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Development of a Polymeric Detection System for Salivary Annexin-1: A Potential Tool for Point-of-Care Diagnostics in Periodontal Disease

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Abstract

Salivary annexin-1, a protein with anti-inflammatory properties, has emerged as a potential biomarker for periodontal disease. However, current detection methods, like ELISA, are often complex and require laboratory settings. This study explores the development of a novel polymeric detection system for the rapid and sensitive identification of salivary annexin-1. This system could leverage the unique properties of polymers to create a point-of-care diagnostic tool for: (1) early detection and monitoring of periodontal disease, particularly in diabetic populations, and (2) providing valuable insights into the inflammatory status of patients. The proposed system has the potential to offer several advantages, including: Rapid and user-friendly testing format suitable for clinical settings. High sensitivity and specificity for accurate annexin-1 detection. Potential for cost-effectiveness and portability compared to traditional methods. The development of such a polymeric detection system could revolutionize the diagnosis and management of periodontal disease, enabling early intervention and improved patient outcomes. Further, this study aimed to conduct a comparative assessment of salivary annexin-1 levels in Type-2 diabetic patients with and without periodontitis. Annexin-1, a glucocorticoid-regulated protein with anti-inflammatory properties, has been implicated in the regulation of inflammatory responses in periodontal disease. In this investigation, salivary annexin-1 levels were measured using enzyme-linked immunosorbent assay (ELISA) in diabetic patients with and without periodontitis, along with a control group of non-diabetic individuals. The results were statistically analyzed to determine any significant differences in annexin-1 levels between the diabetic groups with and without periodontitis, as well as compared to the control group. Findings from this study may provide insights into the role of annexin-1 in the pathogenesis of periodontal disease in diabetic individuals and its potential as a biomarker for periodontal health in diabetic populations.

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INTRODUCTION

Periodontal disease is an ancient condition that

has been demonstrated by fossil evidence showing alveolar bone loss surrounding tooth root surfaces. It continues to be the most prevalent cause of tooth loss to this day [1]. The periodontal diseases range from gingivitis which is relatively benign form of periodontal disease, to chronic and aggressive forms of the diseases which not only affects the dentition and oral cavity but may also be a threat to general health [2].

Periodontitis is an inflammatory condition of bacterial origin that affects the periodontal tissues, causing devastation to the surrounding and supporting structures [3]. The chief cause of gingivitis and periodontitis is the bacterial biofilm. To uphold periodontal health or impede disease advancement, it's essential to concentrate on eliminating supragingival and subgingival bacterial biofilm. In contrast to free-floating planktonic cells, bacteria organized as biofilms display notable resistance to antibiotics and other antibacterial agents. However, there is a great reluctance to specify the clinical features which documents periodontitis for a specific case. Criteria to consider when diagnosing a periodontal condition encompass pocket probing depth, gingival recession, gingival width, probing attachment level, furcation involvement, tooth mobility, suppuration, and any observable bone changes radiographically [4].

Chronic hyperglycemia leads to a persistent condition known as Diabetes Mellitus (DM), stemming from disrupted endocrine and metabolic pathways in glucose utilization. Moreover, diabetes substantially raises the risk of stroke and myocardial infarction, particularly in developing nations. Projections by the WHO estimate a 50% surge in Diabetes Mellitus cases by 2030. Type 2 Diabetes Mellitus, characterized by peripheral insulin resistance (IR) resulting in hyperglycemia, constitutes over 90% of diabetes cases and exhibits a growing global incidence rate [5].

Environmental and genetic factors both contribute to the loss of β-cells and insulin resistance in T2DM. Environmental factors such as increased caloric intake, decreased energy expenditure, and unbalanced diet contributes to onset of T2DM and obesity. Genetic factors such as single nucleotide polymorphysims (SNPs) and various obesity and diabetogenic related genes is vital in susceptibility to T2DM although there is no HLA linkage in T2DM [6]. Microvascular, immunological and neurological changes are seen in T2DM due to altered glucose and lipid metabolism. These changes further lead to diabetes-associated peripheral arterial disease, coronary artery disease, neuropathy, nephropathy, retinopathy and periodontitis [7].

