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CLINICAL RESEARCH:

Gingival Crevicular Fluid and Salivary Expression Levels of IL-23 And IL-27 in Periodontal Health and Disease

Fluido crevicular gingival y niveles de expresión salival de IL-23 e IL-27 en salud y enfermedad periodontal

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ABSTRACT: Periodontal disease is a chronic inflammatory condition marked by the destruction of the supporting apparatus of the tooth. The pathogenesis is largely determined by an imbalance between the pro-inflammatory and anti-inflammatory mediators. IL-23, being pro-inflammatory in nature, contributes to tissue inflammation and deregulation through the production of IL-17. On the other hand, IL-27 exerts an anti-inflammatory effect by regulating the immune response by inhibiting IL-17. The current study aimed to assess IL-23 and IL-27 levels in gingival crevicular fluid (GCF) and saliva in periodontal health and disease. Forty systemically healthy subjects were allocated into three groups: healthy (Group A, n=10), gingivitis (Group B, n=15), and periodontitis (Group C, n=15). Clinical parameters including probing depth (PD) and clinical attachment loss (CAL) were recorded. GCF and saliva samples were collected to quantify IL-23 and IL-27 levels which were analyzed using a multiplex ELISA (ProcartaPlex™ Human Th9/Th17/Th22 Cytokine Panel). The results were statistically analysed using SPSS software (version 21.0, IBM, USA). IL-23 levels in both GCF and saliva significantly increased from healthy to gingivitis to periodontitis ($p < 0.05$). Conversely, IL-27 levels decreased progressively across the same groups ($p < 0.05$). IL-23 levels showed a strong positive correlation with PD and CAL, while IL-27 levels were negatively correlated with these parameters, particularly in the periodontitis group. Elevated IL-23

levels are associated with greater disease severity, whereas IL-27 appears to exert a protective, anti-inflammatory effect. The study highlights the potential of both cytokines as biomarkers for diagnosing and monitoring periodontal conditions. However, to confirm their clinical relevance, further longitudinal studies with larger cohorts are recommended.

KEYWORDS: Interleukin-23; Interleukin-27; Periodontitis; Biomarkers; Saliva; Gingival crevicular fluid.

RESUMEN: La enfermedad periodontal es una condición inflamatoria crónica caracterizada por la destrucción del aparato de soporte del diente. Su patogénesis está determinada principalmente por un desequilibrio entre mediadores proinflamatorios y antiinflamatorios. La IL-23, de naturaleza proinflamatoria, contribuye a la inflamación tisular y a la desregulación mediante la producción de IL-17. Por el contrario, la IL-27 ejerce un efecto antiinflamatorio al modular la respuesta inmune mediante la inhibición de IL-17. El presente estudio tuvo como objetivo evaluar los niveles de IL-23 e IL-27 en fluido crevicular gingival (FCG) y saliva en condiciones de salud y enfermedad periodontal. Cuarenta sujetos sistémicamente sanos fueron distribuidos en tres grupos: sanos (Grupo A, n=10), gingivitis (Grupo B, n=15) y periodontitis (Grupo C, n=15). Se registraron parámetros clínicos, incluyendo profundidad de sondaje (PS) y pérdida de inserción clínica (PIC). Se recolectaron muestras de FCG y saliva para cuantificar los niveles de IL-23 e IL-27, los cuales fueron analizados mediante un ensayo multiplex ELISA (ProcartaPlex™ Human Th9/Th17/Th22 Cytokine Panel). Los resultados se analizaron estadísticamente utilizando el software SPSS (versión 21.0, IBM, EE. UU.). Los niveles de IL-23 en FCG y saliva aumentaron significativamente de los sujetos sanos a los de gingivitis y periodontitis ($p<0.05$). En contraste, los niveles de IL-27 disminuyeron progresivamente a través de los mismos grupos ($p<0.05$). Los niveles de IL-23 mostraron una fuerte correlación positiva con PS y PIC, mientras que los niveles de IL-27 se correlacionaron negativamente con estos parámetros, particularmente en el grupo con periodontitis. Los niveles elevados de IL-23 se asocian con una mayor severidad de la enfermedad, mientras que la IL-27 parece ejercer un efecto protector y antiinflamatorio. El estudio resalta el potencial de ambas citoquinas como biomarcadores para el diagnóstico y monitoreo de las condiciones periodontales. No obstante, para confirmar su relevancia clínica, se recomiendan estudios longitudinales con cohortes más amplias.

