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Effects of Non Surgical Periodontal Therapy on LL-37 Cathelicidin Levels in Gingival Crevicular Fluid from Chronic Periodontitis Patients with and Without Type 2 Diabetes Mellitus

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ABSTRACT:
Background: Chronic periodontitis (CP) and Diabetes Mellitus (DM) share common mechanisms of pathogenesis and hence can affect the expression of an antimicrobial peptide cathelicidin LL-37. Thus the study aimed to evaluate effect of nonsurgical periodontal therapy (NSPT) on levels of cathelieciddines and clinical parameters in GCF of CP patients with or without type-2 DM.
Methods: 40 subjects were divided into 2 groups as Group 1- those with CP and Group 2 - T2DM plus CP. GCF samples were collected. Clinical parameters were measured at base line and at 3 months after performing NSPT.
Results: At baseline in group 1 the GCF LL – 37 was 8.86±1.17 which was lesser as compared to group 2 (16.25±2.79). The LL – 37 levels were lower in group 1 (2.465±0.87) as compared to group 2 (4.400±1.23)at 3 months follow up. A moderate positive correlation between CAL and LL-37 ($r = 0.384$, $p = 0.014$) was noted indicating that as one parameter increases the other parameter also increases. A multiple regression analysis to predict LL-37 from variables showed that CAL, HbA1cand Group 2 statistically significantly predicted LL-37.
Conclusion: The results highlighted that following the non-surgical periodontal therapy a considerable decrease in the periodontal inflammation was noted suggesting the efficiency of the treatment in periodontal disease.

KEYWORDS: Type -2Diabetes Mellitus, LL-37 Cathelicidins, Chronic periodontitis, Non-surgical periodontal therapy

I. INTRODUCTION

Periodontal disease, is a widespread inflammatory condition of the supporting tissues of the teeth, leading to progressive tissue destruction and potentially tooth loss if untreated. It is the sixth most common oral disease manifested by individuals worldwide, with an overall prevalence of 11.2% (1). The condition has been driven by a complex interface between bacterial pathogens and the host's immune response and thus has been linked to both oral manifestations and systemic health issues (2). Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder characterized by hyperglycemia and insulin resistance, is known to both increase susceptibility to and exacerbate the progression of periodontal disease(3,4). Chronic hyperglycemia in T2DM patients fosters a pro-inflammatory environment, aggravating the immune response to periodontal pathogens. Research has consistently shown a bidirectional relationship between diabetes and periodontal disease, where each condition can negatively impact the other, complicating disease management for affected patients (3–5).

One important aspect of the host immune response in periodontal disease is the production of antimicrobial peptides (AMPs), including LL-37, a member of the cathelicidin family. LL-37 plays a critical role in the innate immune response by directly killing pathogens, modulating inflammation, and promoting tissue repair(6,7). In the context of periodontal disease, LL-37 is secreted in gingival crevicular fluid (GCF) and is believed to contribute to the body's natural defense against bacterial colonization in periodontal pockets. Additionally, LL-37 modulates immune cell recruitment and cytokine release, potentially influencing the inflammatory balance within the periodontal tissues (8). This makes LL-37 a

potential biomarker for periodontal health and a mediator of disease progression, especially in individuals with compromised immune systems, such as those with T2DM.

Among the various modalities available for treating periodontitis, non-surgical periodontal therapy (NSPT) has been considered as an effective measure in treating periodontitis. NSPT includes scaling and root planning which tends to mechanically remove the bacterial deposits and is considered as a standard approach to reduce this microbial load and control inflammation(9). Despite the established effectiveness of NSPT in managing periodontal disease, patient outcomes can vary significantly, especially in individuals with systemic conditions such as type 2 diabetes mellitus (T2DM), which is known to exacerbate periodontal inflammation and complicate disease progression(10).

In addition, despite the recognized importance of LL-37 in immune defense, there remains a significant gap in understanding how LL-37 levels respond to non-surgical periodontal therapy (NSPT), especially in chronic periodontitis patients with and without T2DM. Existing studies have predominantly focused on clinical outcomes of NSPT, such as reductions in probing depth and improvements in clinical attachment levels(11–13). Less attention has been given to the biochemical and immunological shifts, such as changes in LL-37, that may underpin these clinical improvements(14). Furthermore, it is unknown whether the diabetic status of patients affects LL-37 modulation following periodontal therapy. Given the altered immune response in diabetic patients, understanding whether NSPT can effectively restore LL-37 levels or modulate its activity in these individuals is critical. Thus the study aims to addresses these gaps by investigating the effects of NSPT on LL-37 levels in the GCF of chronic periodontitis patients, both with and without T2DM.