Periodontal tissues are impacted by DM in multiple ways which includes microvascular alterations, immunological dysfunctions and changes in extracellular matrix [8]. Individuals with diabetes mellitus (DM) often exhibit a higher prevalence and severity of periodontitis, attributed to various factors such as impaired neutrophil margination along the gingival endothelium, hyper-responsiveness of monocytes, and alterations in chemotaxis and phagocytosis [9]. Patients with diabetes mellitus (DM) may experience bone resorption, primarily attributed to a reduced OPG/RANKL ratio in the periodontal tissues. Due to dysregulated inflammatory biomarkers such as cytokines, chronic and systemic inflammation is a prominent feature of T2DM. It is also associated with abnormal clot formation [10].

In the host inflammatory response, endogenous anti-inflammatory pathways play a crucial role in regulating and controlling inflammation. These mediators can act at various stages of the inflammatory response, including through gene deletion to block their actions or remove their presence, thereby modulating the inflammatory process [11].

In the disease process, there is an early occurrence of insulin resistance which precedes the development of type 2 diabetes. Thus, to elucidate the molecular pathogenesis of the disease the identification of molecules is important that contribute to insulin resistance and lead up to type 2 diabetes. The expression of ANXA1 is regulated by glucocorticoids (GC), which mediate the anti-inflammatory actions of GC. Pro-inflammatory cytokines, such as IL-6, counter-regulate the expression of ANXA1. The etiology of the inflammatory disease can be contributed by ANXA1 deficiency [12].

The connection between periodontal diseases and systemic diseases has been a subject of study among professionals, clinicians, and scientists over the years. However, there remains controversy regarding the validity of this relationship, puzzling the academic community. The extent to which common immune deregulation resulting from genetic factors contributes to the association between chronic periodontitis and systemic conditions like diabetes mellitus is not fully comprehended. Our comprehension of the spatial and temporal correlations between local and systemic events in the onset of diabetes mellitus plays a critical role in determining therapeutic efficacy and related complications such as chronic periodontitis [13].

Till date none of the studies have examined the association of Annexin-1, an anti-inflammatory protein with periodontitis in patients with type-2 Diabetes using saliva sample. To gain a better insight into the role of salivary ANXA1 in Type-2 Diabetes Mellitus patients with and without periodontitis we have used a translational approach in the current study. Understanding role of Annexin1 in periodontitis and in type-2 Diabetes will help us to formulate new treatment strategies for host modulation. The aim of the research is to determine the levels of salivary Annexin-1 in Type-2 Diabetic patients with and without generalized Stage II Grade B/ Grade C periodontitis and patients with generalized Stage II Grade B/ Grade C periodontitis.

MATERIALS AND METHOD

Detailed Research Plan

After receiving the due approval from the Ethical Committee of Krishna Institute of Medical Sciences, deemed to be University, Karad (Protocol number: 156/2019-2020), the subjects were selected from the patients attending outpatient department (OPD) of Department of Periodontology, School of Dental Sciences, KIMSDU, Karad.

Subjects were explained about the study in detail and after obtaining their consent they were included in the study.

Methodology

The study comprised of 90 individuals who were further divided into 3 groups who fulfilled the inclusion criteria for that particular group. Subjects from both the gender within the age category of 30-65 years were included in the study. The purpose of the study design was explained to each subject before enrolling them in the study. The subjects were evaluated before the treatment in the outpatient department for clinical and biochemical parameters. The subjects with and without periodontitis were diagnosed and selected according to AAP World Workshop on Classification of Periodontal and Peri-implant diseases and conditions, 2017. The subjects with and without Type-2 Diabetes mellitus were diagnosed based on the criteria by American Diabetes Association (2010).

A standard proforma consisting of data like name, age, gender, past dental and medical history, Russell's Periodontal Index was prepared. Data for each patient was recorded in the designed format.

Selection Criteria

Staging and Grading Criteria: (Tonetti MS et al 2017)

- Based on the clinical and radiographic evaluation, Staging and Grading of periodontal diseases was performed.
- Subjects of Group 1 and Group 2 for periodontitis will be selected belonging to Stage II and Grade B and Grade C of the diseases.

