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Expression of Salivary Interleukin 17A in Chronic Periodontitis

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ABSTRACT

Background: A wide range of cytokines contribute significantly to the development and progression of numerous inflammatory conditions, such as diabetes, psoriasis, arthritis, and periodontal disease. Diabetes and periodontitis have been linked to elevated serum interleukin IL-17A, concentrations. This study will look at the levels of salivary interleukin 17A in patients with chronic periodontitis (CP), type 2 diabetes, and healthy controls.

Methodology: This cross-sectional study was conducted at the Institute of Pathology and Diagnostic Medicine (IP&DM), Khyber Medical University (KMU) Peshawar and in the periodontology department of Saidu College of Dentistry, Swat among 96 individuals of 30-to-50-year age group including both male & female. After obtaining informed consent and completing the questionnaire, periodontal assessments including periodontal index (PI), bleeding on probing (BOP), periodontal pocket depth (PPD), and clinical attachment loss (CAL)—were recorded to evaluate the presence and severity of periodontal disease. Blood sugar levels were assessed for known diabetic patients. Saliva was collected using resting drooling method. ELISA was done for IL-17A using standard kits.

Result: Mean and standard deviation values of salivary IL-17A concentrations observed in Non-diabetic CP were 8.854±0.975 (pg/ml), in diabetic CP group were 9.815± 1.094(pg/ml), in periodontal healthy group were 3.878± 0.9090(pg/ml). Concentration of salivary IL-17A for moderate and poor oral health statuses in diabetics CP are 8.96(pg/ml) and 10.43(pg/ml) respectively. Whereas in non-diabetics CP the concentration of IL-17A levels for moderate and poor oral hygiene cases were 8.62 & 10.02(pg/ml) respectively. The mean values in the healthy control (diabetics and non-diabetics non-CP) observed were 3.18(pg/ml) and 4.07(pg/ml) respectively. A P value of 0.001 was observed, signifying that the alterations in mean IL-17A levels are statistically significant when associated within each group. The mean concentration observed in both diabetic and non-diabetic CP was higher than the healthy control non-CP.

Conclusion: Within the limitations of this investigation, it may be concluded that elevated levels of IL-17A in the saliva of people suffering from untreated chronic periodontitis may function as a suggestive noninvasive biomarker for periodontal disease. Salivary IL-17A levels were highly related with periodontitis. This finding highlights the potential for salivary IL-17alpha to be used as a diagnostic marker, offering a non-invasive way to gauge the severity of periodontal diseases.

Introduction

Periodontitis is an inflammatory disease of supporting structures of the teeth affecting the soft and hard tissues surrounding the teeth.[1] periodontal diseases includes gingivitis and periodontitis.[2] Gingivitis is a reversible condition characterized by inflammation limited to the gingival tissue without affecting the deeper structure of Periodontium when promptly addressed with good oral hygiene practice and proper scaling procedure can be effectively controlled.[2,4]

However, if left untreated, gingivitis has the potentials to progress onto periodontitis.[3] Chronic periodontitis seldom occurs within the initial three decades of life and exhibit a slow rate of advancement.[4] There has long been evidence of a strong connection between diabetes mellitus and periodontitis.[5] Untreated periodontitis appears to impair glycemic regulation, and patients with diabetes mellitus are more likely to acquire the condition.[6] Periodontitis is frequently associated with systemic chronic inflammatory disorders. Diabetes mellitus is recognized as a significant risk factor for periodontitis, often described as the sixth complication of the disease. In addition, chronic periodontitis is closely linked to inadequate glycemic control, with poorer control associated with more severe periodontal outcomes.[5] individuals suffering from periodontitis and diabetes mellitus may produce more inflammatory cytokines due to altered apoptosis, elevated adipokine production, and improved PMN function. Periodontal disease affects an individual's physical, social and psychological quality of life. Periodontal diseases are a significant oral health issue, playing a crucial role in the overall burden of chronic diseases worldwide.[7,8] Cytokines plays a fundamental role in the inflammation and are the key inflammatory mediators in periodontal disease.[9] Interleukin-17A (IL-17A) plays an important role in oral immunity, and its specific relevance to periodontal health and disease is crucial in understanding the Immunopathogenesis of periodontitis.[11] IL-17A has both a preventive and detrimental impact in the course of chronic periodontitis.[11] At the onset of periodontal infection, neutrophils rapidly migrate out of the bloodstream and are the earliest immune cells to arrive at the site of infection. IL-17A plays a key regulatory role in this process by promoting the release of neutrophils from the bone marrow into circulation and guiding their recruitment to inflamed periodontal tissues. Many studies have reported salivary biomarkers for many disorders of systemic and oral cavity as a diagnostic medium.[10] Different Salivary biomarker for periodontal diseases have been published.[12] most researchers agree that the best bodily fluid for assessing inflammatory activities is blood. However, participants may experience temporary discomfort, bruising, infection at the venipuncture site, during blood collection.[14] additionally, blood collection is less preferred for studies involving children and other study subjects (e.g., the elderly or seriously ill) for whom venous access is challenging. On the other hand, passive saliva samples are thought to be the best way to analyzes pathology particularly oral pathologies such as periodontitis.[13,14] Understanding the specific role of IL-17A in oral immunity, particularly in the context of periodontal health and disease, provides insights into potential therapeutic strategies for managing periodontitis.