II. METHODOLOGY

A Pre and post interventional study was conducted for a period of 1 year between September 2023 and August 2024 on patients reporting to the out-patient section of theDepartment of Periodontology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences. Ethical clearance was obtained from the institutional review board. 40 subjects were selected based on the inclusion and exclsuion criteria and divided into 2 groups.

Inclusion criteria:

- Chronic periodontitis subjects as defined by CDC (at least one site with pocket depth ≥4mm and CAL ≥ 3mm)
- Subjects with HbA1c ≥ 6.5% for periodontitis with type 2 diabetes group
- Subjects with RBS ≤ 140mg/dL for periodontitis without type 2 diabetes group
- Patients between 35-60 years.
- Subjects with ≥20 completely erupted teeth.

Exclusion criteria:

- Subjects with systemic conditions other than Type 2 Diabetes Mellitus
- Pregnant and lactating subjects
- Former/ current smokers
- History of periodontal intervention within the last 6 months
- Antibiotic treatment within the last 3 months.

Group 1 consisted of 20 patients with chronic periodontitis (CP) and Group 2 consisted of 20 patients with chronic periodontitis and Type-2 Diabetes Mellitus (DM). The values of HbA1c were utilised as diagnostic criteria for diabetes mellitus in this investigation since they indicated an individual's total glycaemic level over three months. An HbA1c level of 6.5% was recommended as the cut point for diagnosing diabetes.

A written informed consent was obtained from all the study participants. All of the participants underwent a full-mouth periodontal examination using a sterile Williams's probe and mouth mirror. For each participant in Group 1 and 2, the area with the greatest Clinical attachment loss (CAL), probing pocket depth (PPD) was recorded and gingival index (GI), plaque Index (PI) and radiographic confirmation of bone loss was done. After clinical examination, the individuals were instructed to swiftly rinse their mouth with water in order to remove loosely adhered soft debris from their teeth. The areas were gently dried using compressed air and were isolated with sterile cotton rolls. To prevent contamination and blockage of the microcapillary pipette, supra gingival plaque was eliminated. GCF was collected by placing a 1 – 5 microliter calibrated volumetric microcapillary pipette extra – crevicularly for 5 – 20 minutes without touching the marginal gingiva. From each test area, a standardized volume of 2 – 3 microliter was collected. The collected GCF was immediately transferred to vials containing 100 microliter phosphate buffer saline and the samples were stored at -80 degree Celcius. Samples were investigated using commercially available enzyme-

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linked immunosorbant assay (ELISA) for LL-37 levels.

Non-surgical periodontal therapy was provided to patients in both the groups. It involved removal of supragingival plaque and calculus. Scaling and root planing were performed in one session using hand and ultrasonic devices under local anaesthesia (2% lignocaine hydrochloride with 1: 80,000 adrenaline).

Patients were recalled after 3 months and GCF sample collection was repeated using the same procedure and assayed as per manufacturer's instructions.

Statistical analysis

Statistical package for social sciences (SPSS) for windows version 21.0 released 2021, Armonk NY,IBM Corpwas used to analysis the data.Independent Student t Test was used to compare the mean values of clinical parameters between two groups.Pearson's correlation test was used to estimate the relationship between GCF cathelicidines levels andthe clinical parameters in each study group.Stepwise Multiple Linear Regression Analysis was performed to predict the expressions of cathelicidinesby using clinical parameters as independent variables in each study group.The level of significance [p-Value] was set at $P<0.05$.

III. RESULTS

The mean PI scores in both group 1 and group 2 subjects at baseline were 2.55±0.51 which shows that both the groups were comparable at baseline. At 3 months follow up the mean PI score decreased to 1.25±0.55 in group 1 and in group 2 it decreased to 0.75±0.55. The mean PI score was lower in group 2 as compared to group 1 and this difference was statistically significant (p=0.007) (Table 1).

The mean GI score in both group 1 and group 2 was 2.55±0.51 at baseline. At 3 months follow up the GI score decreased to 1.25±0.55 in group 1 and in group 2 it was 0.90±0.64. The mean GI score was lower in group 2 as compared to group 1 but this difference was not statistically significant (p=0.072) highlighting that there was no difference in the GI scores between the 2 groups (Table 1).