Stage II (Moderate Periodontitis)

- Interdental CAL 3-4 mm at the site of greatest loss
- ≤ 5 mm of maximum probing depth
- Horizontal pattern of bone loss
- 15%–33% of radiographic bone loss at the coronal third

Grade B (Moderate Rate of Evolution)

- Direct proof of < 2 mm evolution over five years.
- Indirect proof of evolution of 0.25 to 1 (%bone loss / age).
- Indirect proof of destruction that commensurate with the biofilm deposits.

Grade C (Fast Rate of Evolution)

- Direct proof of ≥ 2 mm evolution over five years.
- Indirect proof of evolution of > 1 (%bone loss / age)
- Indirect proof of destruction with specific clinical patterns suggestive of periods of fast evolution
- Grade modifier – HbA1c ≥ 7% in individuals with diabetes.

Inclusion Criteria

- *For category 1:* (Systemically healthy subjects with generalized periodontitis)
  - Systemically healthy patients.
  - Patients with generalized periodontitis as per AAP criteria 2017.
  - Age ≥30 years.
  - More than 20 teeth present.

- *For category 2:* (Subjects with generalized periodontitis and type-2 diabetes mellitus)
  - Patients with generalized periodontitis as per AAP criteria 2017.
  - Good or fair glycemic control (confirmed with HbA1c values <8)
  - Age ≥30 years.
  - Patients pre-diagnosed with Type-2 Diabetes mellitus as per data obtained from their medical records.
  - More than 20 teeth present.

- *For Category 3:* (Periodontally healthy subjects with type-2 Diabetes)
  - Good or fair glycemic control (confirmed with Hba1c values <8)
  - Periodontally healthy patients.
  - Good oral hygiene.
  - Patients pre-diagnosed with Type-2 Diabetes mellitus as per data obtained from their medical records.
  - Age ≥30 years.
  - More than 20 teeth present.

Exclusion Criteria

- Pregnant women
- Lactating females
- History of periodontal therapy in past six months.
- Use of medications which can influence the periodontal conditions.
- Tobacco in smoking or chewing form.
- Subjects not willing to give consent for their enrollment in the study.

RESULTS

Total 90 enrolled study subjects were divided into three categories based on the study design. It was observed that out of the total 90 subjects who participated in the study, majority of the study population of about 61.2% were Males (n=55) while only 38.8% of the study population were females (n=35). The values are represented in the form of bar graph in Figure 1.

Figure 2. depicts the distribution of the study population in different groups according to the study design depending on their age. The population was categorized under three different age groups from

31 to 40 years, 41 to 50 years and 51 to 60 years based on the inclusion criteria for the study. On basis of age distribution, it was observed that many of the subjects participating in the study from category 1 (Periodontitis group) and category 2 (Diabetes with periodontitis group) mainly belonged to age group ranging from 51-60 years. Majority of the subjects from Group 3 i.e., Diabetes group belonged to age group ranging from 41-50 years followed by 51-60 years respectively. Difference in number of participants among various study groups was statistically significant ($p < 0.0001$).