Methodology

This was a Cross-sectional study and was conducted at Periodontology department of Saidu College of dentistry, swat and KMU Peshawar after obtaining Ethical approval from Khyber medical university ethical approval committee vide letter no: KMU/IPDM/IEC/2023<u>24</u> dated August 2023. Study duration was Six months. Both males and females were included in the study, Age limit was 30 to 50 years. This study includes a total of n=89 subjects with 9 controls, 59 non-diabetic chronic periodontitis and 21 Diabetic chronic periodontitis individuals. Inclusion criterion includes, Patient diagnosed with chronic periodontitis with and without diabetes Following patients were excluded from the study, Recent periodontal treatment within the past 6 months, Pregnant women, Individuals with chronic conditions such as cancer, autoimmune disorders, infectious diseases, tooth loss, dry mouth, or oral ulcers were excluded, Patients who wore dentures or had dental prosthetics, Individuals with periodontitis types other than calculus-associated chronic periodontitis, such as aggressive periodontitis, periodontitis linked to systemic diseases, or necrotizing periodontitis, were not part of the study, Antibiotic usage in the last 3 months, Non cooperative individuals were excluded. Written Consent was obtained from the patients before enrolling in the study. The diagnosis for periodontitis was established on radiographic and clinical criteria used in 2018 by NCPD.[15] Patients with ≥4 teeth with ≥1 sites presenting a probing depth ≥3 mm, clinical attachment level ≥3 mm, as well as bleeding on probing at the same site were considered to have periodontitis and were selected, their clinical diagnosis was made, and the participant were informed of the relevance of the study. Participants were instructed to avoid from drinking and food and were called in the morning after clinical examination they assumed a relaxed sitting position on a dental chair with open eyes, gently tilting their heads forward. Saliva collection method describe by Francesca et al was used in this study.[16] Various periodontal parameters, including periodontal index (PI), bleeding on probing (BOP), and periodontal pocket depth (PPD), and clinical attachment loss (CAL), number of remaining teeth were meticulously recorded for each patient by using the Community Periodontal Index of Treatment Needs (CPITN) probe. Collection of saliva was done by simple drooling method. Saliva collection ensued using a simple drooling method into 15ml sterile Falcon tubes as described in an overview.[16] each tube was appropriately labeled and coded before immediate transfer to the laboratory for centrifuge in 30 minutes. After centrifugation the supernatant was transferred to Eppendorf tubes and stored in a refrigerator at -80°C at KMU Lab. Following the collection of all samples, and centrifuge, an enzyme-linked immunosorbent assay (ELISA) for IL-17α was performed. The Human IL-17α ELISA kit (Shanghai ideal medical technology Co. Ltd) was used to analyze the concentration of IL-17α in saliva samples. The manufacturer guidelines were followed in each and every

step. The concentration of IL-17A in the saliva were determined by comparing the average absorbance reading of each sample with the concentration in the assay standard curve. The results were expressed as pg/ml. the lower threshold for IL-17A were 0.5 respectively. The data was entered and analyzed using IBM SPSS 27 software. Independent samples t-test was used for comparisons between two groups. The ANOVA test was used to compare group means, standard deviation. P<0.05 was considered statistically significant. Graph pad prism was used for graphical work.

