Deviation	p-value
Thrombospondin-1	**Healthy (I)**	30	112.40	76.07	< 0.001*
	Periodontitis without type II Diabetes Mellitus (II)	30	279.54	86.93	
	Periodontitis with type II Diabetes Mellitus (III)	30	469.92	123.30	
p-value based on Analysis of Variance (ANOVA). * = Statistically Significant (p < 0.05)					

The mean age of the healthy group was 36.50±4.81 years, Periodontitis without type II Diabetes Mellitus was 48.26±8.81 years, Periodontitis with type II Diabetes Mellitus was 49.66±7.84 years.

Table 1: Comparison of age between Group I (Healthy), Group II (Periodontitis without type II Diabetes Mellitus) and Group III (Periodontitis with type II Diabetes Mellitus)

Age	**Healthy (I)**		**Periodontitis without type II Diabetes Mellitus (II)**		**Periodontitis with type II Diabetes Mellitus (III)**	
	Count	**Percent**	**Count**	**Percent**	**Count**	**Percent**
30-40	23	77	7	23	5	16
40-50	7	23	9	30	8	27
50-60	0	0	14	47	17	57
Mean ±SD	**36.50±4.81**		**48.26±8.81**		**49.66±7.84**	

P<0.05

The overall comparison of salivary Thrombospondin-1 level among all the three groups were calculated using ANOVA (Analysis of Variance) (Table 2) and shows a statistically significant difference with higher levels in Group III (469.92±123.30 and p-value < 0.001).

The inter-group pair- wise comparison of salivary Thrombospondin-1 level between all the three groups were done by post-hoc analysis using Bonferroni test (Table 3). There was statistically significant difference between Group I and II, Group I and III and Group II and III with p-value < 0.001.

Table 3: Inter- group Pair- wise Comparison of salivary Thrombospondin- 1 level in Group I (Healthy), Group II (Periodontitis without type II Diabetes Mellitus) and Group III (Periodontitis with type II Diabetes Mellitus)

			p-value
Thrombospondin-1	**Healthy (I)**	**Periodontitis without type II Diabetes Mellitus (II)**	<0.001*
		Periodontitis with type II Diabetes Mellitus (III)	<0.001*
	Periodontitis without	**Periodontitis with type II Diabetes Mellitus (III)**	<0.001*

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	type II Diabetes Mellitus (II)		

p-value based on post-hoc analysis using Bonferroni test after adjusting for multiple comparisons

* = Statistically Significant ($p < 0.05$)

The overall comparison of PISA score among all the three groups were calculated using ANOVA (Analysis of Variance) (Table 4) and shows a statistically significant difference with higher levels in Group III (3190.34±570.53 and p-value < 0.001).

Table 4: Comparison of PISA Score in Group I (Healthy), Group II (Periodontitis without type II Diabetes Mellitus) and Group III (Periodontitis with type II Diabetes Mellitus)

		N	Mean	Standard Deviation	p-value
PISA	**Healthy (I)**	30	26.03	13.07	< 0.001*
	Periodontitis without type II Diabetes Mellitus (II)	30	1140.72	205.14	
	Periodontitis with type II Diabetes Mellitus (III)	30	3190.34	570.53	

p-value based on Analysis of Variance (ANOVA).

* = Statistically Significant ($p < 0.05$)

The inter-group pair-wise comparison of PISA score between all the three groups was done by post-hoc analysis using Bonferroni Test (Table 5). There was statistically significant difference between Group I and II, Group I and III and Group II and III with p-value < 0.001.

Table 5: Inter- group Pair- wise Comparison of PISA score in Group I (Healthy), Group II (Periodontitis without type II Diabetes Mellitus) and Group III (Periodontitis with type II Diabetes Mellitus)

			p-value
PISA	**Healthy (I)**	**Periodontitis without type II Diabetes Mellitus (II)**	<0.001*
		Periodontitis with type II Diabetes Mellitus (III)	<0.001*
	Periodontitis without type II Diabetes Mellitus (II)	**Periodontitis with type II Diabetes Mellitus (III)**	<0.001*

p-value based on post-hoc analysis using Bonferroni test after adjusting for multiple comparisons

* = Statistically Significant ($p < 0.05$)

The Correlation Assessment of salivary level of Thrombospondin-1 with the PISA score between groups were done using Pearson Correlation Coefficient and scatter plot graphs. There was a weak positive linear relationship in Group I (r=0.154) (Figure 1). There was a weak negative linear relationship in Group II (r=-0.025) (Figure 2). There was a weak positive linear relationship in Group III (r=0.012) (Figure 3).