At baseline,the mean BOP score in group 1 was 41.58±8.59which was lower as compared to group 2 (51.03±14.09). This difference between the groups was statistically significant (p=0.015). At 3 months follow up, the BOP scores decreased in both the groups. In group 1 it was 22.14±5.06 which was higher as compared to group 2 (20.89±7.12). This difference was not statistically significant (p=0.527) showing that there was no difference in BOP scores between the 2 groups(Table 1).

At baseline, the mean PPD in group 1 was 7.36±0.89 and in group 2 it was 7.36±1.02 depicting that there was no difference PPD between the 2 groups (p=0.987). At 3 months follow up, the probing pocket depth decreased in both the groups.In group 1 the PPD was 4.37±0.86 which was lesser than in group 2 (4.77±0.98). However, this difference between the 2 groups was statistically not significant (p=0.180)(Table 1).

At baseline, the mean CAL in group 1 was 2.17±0.55and in group 2 it was 2.82±0.49 depicting a higher CAL score in group 2. This difference between the 2 groups was statistically significant (p=0.000). At 3 months follow up, the mean CAL decreased in both the groups. In group 1 the mean CAL was 1.52±0.69 which was lesser than in group 2 (2.14±0.52). This difference between the 2 groups was statistically significant (p=0.003)(Table 1).

The salivary LL – 37 levels in group 1 was 8.86±1.17 which was lesser as compared to group 2 (16.25±2.79). This difference between the groups was statistically significant (p=0.000). At 3 months follow up, the LL – 37 levels decreased considerably in both the groups wherein in group 1 it was 2.465±0.87 and in group 2 it was 4.400±1.23. The LL – 37 levels were lower in group 1 as compared to group 2 even at 3 months follow up. This difference between the 2 groups was statistically significant (p=0.000)(Table 1).

Table 1: Comparison of Periodontal Parameters and GCF Levels of LL-37 between the Two Groups

Clinical Data		Group 1 Chronic Periodontitis (Mean±SD)	Group 2 Chronic Periodontitis + Diabetes-2 (Mean±SD)	p value
Mean PI	Baseline	2.55±0.51	2.55±0.51	1.000
	3 Months	1.25±0.55	0.75±0.55	0.007**
Mean GI	Baseline	2.55±0.51	2.55±0.51	1.000
	3 Months	1.25±0.55	0.90±0.64	0.072

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Mean BOP (%)	Baseline	41.58±8.59	51.03±14.09	0.015*
	3 Months	22.14±5.06	20.89±7.12	0.527
Mean PPD	Baseline	7.36±0.89	7.36±1.02	0.987
	3 Months	4.37±0.86	4.77±0.98	0.180
Mean CAL	Baseline	2.17±0.55	2.82±0.49	0.000**
	3 Months	1.52±0. 69	2.14±0.52	0.003**
LL – 37 (ηg/mL)	Baseline	8.86±1.17	16.25±2.79	0.000**
	3 Months	2.465±0.87	4.400±1.23	0.000**
PI- Plaque index, GI- Gingival index, BOP- Bleeding on probing, PPD- Probing pocket depth, CAL- Clinical attachment level **Highly Significant *Significant				