Results

Demographic details of the study by Gender, Age, Diabetic/Non-diabetic is provided in Table 1. Of the total 89 subjects with 9 controls and 80 chronic periodontitis patients were recruited in the study. Most of the participant were males. All the subjects were divided into three groups. Group A control (9 subjects both male and females), group B (59 subjects both males & females) non-diabetic chronic periodontitis, and group C (21Subjects both males & females) diabetic chronic periodontitis. In this study male subject were in greater number than females subjects. Male to female ratio was 3:2. Out of total 89 subjects with minimum age range was 26yr and the maximum age range was 63yr. 45-55 year age subject were the highest frequency of individuals participated in the study as summarize in Table 1.

The mean and standard deviation value of various periodontal parameters in diabetic/Non-diabetic CP group are summarized in Table 2. Mean± STD deviation of full mouth clinical attachment loss (CAL) in diabetic/ non-diabetic CP was observed 4.7± 1.3mm and 4.2± 1.1mm (P=<0.001), Bleeding on Probing (BoP) in diabetic/ non-diabetic CP was 50.24±25.11% and 44.24±21.03% (P=<0.003), whereas Periodontal depth (PD) observed in diabetic/ non-diabetic CP was 4.13± 1.04mm and 3.94.13± 0.95 (P=<0.001), and the mean of no of teeth remaining in both group was 19.7±3.40 and 22.37±4.6 (P=<0.001) respectively.

Table 1. Demographic details of the study

Subject's characteristics	N	Frequency	Percent	Cumulative Percent
Gender				
Male	52	58.4	58.4	100.0
Female	37	41.6	41.6	41.6
NDCP/ T2DCP				
NDCP	66	74.2	74.2	74.2
T2DM CP	23	25.8	25.8	100.0
Age				
26-35 years	10	10	11.2	11.2
36-45 years	31	31	34.8	34.8
46-55 years	35	35	39.3	39.3
56 & above	13	13	14.6	14.6
Total	89	89	100.0	100.0

NDCP= Non diabetic chronic periodontitis, T2DMCP= type 2 diabetic chronic periodontitis.

Table 2 Periodontal parameters of the subjects

Periodontal parameters	Diabetic CP	Non-diabetic CP	p-value
	Mean± STD deviation	Mean ±STD deviation	
CAL(mm)	4.7± 1.3	4.2± 1.1	<0.001
BOP (%)	50.24±25.11	44.24±21.03	<0.003
PD (mm)	4.13± 1.04	3.94.13± 0.95	<0.001
No of remaining teeth	19.7±3.40	22.37±4.6	<0.001

CAL= clinical attachment loss, BOP=Bleeding on probing, PD= Periodontal depth, CP= chronic periodontitis, STD= Standard deviation.

Table 3. Subjects' distribution on the basis of periodontal severity

Periodontal Severity	DM (yes/no)	N	% of Total N
Control	No	7	7.9%
	Yes	2	2.2%
	Total	9	10.1%
Mild	No	7	7.9%
	Total	7	7.9%
Moderate	No	37	41.6%
	Yes	8	9.0%
	Total	45	50.6%
Severe	No	15	16.9%
	Yes	13	14.6%
	Total	28	31.5%
Total	No	66	74.2%
	Yes	23	25.8%
	Total	89	100.0%

DM= Diabetes mellitus

Subject distribution on the basis of periodontal severity in controls, Non-diabetic CP and Diabetic CP patients are summarized in Table 3. Out of total 89, 9 was taken as control with no chronic periodontitis with n=7 (non-diabetic) and n=2 (diabetic). 80 periodontitis subjects were recruited in which 59 subjects were non diabetic chronic periodontitis and 21 with diabetic chronic periodontitis.

Salivary IL-17A levels between diabetic group and non-diabetic group shows no significant difference. P value <0.001 was observed in both groups. Mean value observed in Diabetic-CP are 9.2900pg/ml, with standard deviation value are 2.19024. While the mean value observed for non-diabetic chronic periodontitis are 8.3470pg/ml with standard deviation value 1.76798. The mean ±Std value observed for Diabetic-CP group is higher from Non-diabetic CP group as shown Table 4.