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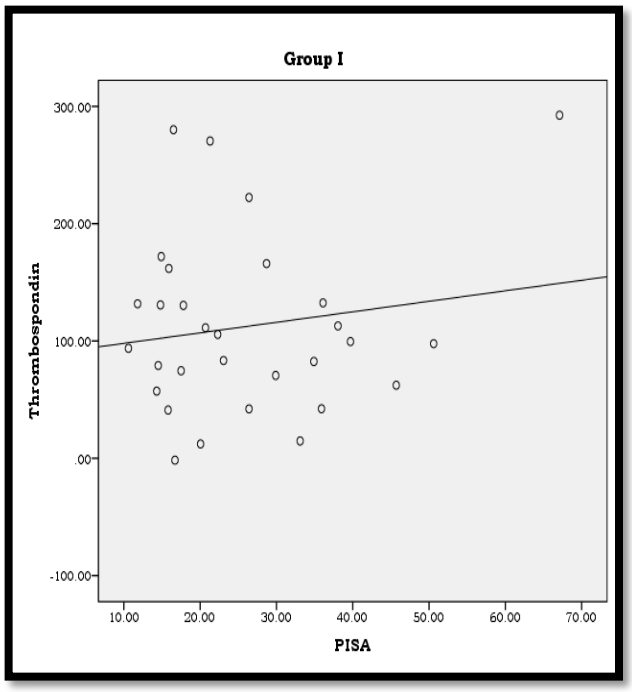

Figure 1: Scatter plots for correlation of salivary Thrombospondin-1 level with PISA score in Group I (Healthy)

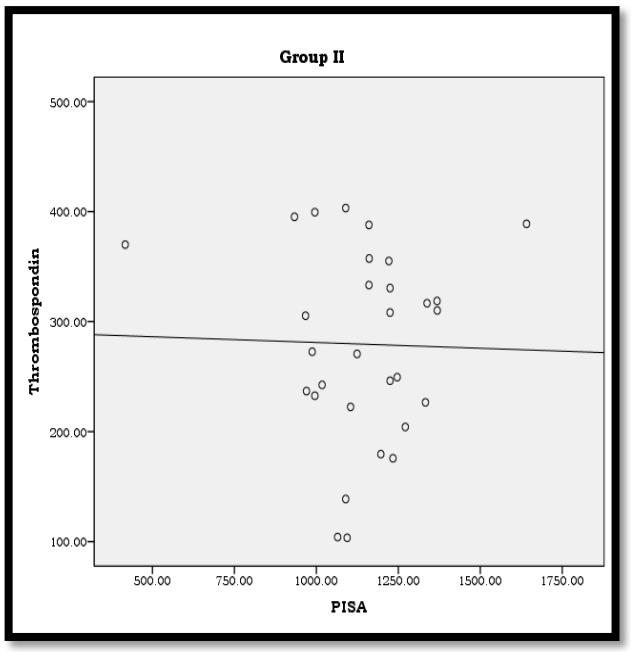

Figure 2: Scatter plots for correlation of salivary Thrombospondin-1 level with PISA score in Group II (Periodontitis without type II Diabetes Mellitus)

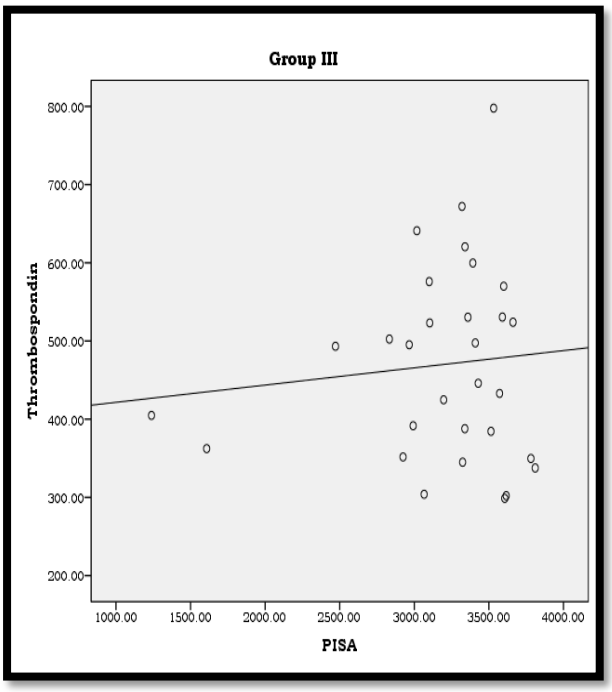

Figure 3: Scatter plots for correlation of salivary Thrombospondin-1 level with PISA score in Group III (Periodontitis with type II Diabetes Mellitus)

4. DISCUSSION

In the present study, a total of 90 subjects were selected and categorized into 3 groups, each group consisting of 30 subjects- Group I (Healthy controls), Group II (Periodontitis without diabetes mellitus) and Group III (Periodontitis with type II diabetes mellitus). Mean age for Group I was 36.50±4.81 years, Group II was 48.26±8.81 years and Group III was 49.66±7.84 years.