PALABRAS CLAVE: Interleucina-23; Interleucina-27; Periodontitis; Biomarcadores; Saliva; Fluido crevicular gingival.

INTRODUCTION

Periodontal disease is a chronic inflammatory disease, causing damage to the tooth supporting structures. A hallmark of the disease is resorption of alveolar bone, which is driven by cytokines, with a further imbalance in pro-inflammatory and anti-inflammatory ones (1). Although plaque microbiota triggers the disease, the host immune response influences its progression. T cells are essential in both maintaining periodontal health and contributing to disease process, as they regulate both humoral and cell-mediated immunity. The traditional Th1/Th2 paradigm was once thought to control disease progression, with Th1-associated cytokines enhancing phagocytosis and helping to limit infection in stable lesions. However, an insufficient innate response combined with low IL-12 production may result in an ineffective Th1 response, which fails to control the infection. Mast cells stimulation and IL-4 release stimulates a Th2 response, which activates B cells

and leads to antibody production. Persistent B cell activation can elevate IL-1 levels, leading to tissue destruction. However, the discovery of Th17, Treg, and Th22 subsets expanded the fundamental understanding of immune regulation in periodontal pathogenesis (2).

IL-23 is pro-inflammatory cytokines belonging to IL-12 family, promotes the secretion of IL-17 by stimulating Th17 cells, which further secretes IL-1, IL-6, and TNF-α. These, in turn contribute to neutrophil proliferation, offering immediate protection against bacterial infection. Additionally, IL-17 activates natural killer cells, and regulating antibody production. However, the activation of this pathway can compromise immunity against autoantigens, increasing the risk of developing severe autoimmune diseases (3). On the other hand, IL-27, another member belonging to IL-12 family, possesses both pro-inflammatory and anti-inflammatory effects (4). Unlike IL-23, IL-27 suppresses the release of IL-17 by inhibiting Th17 cells (5).

Traditionally, periodontal disease diagnosis relies upon clinical and radiographic findings, which are limited in predicting disease pathogenesis and progression (6). There is a myriad of molecules that have been investigated to understand periodontal disease initiation and progression. A biomarker is a substance that gives an objective measure to indicate a biological process in health and disease or a pharmacological response to a therapy. Biomarkers in saliva, gingival crevicular fluid (GCF), and blood offer a promising diagnostic adjunct (7).

This study aimed to examine the expression levels of IL-23 and IL-27 in gingival crevicular fluid and saliva to better understand their roles in the progression of periodontal disease. The objectives were to assess and compare their concentrations in saliva and GCF from participants with periodontal health, gingivitis, and periodontitis, as well as to assess their relationship with clinical parameters in periodontitis.

MATERIALS AND METHODS

The required sample size for the present study was calculated using G*Power software version 3.1.9.4, based on data from a previous study by Tiba Faiz Kamil *et al*. (8). An a priori power analysis was performed using the F-test family for one-way ANOVA (fixed effects, omnibus). The parameters were set with an effect size derived from the literature, a power (1-β) of 0.95, and a significance level (α) of 0.05, with three comparison groups. The analysis yielded a total sample size of 40 subjects (numerator degrees of freedom=2; denominator degrees of freedom=37; actual power=0.964). Accordingly, the study included 10 systemically healthy individuals (Group A), 15 subjects with gingivitis (Group B), and 15 subjects with periodontitis (Group C).

STUDY GROUPS

This study involved 40 patients who reported to the department of periodontics at Ragas Dental College, Chennai, India. Participants were allocated into three groups according to the 2017 World Workshop classification of Periodontal and Peri-Implant Diseases and Conditions. Group A (n=10) consisted of healthy subjects with a probing sulcus depth of ≤3mm, no clinical attachment loss, and bleeding on probing (BOP)<10% (8). Group B (n=15) included patients with gingivitis, with a sulcus depth of ≤3mm, no clinical attachment loss, and bleeding on probing >30% (9). Group C (n=15) included patients with Stage III-IV and grade A periodontitis, presenting with a probing pocket depth (PPD) of ≥4mm, clinical attachment loss (CAL) ≥5mm, and bleeding on probing (10).

All the participants provided informed consent before commencement and the proposal was approved by the institutional review board (Ref

No: EC/NEW/INST/2023/4006). Participants were enrolled according to a stringent selection criteria. The subjects who were systemically healthy, either presenting with clinically healthy gingiva, or gingivitis, or chronic periodontitis were included in the study. Smokers, alcoholics, individuals who were under antimicrobial therapy in the past three months, pregnant and lactating women, were excluded from the study. In addition, patients with a history of antibiotic therapy or surgical periodontal management in the past three months, those with active oral infections or lesions were are also excluded.