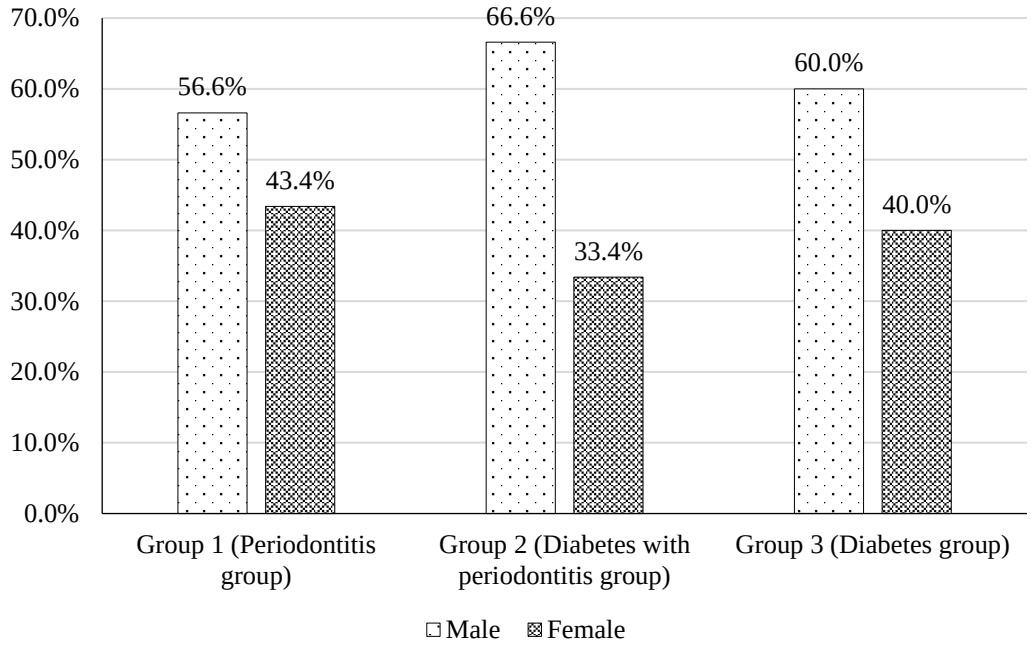

Figure 1. Demographic data-gender distribution.

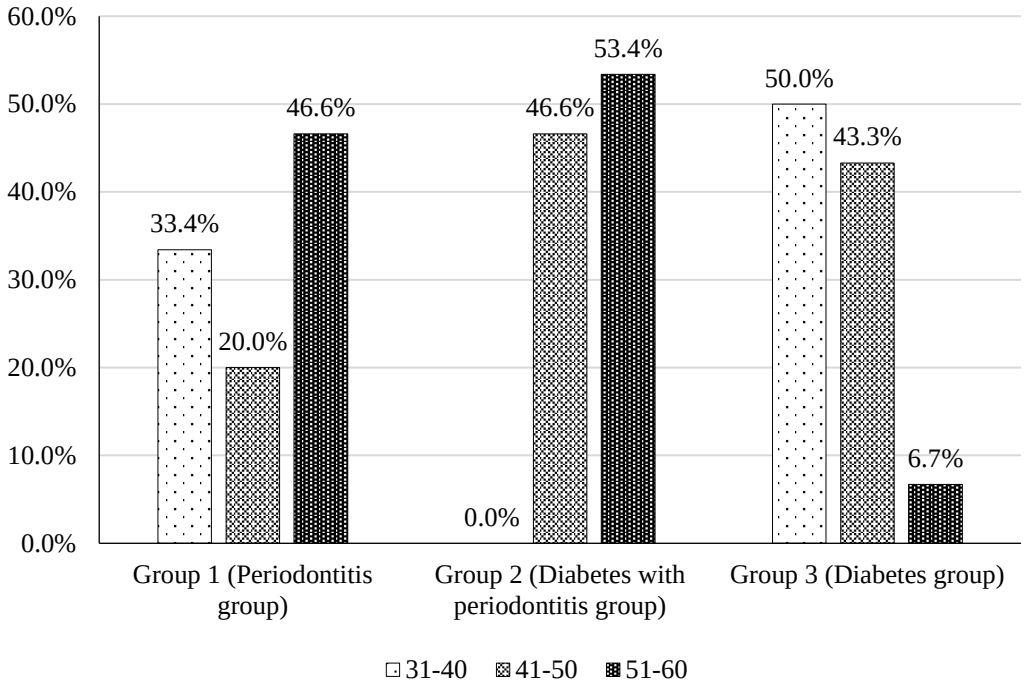

Figure 2. Demographic data-age distribution.

Table 1 shows the frequency of Oral Hygiene Practice of 90 subjects that an individual undertook. Accordingly, the subjects were classified into two categories, one who practised oral hygiene once a

day while another who practised oral hygiene twice a day. It was observed that there was no mathematical difference in oral hygiene practice between category 1 belonging to periodontitis group and Category 2 belonging to Diabetes with periodontitis group. In both the cases around 13% people happen to practice healthy oral hygiene twice a day and 87% practised only once a day. Higher number of individuals of category 3 (Diabetes group) practiced oral hygiene twice daily (20%) when compared to category 1 (Periodontitis group) and category 2 (Diabetes with periodontitis group).