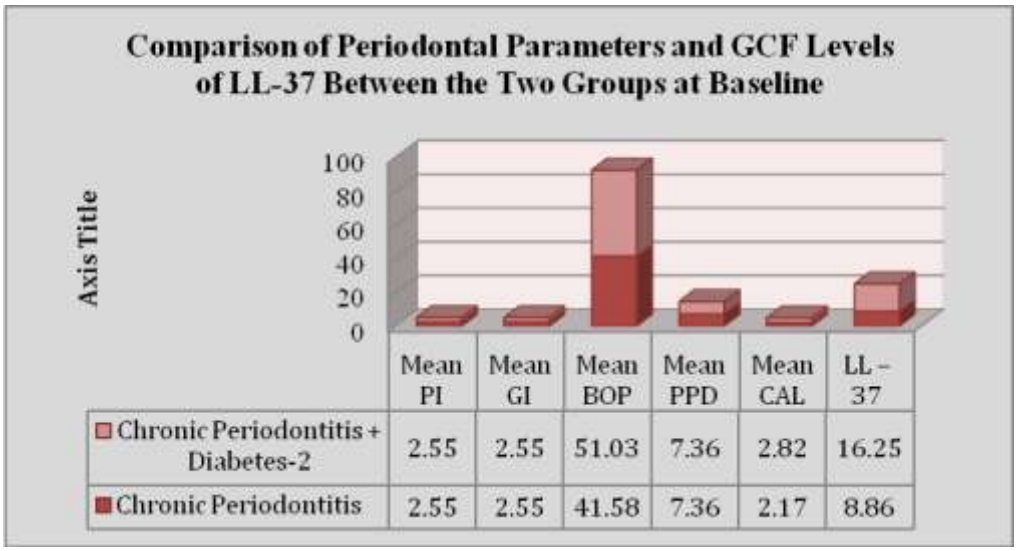

Figure 1: Comparison of Periodontal Parameters and GCF Levels of LL-37 between the Two Groups at Baseline

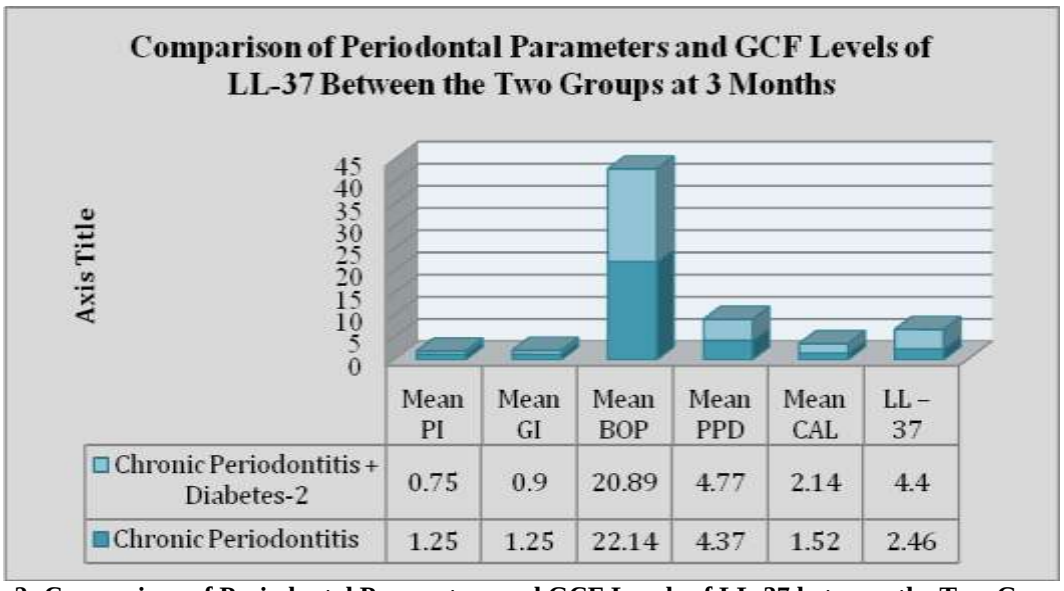

Figure 2: Comparison of Periodontal Parameters and GCF Levels of LL-37 between the Two Groups at 3 Months

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The correlation between gender, salivary levels of periodontal parameters in both groups was assessed using Pearson's correlation coefficient. It was found that gender had a statistically significant negative correlation with BOP (r = -0.359, p = 0.023) indicating that as one variable increases, the other tends to decrease. There were no statistically significant correlations between gender and the other parameters.Plaque index had a strong positive correlation with gingival index (r = 0.904, p = 0.000) indicating that as plaque index increased gingival index also increased. BOP showed a significant negative correlation with only gender (r = -0.359, p = 0.023). With respect to PPD, no significant correlations with any parameters were noted. A moderate positive correlation between CAL and LL-37 (r = 0.384, p = 0.014) was noted indicating that as one parameter increases the other parameter also increases (Table 2).

Table 2: Comparison of Gender, GCF Levels of Ll-37 and Periodontal Parameters in Both Groups

		Gender	PI	GI	BOP	PPD	CAL	LL – 37
Gender	r	1	0.256	0.144	-0.359(*)	0.296	-0.117	0.172
	p value		0.110	0.377	0.023	0.064	0.473	0.287
PI	r	0.256	1	0.904(**)	-0.176	-0.018	-0.101	-0.045
	p value	0.110		0.000	0.276	0.911	0.537	0.785
GI	r	0.144	0.904(**)	1	-0.209	-0.094	-0.086	0.055
	p value	0.377	0.000		0.196	0.565	0.600	0.736
BOP	r	-0.359(*)	-0.176	-0.209	1	0.138	0.010	-0.284
	p value	0.023	0.276	0.196		0.397	0.949	0.076
PPD	r	0.296	-0.018	-0.094	0.138	1	0.138	0.101
	p value	0.064	0.911	0.565	0.397		0.395	0.535
CAL	r	-0.117	-0.101	-0.086	0.010	0.138	1	0.384(*)
	p value	0.473	0.537	0.600	0.949	0.395		0.014
LL – 37	r	0.172	-0.045	0.055	-0.284	0.101	0.384(*)	1
	p value	0.287	0.785	0.736	0.076	0.535	0.014	

** Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

A multiple regression analysis was done to predict LL-37 from study variables. CAL statistically significantly predicted LL-37 (β=0.204, p=0.048). HbA1c statistically significantly predicted LL-37 (β=0.480, p=0.036). Group 2 statistically significantly predicted LL-37 (β=0.731, p=0.032). All other variables added no statistical significance to the prediction (p> 0.05)(Table 3).

Table 3: Stepwise Multiple Linear Regression Analysis

Independent Variable	Dependent Variable (LL[ηg/mL])		
	β	SE	p value
Constant	0.201	1.323	0.880
PI	0.266		0.740
GI	0.294		0.680
BOP	-0.031		0.328
PPD	-0.085		0.677
CAL	0.204		0.048*
HBA1C	0.480		0.036*
Group 1	0.442		0528
Group 2	0.731		0.032*

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IV. DISCUSSION

Type 2 DM negatively affects the health of the periodontal tissues exaggerating the destruction of the periodontal tissues. Periodontal inflammation conversely can worsen the glycemic control in individuals creating a vicious cycle of local and systemic inflammation(15). Among the various treatment modalities available for periodontitis, non -surgical periodontal therapy (NSPT) has been considered as an effective measure(9). Despite the established effectiveness of NSPT in managing periodontal disease, patient outcomes can vary significantly, especially in individuals with systemic conditions such as T2DM, which is known to exacerbate periodontal inflammation and complicate disease progression(10).

One important aspect of the host immune response in periodontal disease is the production of antimicrobial peptides (AMPs), including LL-37, a member of the cathelicid in family. Given the increased severity of periodontal disease in diabetic patients, it is crucial to investigate whether diabetes alters LL-37 levels in GCF and how these levels respond to periodontal therapy. While there is substantial research on LL-37's role in various infectious and inflammatory diseases, its specific role in periodontal disease, particularly in the context of systemic conditions like T2DM, is not yet fully elucidated(16).

In the present study it was found that the plaque index and gingival index scores following the NSPT showed a decrease in both the groups at follow up, highlighting the effectiveness of the intervention.

A study by Singh S etalso found similar results wherein patients who underwent NSPT had lower plaque and gingival index scores at follow up as compared to the control group who did not undergo any intervention(17). NSPT targets the removal of deposits of plaque from both supragingival and subgingival areas, disrupting the biofilm that harbors pathogenic bacteria. By thoroughly cleaning these areas, plaque accumulation decreases, contributing to a lower plaque score and improved health of the gingival tissues(18).

In addition, the present study also showed that the mean plaque index and gingival index scores were lower in patients with CP with Type-2 DM as compared to patients with CP at follow up. Contrary to our findings,a study by GD G et alfound that subjects with CP had a plaque score of 1.40±0.31and subjects with CP and DM had a plaque score of 1.86±0.12 which was higher than the other group(18). A study by Singh et al found that the gingival index scores was significantly lower in patients with only chronic periodontitis as compared to patients with chronic periodontitis and DM(17). The higher plaque and gingival index scores in patients with DM and periodontitis may be due to the impaired immune response and delayed healing in diabetic patients. In contrast, our study showed lower plaque scores in the diabetic group, which might be explained by more frequent follow-up care, greater adherence to oral hygiene practices, or better glycemic control among the diabetic participants in our sample(19).

The present study showed that the mean bleeding on probing score decreased at 3 months follow up period in both the groups. Similar findings were foundwherein among the several periodontal parameters assessed BOP was found to decrease at all the follow ups but the decrease was not significant(20).The present study showed that, the BOP was higher in patients with DM and CP as compared to patients with only periodontitis but was not statistically significant. A study by Zainab et al which assessed the periodontal parameters in individuals with chronic periodontitis with type 2 DM also showed that BOP was observed in both the groups irrespective of the presence of DM or not(19). These findings highlight the fact that NSPT facilitates the decrease in bacterial load and inflammation, thus increasing the integrity of the gingival tissues and thus the gums tend to heal reducing the bleeding of probing(20).