Table 4 ELISA levels of IL-17A in (pg/ml) between diabetics and non-diabetics

	N	Mean	Std. Deviation	Std. Error Mean	P value
ND CP	66	8.3470	1.76798	.21762	<0.001
Diabetic CP	23	9.2900	2.19024	.45670	<0.001

NDCP=Non diabetic chronic periodontitis.

Figure 1 simple box plot providing information on concentration of salivary IL-17A among diabetic and non-diabetic chronic periodontitis individuals. A high concentration was observed in Diabetic CP.

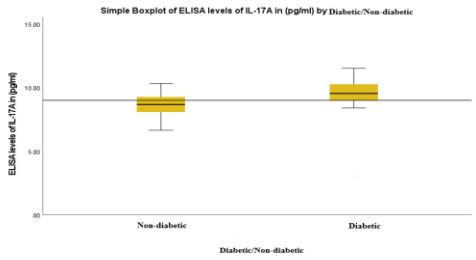

Figure 1: A box plot chart presenting salivary Elisa IL-17A levels among diabetic and non- diabetic.

The Mean and standard deviation value of salivary Interleukin-17Alpha (IL-17A) in individuals with different oral hygiene states distinguished by diabetic and non-diabetic status are summarized in Table 4. In both diabetic and non-diabetic groups, the mean salivary IL-17A concentrations, along with their standard deviations, show a consistent upward trend as

periodontal disease becomes more severe. This indicates a clear association between elevated IL-17A levels and worsening periodontal status in both populations. A similar pattern is evident among diabetic participants, where the mean IL-17A levels reach 8.96 pg/mL in moderate cases and 10.43 pg/mL in severe cases. Notably, diabetics with severe periodontal disease exhibit the highest IL-17A values recorded across all study groups. A statistically significant difference was observed among all categories, with $p < 0.001$ in table 5.

When associating these findings to control groups, it is clear that both non-diabetic and diabetic controls have considerably lower IL-17A levels, with means of 4.07 pg/ml and 3.18 pg/ml, respectively. The sample sizes vary across the groups, ranging from as few as 2 in the control diabetic group to as many as 37 in the non-diabetic moderate group. The p-values related with each group are all less than 0.001, signifying that the alterations in mean IL-17A levels are statistically significant when associated within each group.

Table 5. Salivary IL-17A levels in diabetic/non diabetics based on severity.

	Oral Hygiene Status	**N**	**Mean**	**STD. Deviation**	**P values**
ND-CP	Mild CP	7	7.5686	.50759	<0.001
	Moderate CP	37	8.6251	.55490	<0.001
	Severe CP	15	10.0173	.79095	<0.001
D-CP	Moderate CP	8	8.9600	.39250	<0.001
	Severe CP	13	10.4323	.99292	<0.001
Control					
ND-NCP		7	4.0757	.92410	<0.001
D-NCP		2	3.1850	.50205	<0.001

CP= Chronic periodontitis, ND-CP= non-diabetic chronic periodontitis, D-CP=Diabetic chronic periodontitis, ND-NCP=non-diabetic non periodontitis, D-NP= diabetic- non periodontitis.

The Table 6 presents an Independent T test salivary analysis of ELISA levels of the cytokine IL-17A in (pg/ml) across gender. In males, the mean salivary IL-17A concentration is 8.60 pg/ml with a SD of 2.11, representing some variability within this group. The standard error of the mean is 0.29, which provides an estimate of the accuracy of the mean IL-17A level for males. For Females, the mean salivary IL-17A levels is 8.5724 pg/ml with a standard deviation of 1.62806, slightly lower than the male, suggesting that the female IL-17A levels are somewhat less variable than the males. The standard error of the mean for females is 0.26765, which is also slightly lower than that of the males, indicating a marginally higher precision in the mean estimate for females. The P-value observed for male was 0.94, for female was 0.938.

Table 6. An independent sample T Test of Salivary IL-17A levels on gender basis.