CLINICAL EVALUATION AND SAMPLE COLLECTION

Full mouth PPD and CAL were measured using William's periodontal probe by a single calibrated periodontist. Intraoral periapical radiographs were also accompanied with clinical measurements wherever needed. Saliva samples were collected following the protocol described by Navazesh *et al*. (11). The patients were advised to refrain from eating or drinking anything except water for at least an hour before sample collection. They thoroughly rinsed their mouths with water and were instructed to lean forward, and allow saliva to passively drool into a sterile container over a five minute period. The collected samples were then immediately stored at -80°C until further analysis.

GCF COLLECTION AND PREPARATION

The GCF was collected according to the technique described by Krasse & Engelberg, 1962. The supra gingival plaque was gently removed using an ultrasonic scaler prior to sample collection and the site was isolated thoroughly to prevent any contamination. A color-coded, 1-5 µl pipette was used to collect 2 µl of GCF at the isolated site. Collected fluid was transferred to a sterile Eppendorf tube containing 200 µl of phosphate buffered saline and then immediately stored at -80°C until further processing.

IL-23 AND IL-27 ASSAY

The stored GCF and saliva samples were centrifuged at 2000 rpm x g for 5 minutes and then assayed for IL-23 and IL-27 with multiplex ELISA (ProcartaPlex Human Th9/Th17/Th22 Cytokine Panel), strictly following the manufacturer's instructions (12).

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel and analyzed using SPSS software (version 21.0, IBM, USA). Normality was assessed using the Kolmogorov-Smirnov test. To compare the groups, parametric ANOVA test was used, followed by post-hoc analysis with the Bonferroni or Tukey test for multiple comparisons. Furthermore, the correlation between the groups and parameters was evaluated using the Pearson correlation coefficient test, with statistical significance determined by a p-value of ≤ 0.05.

RESULTS

Table 1 presents the demographic and clinical profiles of participants across the three groups: health, gingivitis, and periodontitis. Gender distribution was comparable among the groups, with no statistically significant differences ($p>0.05$). However, mean age varied significantly between groups ($p=0.004$), with the periodontitis group exhibiting a higher average age (42.1±10.65 years) than the gingivitis (29.9 ± 8.39 years) and healthy (32±10.38 years) groups. Clinical parameters, including PPD and CAL, showed highly significant differences among the groups ($p<0.001$). Mean PD increased progressively from healthy group (1.70±0.48 mm) to gingivitis (2.53±0.51

mm) and was highest in the periodontitis group (5.67±0.81 mm). CAL was absent in both the healthy and gingivitis groups but was markedly elevated in the periodontitis group (4.93±1.03 mm), indicating substantial periodontal breakdown in this cohort.

Table 2 presents the comparison of IL-23 and IL-27 levels in GCF and saliva across three groups. The average IL-23 levels in GCF were 4.634 pg/ml for healthy group, 8.229 pg/ml for gingivitis group, and 12.218 pg/ml for periodontitis group, with a statistically significant difference (p=0.007). A similar pattern was observed in salivary IL-23 levels, in which, the average IL-23 concentrations were 14.511 pg/ml for healthy group, 24.343 pg/ml for gingivitis group, and 35.538 pg/ml for periodontitis group, again exhibiting significant variation among the groups (p=0.030). However, conversely, IL-27 levels exhibited a downward trend from health to disease in both biological fluids. The average IL-27 levels in GCF were recorded at 70.295 pg/ml for healthy group, 57.118 pg/ml for gingivitis group, and 41.943 pg/ml for periodontitis group, with statistical significance (p=0.004). In saliva, the average IL-27 levels were 47.155 pg/ml for healthy group, 39.712 pg/ml for gingivitis group, and 36.372 pg/ml for periodontitis group, (p=0.049).

Table 3 represents the correlation between GCF and salivary IL-23 and IL-27 with periodontal clinical parameters in Group C patients. Pearson correlation analysis revealed a significant positive correlation between IL-23 levels and both PPD and CAL among patients with periodontitis. More specifically, IL-23 levels in GCF were positively correlated with PD (r=0.61, p=0.002) and CAL (r=0.34, p=0.018). Salivary IL-23 also presented a strong positive correlation with PD (r=0.87, p=0.040) and CAL (r=0.52, p=0.021). In contrast, IL-27 levels in GCF exhibited a statistically significant negative correlation with PD (r=–0.23, p=0.032) and CAL (r=–0.45, p=0.049). Salivary IL-27 also exhibited a strong negative correlation with PD (r=–0.95, p=0.040) and CAL (r=–0.34, p=0.023).