In the present study, the probing depth decreased at the 3 month follow up visit following NSPT. Similar results were found in various studies by wherein following NSPT a reduction in the PPD scores were noted at subsequent follow up visits(17,20,21).The probing depth and CAL in patients with CP was lesser as compared to individuals with both DM and CP. This finding is in contrary to a study by GD et al wherein the patients with chronic periodontitis had a higher probing pocket depth and CAL as compared to patients with DM and CP (18). Following NSPT, as the bacterial load reduces, the inflammation subsides, leading to tissue reattachment and a reduction in pocket depth and CAL, thus reflecting a successful therapeutic response in both diabetic and non-diabetic patients (22).

In the present study, it was found that at 3 months follow up the LL–37 levels decreased considerably in both the groups after NSPT and it was significantly lower in group 1 as compared to group 2. In a similar study by Xiao et al it was found that type 2 DM patients having moderate or severe CP had higher levels of LL-37(16). Another study byZainab et al showed that LL-37

concentrations were higher in patients with both periodontitis and DM when compared to patients who had only chronic periodontitis(19). These findings could be due to the shared impact of inflammatory factors (systemic and local) in patients with both DM and chronic periodontitis. In addition, the condition of hyperglycemia in type 2 DM promotes the production of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6, which further stimulate the production of LL-37 due to the body's response to infection and tissue damage (16).

On assessing the correlation of the various parameters in our study, gender had a statistically significant negative correlation with BOP ($r = -0.359$, $p = 0.023$). Plaque index had a strong positive correlation with gingival index ($r = 0.904$, $p = 0.000$). With respect to PPD, no significant correlations with any parameters were noted. A moderate positive correlation between CAL and LL-37 ($r = 0.384$, $p = 0.014$). A study byZainab et al showed that PI had a strong positive correlation with age, LL-37, HbA1c, PPD and CAL(19).

On analysing LL-37 from various variables, it was found that CAL, HbA1c and group 2 variable statistically significantly predicted LL-37. A study byZainab et al showed that age significantly predicted LL-37 ($\beta=8.775$, $F= 21.127$, $p <0.001$)(19). CAL is a critical indicator of periodontal disease severity, and its relationship with LL-37, a key antimicrobial peptide in innate immunity, highlights the role of periodontal inflammation in influencing systemic antimicrobial activity. Similarly, HbA1c, a marker of long-term glycemic control, links metabolic status with immune regulation, as hyperglycemia can impair immune responses and exacerbate periodontal inflammation (16). The significance of group 2 variables further underscores the complex interaction between various systemic and local factors in predicting LL-37 levels.

The study had certain limitations that should be acknowledged. Firstly, the sample size was relatively small, which may limit the generalizability of the findings to a broader population. A larger sample size would enhance the statistical power and provide more robust conclusions. Secondly, the duration of the follow up was small, which could restrict the assessment of sustained effects of periodontal therapy on LL-37 levels over time. Variability in patient compliance with oral hygiene practices following non-surgical periodontal therapy could also influence the outcomes and introduce bias. Furthermore, potential confounding factors, such as variations in systemic inflammation, medication use, and individual metabolic control in diabetic patients, may not have been fully accounted for, possibly influencing the study results. Finally, the study did not explore other biomarkers of immune response or inflammation that could provide a more comprehensive understanding of the effects of periodontal therapy.

V. CONCLUSION

The results highlight that following the non-surgical periodontal therapy a considerable decrease in the periodontal inflammation was noted suggesting the efficiency of the treatment in periodontal disease. In addition, the decrease in LL-37 marker among both the study groups showed that it could be a significant biomarker in the progress of periodontal disease.

A longitudinal study design with extended follow-up periods would advance the generalizability of the results, allowing for better understanding of the effects of periodontal treatment across different demographic groups and provide perceptions into the long-term effects of non-surgical periodontal therapy on LL-37 levels, including potential relapse or sustained improvements in immune response. Stratifying patients based on the severity of diabetes or metabolic control could reveal more nuanced outcomes. By addressing these areas, future research can build a more comprehensive understanding of the role of LL-37 in periodontal health and disease, as well as the impact of therapy in diabetic and non-diabetic populations.

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Fig 1 Collection of GCF sample

Fig 2. Measurement of PPD at Baseline

Fig 3. Measurement of PPD at 3-month follow-up