Table 1. Oral Hygiene Practice among subjects of Category 1(Periodontitis group), Category 2 (Diabetes with periodontitis group) and Category 3 (Diabetes group) by Chi-square test

Oral Hygiene Practice	**Category 1 (Periodontitis group)**		**Category 2 (Diabetes with periodontitis group)**		**Category 3 (Diabetes group)**		**Total**		**Chi-square test**	**p-value**
	F	***%***	***F***	***%***	***F***	***%***	***F***	***%***		
Once a day	26	86.6	26	86.6	24	80	76	84.5	0.676	0.712
Twice a day	04	13.4	04	13.4	06	20	14	15.5		
Total	*30*	*100*	*30*	*100*	*30*	*100*	*90*	*100*		

The subjects under study were analysed for their OHI-S Score which was bucketed into 3 categories of Good, Fair and Poor scores. The periodontitis group showed no individual with Good OHI-S score, while Diabetes with periodontitis and Diabetes group showed a minimal of 3.4% study participants belonging to this category. Maximum participants (56.6) in Periodontitis group demonstrated Poor OHI-S Score while 20% from Group 2 and 16% from group 3 had poor OHI-S. Majority of subjects in Group 2 and Group 3 had Fair OHI-S Score with 76% and 80% respectively (Figure 3.)

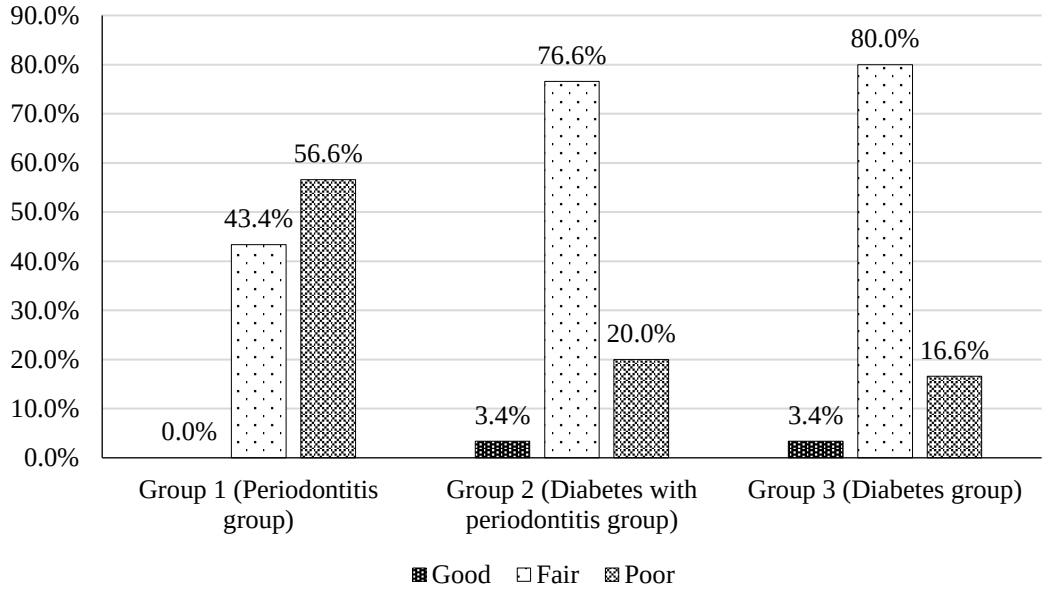

Figure 3. OHI-S Score.

The Analysis of Gingival Index Score had shown the interesting results, with no subjects from Periodontitis group and Diabetes with periodontitis group showing mild gingival index score while there were no subjects in Diabetes group showing severe gingival score. Majority of Group 1 and Group 2 participants had concentration in severe gingival index score with around 80% each while diabetes group had three-fourth subject population in severe gingival index score category. Moderate Gingival Index was observed in 16% Periodontitis subjects, 20% Diabetes with periodontitis subjects and 26% Diabetes subjects. The difference between gingival score categories among all the study category were

mathematically significant (p<0.0001**)** (Table 2.)