Table 1. Patient demographic and clinical data.

Demographic and clinical parameters	Group A Health (n=10)	Group B Gingivitis (n=15)	Group C Periodontitis (n=15)	p-value
Gender				
Male	7	9	8	0.745
Female	3	6	7	
Age (years; mean ±SD)	32 ± 10.38	29.9 ± 8.39	42.1 ± 10.65	0.004*
PD (mm; mean ±SD)	1.70 ± 0.48	2.53 ± 0.51	5.67 ± 0.81	<0.001*
CAL (mm; mean ±SD)	0	0	4.93 ± 1.03	<0.001*

* Significance level p<0.05.

Table 2. Comparison of IL-23 and IL-27 levels in GCF and saliva in all groups.

Biomarker	Samples-Biological fluid	Group A Health	Group B Gingivitis	Group C Periodontitis	p-value
IL-23 (pg/ml; mean±SD)	GCF	4.63 ± 3.83	8.22 ± 5.49	12.21 ± 6.49	0.007*
	Saliva	14.51 ± 18.30	24.34 ± 30.15	35.53 ± 42.91	0.030*
IL-27 (pg/ml; mean±SD)	GCF	70.29 ± 48.81	57.11 ± 53.28	41.94 ± 31.00	0.004*
	Saliva	47.15 ± 44.41	39.71 ± 28.15	36.37 ± 38.87	0.049*

*Significance level p<0.05.

Table 3. Correlation between GCF and Saliva IL-23 & IL-27 to periodontal clinical parameters among Group C patients.

	Parameters	Samples-Biological fluid	Pearson's correlation	p-value
IL-23	PD	GCF	0.61	0.002*
		Saliva	0.87	0.040*
	CAL	GCF	0.34	0.018*
		Saliva	0.52	0.021*
IL-27	PD	GCF	-0.23	0.032*
		Saliva	-0.95	0.040*
	CAL	GCF	-0.45	0.049*
		Saliva	-0.34	0.023*

*Significance level P<0.05.

DISCUSSION

Periodontitis is a long-term inflammatory condition resulting in gradual deterioration of tissues that support teeth. While periodontopathic bacteria are the primary agents responsible for the destruction, the progression of disease is considerably influenced by the host's immune response. Recent studies have focused on biomarkers to gauge disease advancement, anticipate risks, and assess treatment outcomes. Several inflammatory mediators, and tissue degradation products found in GCF and saliva serve as crucial indicators for disease activity (13).

T cells play a vital role in regulating adaptive immunity by releasing cytokines. T cell subsets such as Th17, Treg, and Th22 has deepened our understanding of immune regulation in periodontitis. A key component of this immune response is IL-23/IL-17 axis, which becomes activated when bacterial infections stimulate IL-23 production, thereby regulating inflammation (14, 15). In addition, IL-27, is known to exhibit both immunostimulatory and immunosuppressive properties, which inhibits IL-17 production by preventing Th17 differentiation (5). This study investigated the concentrations of IL-23 and IL-27 in individuals at healthy and diseased periodontal states, and to examine their association with various clinical parameters.

The GCF IL-23 concentrations were found to be highest in the periodontitis group followed

by the gingivitis group and lowest in the healthy group. Likewise, salivary IL-23 concentrations were elevated in the periodontitis group followed by gingivitis and healthy subjects with notable statistical differences detected among the groups. This finding aligns with previous research by Himani GS *et al*. (3), who reported a significant increase in IL-23 levels in gingival crevicular fluid, correlating with the extent of periodontal destruction. Similarly, Joonas Liukkonen *et al*. (16) observed elevated salivary IL-23 concentrations in individuals with localized periodontitis compared to healthy controls. Althebeti *et al*. (17) also reported significantly higher IL-23 levels in both the GCF and blood samples of patients with chronic periodontitis relative to those in the gingivitis and healthy groups. Furthermore, a systematic review by Alarcon *et al*. (18) concluded that the IL-23/IL-17 axis is elevated in the GCF of patients with chronic periodontitis and gingivitis compared to periodontally healthy individuals. These findings highlight its potential as a diagnostic marker in distinguishing different stages of periodontal disease.

However, our results are in contrast to those of Sadeghi *et al*. (19), who found higher IL-23 levels in the healthy control group than in the diseased groups. Furthermore, Kamil *et al*. (8) identified a significant negative correlation between salivary IL-23 levels and all disease groups (gingivitis and periodontitis), as compared to the healthy control group.