Hormone	**Gender**	**N**	**Mean**	**Std. Deviation**	**P value**
ELISA levels of IL-17A in (pg/ml)	Male	52	8.6037	2.11641	0.94
	Females	37	8.5724	1.62806	0.938

Figure 2 is a simple box plot showing ELISA IL-17A levels across male and female in the study. In males, the mean salivary IL-17A concentration is 8.60 pg/ml with a SD of 2.11, representing some variability within this group. For Females, the mean salivary IL-17A levels is 8.5724 pg/ml with a standard deviation of 1.62806, slightly lower than the male, suggesting that the female IL-17A levels are somewhat less variable than the males.

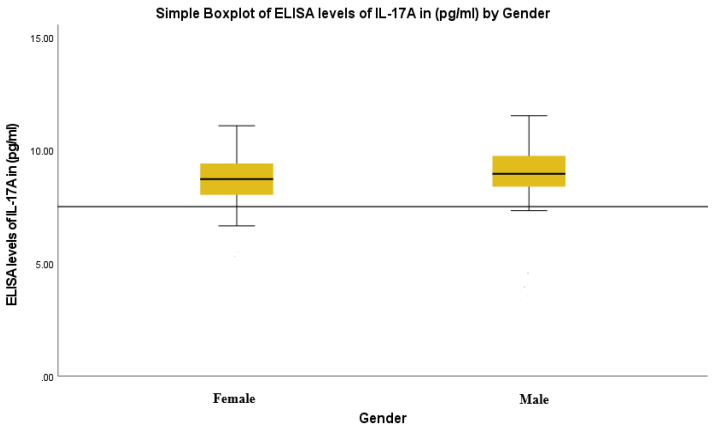

Figure 2: Box plot presenting ELISA IL-17A levels on Y-axis and Gender distribution on X-axis.

Salivary IL-17A levels between diabetics and non-diabetics chronic periodontitis individuals their mean values, standard deviation, mean difference and p value <0.001 are given in Table 4. Salivary IL-17A levels between diabetic and non-diabetics shows no significant difference. While a higher mean was observed in the diabetic group as compared to non-diabetic group. Table 6. However, according to periodontal status, a high level of salivary IL-17A was observed in chronic periodontitis in contrast to control with no periodontitis. According to periodontal status a high level of IL-17A was observed in more advance stage of periodontal disease as compared to initial or in mild stage of chronic periodontitis as shown in Table 7.

Table 7. Salivary IL17-A levels in (diabetic &non-diabetic) and according to severity

DM severity	Periodontal	N	Mean	Std. Deviation	P Value
	Control	7	4.0757	0.92410	<0.001
	Mild	7	7.5686	0.50759	
	Moderate	37	8.6251	0.55490	<0.001
	Severe	15	10.0173	0.79095	
	Total	66	8.3470	1.76798	<0.001
NDCP					
					<0.001
	Control	2	3.1850	0.50205	<0.001
	Moderate	8	8.9600	0.39250	
	Severe	13	10.4323	0.99292	<0.001
DCP	Total	23	9.2900	2.19024	
					<0.001

NDCP= Non diabetic chronic periodontitis, DCP= Diabetic chronic periodontitis.

Salivary ELISA IL-17A concentration in different stages of periodontal diseases in male and females are summarize in figure 3. A rise in IL-17A levels were observed as the severity of periodontitis increase. However, in males salivary IL-17A concentrations were exaggerated as compared to female in severe and moderate stage of the disease.

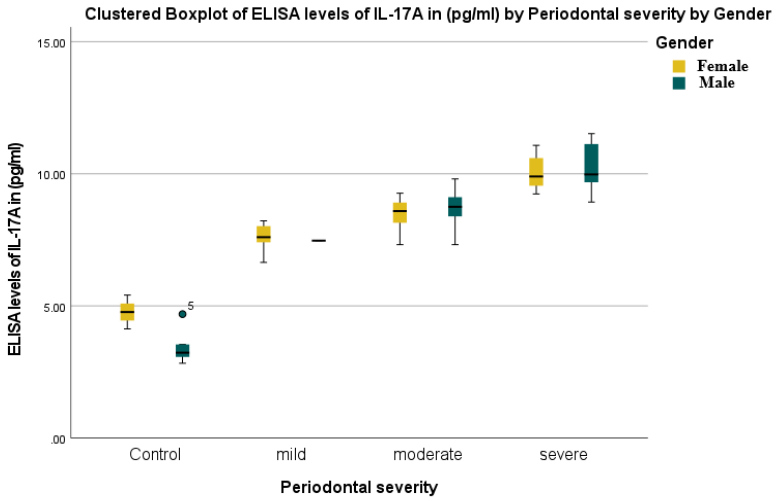

Figure 3: A clustered Boxplot presenting Salivary Elisa IL-17A levels on the basis of severity and Gender.