The aim of the present study was to compare and correlate the salivary Thrombospondin-1 levels in periodontitis patients with and without type II diabetes mellitus and healthy subjects.

The results of our study proved that Group III individuals have significantly higher salivary Thrombospondin-1 level (469.92±123.30, $p<0.001$) as compared to Group II (279.54±86.93, $p<0.001$) and Group I (112.40±76.07, $p<0.001$) which was statistically significant.

Our study is in agreement with various previous studies which have demonstrated an increased salivary

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Thrombospondin-1 level in chronic inflammatory disease like periodontitis.

In a recent study by Liu X et al 2021 [16] proved that in response to P. gingivalis LPS, hPDLFs facilitated the expression of TSP-1 at the protein level, while producing a range of MMPs (MMP-2 and MMP-9), which are responsible for ECM degradation and the stimulation of hPDLFs with P. gingivalis LPS induced RANKL expression, while OPG expression was downregulated.

We have also evaluated intergroup pair- wise comparison of salivary Thrombospondin-1 level, which shows that there was statistically significant difference noted between Group I and II, Group I and III and Group II and III. The findings of our study were supported by the results of various previous studies done by Kong P et al 2013 [17], Al-Kraity et al 2015 [18], Guo N et al 2024 [19].

A recent study by Guo N et al 2024 [19] concluded that the level of circulating TSP-1 was elevated in patients with diabetes, and were further elevated in diabetes patients with vascular complications. This change trend of TSP-1 indicates that the level of circulating TSP-1 increases with the progression of diabetes. Circulating TSP-1 was significantly positively correlated with FPG and glycated haemoglobin, which is in line with the effect of glucose on stimulating TSP-1 production.

To the best of our knowledge this is the first study that has attempted to evaluate and compare the salivary Thrombospondin-1 level in periodontitis patients with and without type II diabetes mellitus and healthy subjects and correlate it with the inflammatory burden of periodontal disease.

In the present study on evaluation, the clinical parameters such as FMPS, FMBS, PPD, CAL were significantly higher in Group III (89.43±5.8, p<0.001; 92.9±4.5, p<0.001; 8.9±0.83, p<0.001; 8.8±0.87, p<0.001) as compared to Group II (74.8±6.00, p<0.001; 81.3±5.08, p<0.001; 6.5±0.71, P<0.001; 6.7±0.85, P<0.001) and Group I (34.7±9.6, p<0.001, 10.8±8.01, p<0.001; 3.03±0.48, p<0.001, 3.13±0.71, p<0.001).

Apart from the conventional parameters, the present study also compared and correlated the PISA score in periodontitis patients with and without type II diabetes mellitus and healthy subjects. The study results demonstrated that Group III individuals have significantly higher PISA score (3190.34±570.53, p<0.001) and in the intergroup pair- wise comparison of PISA score, there was statistically significant difference between Group I and II, Group I and III and Group II and III.

We have also evaluated correlation of salivary Thrombospondin-1 level with PISA score, there was a weak positive linear relationship with Group I (r=0.154) and Group III (r=0.102) and a weak negative linear relationship with Group II (r=- 0.025).

In a recent study by Takeda K et al 2021 [20] reveals that there is a significant association between HbA1c and PISA after adjusting for plaque control record, which is a quantitative measure of full-mouth oral hygiene. PISA was significantly associated with the highest tertile of FPG, independent of possible confounders.

Another observational study by Anil K et al 2021 [21] demonstrated that the uncontrolled T2DM group with and without microvascular complications had a higher percentage of severe periodontitis and a higher mean PISA than the controlled T2DM group. A positive correlation was obtained between PISA and HbA1c. A dose–response relationship between PISA and HbA1c was observed, and an increase of PISA with 168 mm^2 was associated with a 1% increase of HbA1c.

A recent clinical study by Kalyani Y et al 2023 [22] reveals a higher PISA value in the diabetics with periodontitis group as compared to the non-diabetics with periodontitis group. This is attributed to the impaired adherence, chemotaxis, and phagocytosis of neutrophils in diabetic patients, which prevents neutrophil mediated destruction of bacteria in the periodontal pocket, thereby increasing periodontal destruction.

5. CONCLUSION

In line with the aforementioned findings, the results of our study showed a statistically significant salivary Thrombospondin-1 level in periodontitis patients with diabetes mellitus compared to other groups. On correlation salivary Thrombospondin-1 has a positive linear relationship with PISA score in periodontitis patients with diabetes mellitus compared to other groups. The limitation of the present study was the small sample size which was insufficient to make significant correlations with the inflammatory burden of periodontal disease and type II diabetes mellitus. Further research with elaborate study design and larger sample sizes are

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needed to validate the use of Thrombospondin-1 as an inflammatory biomarker to reinforce the concept of bidirectional relationship between periodontal disease and type II diabetes mellitus.

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