Figure 4 shows that group 1 and group 2 did not have gingivitis while all participants from diabetes group had gingivitis. All the subjects in diabetes group had periodontal index score in the category of Gingivitis. Around 80% subjects showed the periodontal Index score of established periodontal disease that belonged to Group 1 and Group 2. Around 20% subjects in both Group 1 and Group 2 had the periodontal Index score lying in the range of beginning of periodontal disease. The difference between PDI score categories among all the group had statistically significant difference p-value <0.0001

Table 2. Gingival Index (GI) Score among category 1(Periodontitis group), category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group) by Chi-square test.

Gingival Index Score	**Category 1 (Periodontitis group)**		**Category 2 (Diabetes with periodon-titis group)**		**Category 3 (Diabetes group)**		**Total**		**Chi-square test**	**p-value**
	F	***%***	***F***	***%***	***F***	***%***	***F***	***%***		
Mild	00	00	00	00	22	73.4	22	24.5	69.267	<0.0001
Moderate	05	16.6	06	20	08	26.6	19	21.1		
Severe	25	83.4	24	80	00	00	49	54.4		
Total	*30*	*100*	*30*	*100*	*30*	*100*	*90*	*100*		

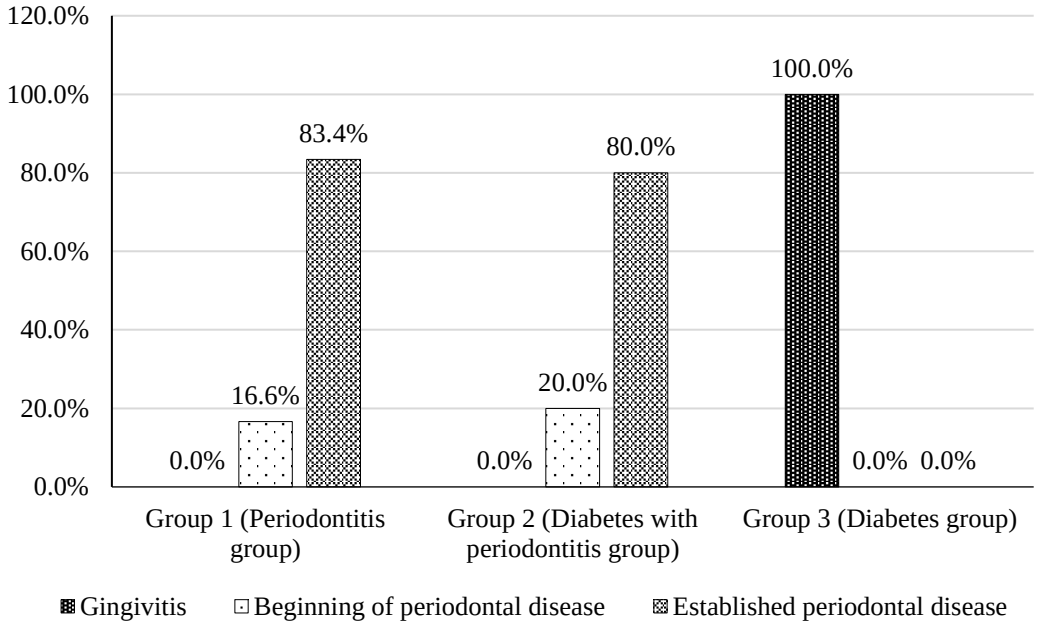

Figure 4. Periodontal Index Score.

According to Tukey Krawer Multiple Comparison Test, salivary Annexin-1 level did not have significant difference between Periodontitis and Diabetes group as well as in between Diabetes and Diabetes with Periodontitis Group. But the value of Annexin-1 in saliva sample was significantly greater in Diabetes with Periodontitis Group as compared to Periodontitis Group. The Mean and standard deviation of Salivary Annexin-1 levels between category 1(Periodontitis group), category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group) was 4.922 ± 4.504, 23.847 ± 41.918 and 8.312 ± 14.802 (ng/ml) respectively (Table 3)

Table 3. Average and SD of Salivary Annexin-1 levels between category 1(Periodontitis group), category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group)

	Category 1	**Category 2**	**Category 3**

	(Periodontitis group)	(Diabetes with periodontitis group)	(Diabetes group)
Average value ± SD	4.922 ± 4.504 (ng/ml)	23.847 ± 41.918 (ng/ml)	8.312 ± 14.802 (ng/ml)

Table 4. shows the Comparison of Salivary Annexin-1 levels between category 1(Periodontitis group) and category 2 (Diabetes with periodontitis group) which was done using unpaired t-test. The t-value between the two groups was 2.459 and the p-value = 0.016 which indicates statistically difference between the annexin-1 levels in category 1 (Periodontitis group) and category 2 (Diabetes along periodontitis group).