Figure 4 summarizes Salivary IL-17A concentration at different stages of periodontal diseases in Diabetic/Non-diabetic groups. A rise in IL-17A levels were observed as the disease progress to advance stage in both diabetic and non-diabetic. In diabetic salivary IL-17A concentrations were recorded high as compared to non-diabetic in severe and moderate stage of the disease. However in control the levels were slightly high in non-diabetic as compared to diabetic.

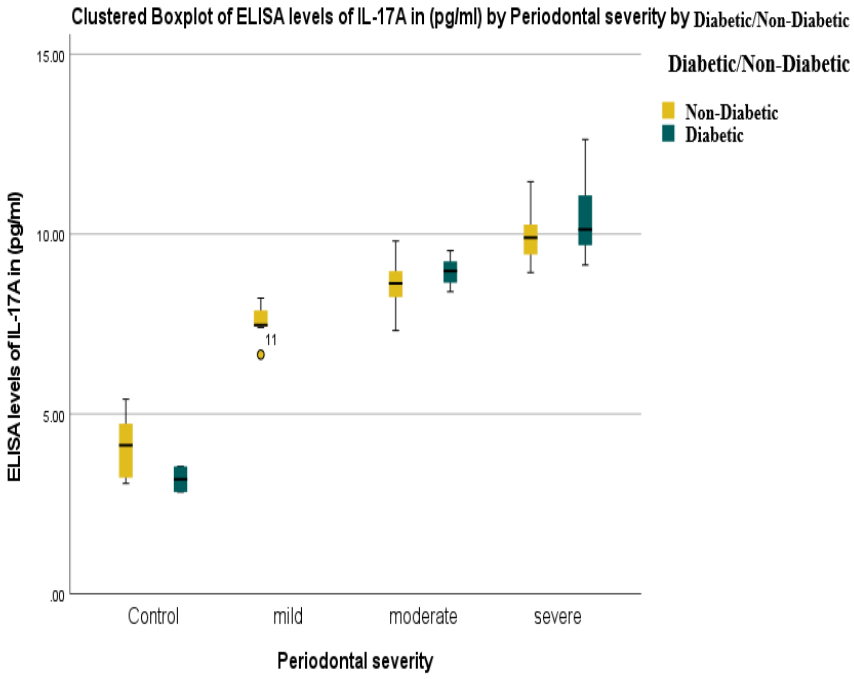

Figure 4: A clustered Boxplot presenting Salivary Elisa IL-17A levels on the basis of severity and diabetics.

Discussion

Our study demonstrated a strong association between salivary IL-17A concentrations and the severity of periodontitis, as shown in Tables 5 and 7 and Figures 13 and 14. Individuals with periodontitis exhibited markedly elevated IL-17A levels compared with those without the disease, and this trend was consistent across the control group, the type 2 diabetes mellitus group, and the non-diabetic chronic periodontitis group. Moreover, IL-17A levels increased progressively with disease severity. These findings align with those of Marta Relvas and colleagues, who also reported elevated IL-17A levels in individuals with more advanced stages and grades of periodontitis [17] this research found no significant correlation of salivary IL-17A levels between diabetic chronic periodontitis group and non-diabetic chronic periodontitis group.

The Mean and standard deviation value of salivary Interleukin-17Alpha (IL-17A) in individuals with different oral hygiene states distinguished by diabetic and non-diabetic status are summarized in Table 4. There was no significant difference in salivary IL-17A levels between diabetic and non-diabetic participants. In both groups, the mean and standard deviation of salivary IL-17A increased progressively with the severity of periodontal disease. This pattern indicates that IL-17A levels are strongly associated with periodontal disease severity, regardless of diabetic status. Our findings align with those of Suteera Techatanawat et al., who also observed a significant relationship between elevated salivary IL-17A concentrations and worsening periodontal conditions, independent of glycemic control.[18] however another reasons why salivary IL-17A levels did not correlate with glycemic status can be described as follows. Although it is widely acknowledged that glycemic status influences periodontal tissue inflammation, this does not always manifest as an increase in salivary IL-17A levels. Gursoy et al. reported no significant difference in salivary IL-17 levels between diabetic participants with well-controlled (HbA1C < 7) and poorly-controlled (HbA1C ≥ 7) glycemic status.[19] They reported an association between periodontal probing depth and salivary IL-17 levels that appeared to be independent of glycemic status. Although individuals with poorly controlled diabetes exhibited more severe periodontal destruction, the authors suggested that factors other than IL-17 might also contribute to periodontal tissue damage in these patients. In our study, we assessed salivary IL-17A concentrations in individuals with chronic periodontitis using saliva samples. This method is straightforward, non-invasive, and convenient for both patients and clinicians. Our investigations observed IL-17A expression in all groups. This research highlights the advantage of using saliva samples for periodontal diagnostics, as we observed that levels of IL-17A in saliva can indicate the severity of periodontitis. While gingival crevicular fluid (GCF) has traditionally been used in periodontal studies, its collection necessitates specialized training.[20]

Our current investigation compared the cytokine IL-17A levels in gender. We identified no significant difference among both gender. Male to female ratio was 3:2. In males, the mean salivary IL-17A concentration is 8.60 pg/ml with a SD of 2.11, representing some variability within this group while in females, the mean salivary IL-17A levels is 8.5724 pg/ml with a standard deviation of 1.62806, slight elevated level is observed in participant in the study as shown in Table 6 & Figure 13. In accordance to our investigation a study by S.Reichert et al suggest that gender may introduce confounding variables in periodontitis research.[21] However MACHION L et al indicate that the higher prevalence among males is primarily linked to individual oral hygiene practices.[22] This implies that variations in oral care routines between genders could contribute to disparities in periodontal health outcomes. However, it's important to consider multifaceted factors such as hormonal differences and genetic predispositions that may also play a role in the observed gender disparities in periodontal disease prevalence. Further research is needed to elucidate the complex interplay between gender, oral hygiene habits, and biological factors influencing periodontal health.

Salivary IL-7A has been suggested as a biomarker for chronic periodontitis and it has also been associated with the pathophysiology of type 2 diabetes. Salivary IL-17A levels were observed in higher amount mostly in individuals having advance stage of disease. Participants with following protocols of oral hygiene practices in both diabetic and non-diabetic chronic periodontitis group show a mean of 8.96 (pg/ml) in the diabetic group as compared to non-diabetic chronic periodontitis group with mean of 8.62(pg/ml), less than the diabetic chronic periodontitis. While the mean value for severe cases in diabetic & non-diabetic chronic periodontitis group are 10.43(pg/ml) and 10.01(pg/ml) (Table 5). Stimulatingly, the IL-17A levels in the diabetic group with severe oral health issues are the highest documented among all groups.

We acknowledge several limitations in this study. The relatively small sample size resulted in a non-normal data distribution. Noticeable variations in age and ethnicity among the patient groups may have introduced potential confounding effects. Furthermore, some participants with type 2 diabetes were already on glucose-lowering therapy and demonstrated well-controlled blood sugar levels. To gain clearer insights into how glycemic status influences cytokine profiles, future studies should consider including individuals with poorly controlled diabetes.

Conclusion

In conclusion, IL-17A has a significant role in chronic periodontitis. Salivary IL-17A levels have been linked to severity of chronic periodontitis. This suggests a relationship between the severity of oral health problems and IL-17A levels in both diabetics and non-diabetics.
Our experiment suggests that salivary IL-17alpha could be employed as a diagnostic marker, providing a non-invasive method for determining the severity of periodontal disorders

Recommendations

A further assessment could be conducted by looking into serum IL-17A levels. People with type 1 diabetes might be studied for it. To clarify the dynamic variations in salivary IL-17A levels over time and their implications for illness prognosis and treatment outcome, more longitudinal research is necessary. Further investigation is required to determine whether tooth paste containing IL-17A inhibitors may be applied topically to treat periodontitis and when best to do so.

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