Table 4. Comparison of Salivary Annexin-1 levels between category 1(Periodontitis group) and category 2 (Diabetes with periodontitis group) by unpaired t-test.

	Category 1 (Periodontitis group)	Category 2 (Diabetes along periodontitis group)	t-value	p-value
Average value ± SD	4.922 ± 4.504 (ng/ml)	23.847 ± 41.918 (ng/ml)	2.459	0.016*

*Statistically significant

Table 5 shows the Comparison of Salivary Annexin-1 levels between category 1(Periodontitis group) and category 3 (Diabetes group) which was performed using unpaired t-test. The t-value = 1.2 and the p-value = 0. 2350. As the p-values was > 0.05, no statistical difference between the salivary annexin-1 levels of category 1 (Periodontitis group) and category 3 (Diabetes group) were noted.

Table 5. Comparison of Salivary Annexin-1 levels between category 1(Periodontitis group) and category 3 (Diabetes group) by unpaired t-test.

	Category 1 (Periodontitis group)	Category 3 (Diabetes group)	t-value	p-value
Average value ± SD	4.922 ± 4.504 (ng/ml)	8.312 ± 14.802 (ng/ml)	1.2	0.2350

Table 6. shows the Comparison of Salivary Annexin-1 levels between category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group) using unpaired t-test. The t-value obtained was 1.914 while the p-value obtained was 0.060. Thus, no statistical difference was observed between the salivary Annexin 1 levels of category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group).

Table 6. Comparison of Salivary Annexin-1 levels between category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group) by unpaired t-test.

	Category 2 (Diabetes with periodontitis group)	Category 3 (Diabetes group)	t-value	p-value
Average value ± SD	23.847 ± 41.918 (ng/ml)	8.312 ± 14.802 (ng/ml)	1.914	0.060

A one-way ANOVA test was performed to compare the Salivary Annexin-1 levels between category 1(Periodontitis group), category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group) the f-value obtained was 4.591 while the p-value obtained was 0.0127 (Table 7.) As the p-value < 0.05, it indicated significant difference in the salivary Annexin 1 levels between category 1(Periodontitis

group), category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group). However, a greater mean and standard deviation was recorded in group 2 (Diabetes along periodontitis group).

Table 7. Comparison of Salivary Annexin-1 levels between category 1(Periodontitis group), category 2 (Diabetes with periodontitis group) and category 3 (Diabetes group) using one way ANOVA test.

	Category 1 (Periodontitis group)	**Category 2 (Diabetes along periodontitis group)**	**Category 3 (Diabetes group)**	**f-value**	**p-value**
Mean ± Standard Deviation (SD)	4.922 ± 4.504 (ng/ml)	23.847 ± 41.918 (ng/ml)	8.312 ± 14.802 (ng/ml)	4.591	0.0127*

*Statistically significant

CONCLUSION

The study yielded several key findings regarding the relationship between T2DM, periodontitis, and salivary Annexin-1 levels. Firstly, it was observed that T2DM and periodontitis were more prevalent among males compared to females in the study population. Secondly, no significant correlation was found between salivary Annexin-1 levels and age. However, inflammatory conditions such as periodontitis and T2DM were associated with elevated levels of salivary Annexin-1. Notably, the group with both periodontitis and T2DM exhibited higher levels of salivary Annexin-1 compared to either condition alone. Additionally, salivary Annexin-1 levels were highest in cases of T2DM with periodontitis, followed by T2DM alone, and then periodontitis alone. These findings shed light on the interplay between T2DM, periodontitis, and salivary Annexin-1 levels, emphasizing the potential diagnostic and therapeutic implications for these conditions.

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