IL-23, widely recognised in linking the innate and adaptive immune responses, promotes the production of chemokines, which aids in the rapid recruitment of neutrophils to areas of injury or infection. Additionally, IL-23 activates natural killer (NK) cells, inhibits Treg cells, and subsequently reduces antibody production. Its ability to enhance the proliferative capacity and stimulate IL-17-producing Th subsets underscores IL-23 as a critical cytokine in the pathogenesis of periodontal disease. IL-23 levels in both GCF and saliva were found to correlate with probing depth (PD) and clinical attachment loss (CAL) in the periodontitis group, as assessed through Pearson correlation analysis. A statistically significant positive correlation was observed between IL-23 concentrations in GCF and saliva with both PD and CAL, further highlighting its role in the progression of periodontal disease.

Conversely, IL-27 showed a distinct pattern. The average levels of GCF and salivary IL-27 were greatest in the periodontally healthy group, trailed by the gingivitis and periodontitis groups. The results aligned with earlier research conducted by Jan Yang Ho *et al*. (20), which demonstrated a comparable pattern in IL-27 levels to those found in the current study. A study by Babaloo *et al*. (21) also found that serum IL-27 levels in periodontitis patients increased following treatment, compared to their baseline levels. This indicates that IL-27 could assist in modulating inflammatory responses by inhibiting Th1 and Th2 pathways. Iwasaki et al (22) also found that IL-27 can stimulate Foxp3-IL-10 producing cells to generate IL-10, it subsequently aids in alleviating inflammation through reducing the secretion of other pro-inflammatory cytokines. Conversely, Akio Mitani *et al*. (23) found higher mRNA levels of EBI3 and IL-12A in the gingival tissues of chronic periodontitis patients, but no expression of IL-27p28 mRNA. They concluded that IL-27 is not a key component in gingival tissue and did not perform ELISA assays for IL-27 in GCF samples. IL-27 is known for its role in regulating immune responses, particularly in promoting Th1 cell development through the STAT-T-bet pathway. It also functions in reverse by inhibiting the growth of the Th17 subset, thus stopping the continuation of inflammatory responses (24).

The link between IL-27 levels and clinical parameters is evident, as a decrease in probing depth and clinical attachment loss in the periodontitis group, compared to the gingivitis group, was accompanied by a reduction in IL-27 expres-

sion in both GCF and saliva. Furthermore, a strong correlation between IL-27 levels in GCF and saliva indicates that saliva could be a reliable diagnostic medium to reflect the periodontal condition and monitor disease activity in larger populations. With the emergence of advanced diagnostic methods, saliva is likely to become the preferred tool in the future (24).

The inverse correlation between IL-23 and IL-27 observed in the study highlights the delicate balance between pro-inflammatory and anti-inflammatory cytokines in the pathogenesis of periodontitis. While higher IL-23 levels are linked to increased disease severity, elevated IL-27 levels seem to help protect against the inflammatory processes characteristic of periodontitis.

Although several studies have widely explored the association of various cytokines in inflammatory conditions, the current study results render a distinctive contribution by defining the expression profiles of IL-23 and IL-27 in the biological fluids, namely the GCF and saliva across different stages of periodontal disease (18,25,26). The present study not shed light on the significance of IL-23/IL-17 axis in periodontal pathogenesis, it also emphasizes the counter regulatory role of interleukin 27. By establishing a consistent inverse correlation between the study's cytokines of interest and their correlation with periodontal clinical parameters, the study outcomes depict new insight into their potential, as non-invasive biomarkers in the prompt diagnosis, clinical staging and longitudinal monitoring of periodontal disease progression.

One limitation of this research is its cross-sectional approach, which captures only a snapshot of cytokine levels at a certain moment, making it challenging to monitor changes over time. To bolster the validation of these cytokines as dependable biomarkers for disease progression, upcoming studies should concentrate on longitudinal research involving larger participant groups.

CONCLUSION

In summary, the findings of this study demonstrate that IL-23 levels increase while IL-27 levels decrease as periodontal disease progresses, suggesting their significant involvement in disease pathogenesis. The results also highlight the potential influence of the imbalance between the pro-inflammatory IL-23 and the anti-inflammatory IL-27 in driving periodontal disease progression. To further establish their utility as reliable biomarkers for diagnosis, management, and disease monitoring, larger-scale longitudinal studies are essential.

AUTHOR CONTRIBUTION STATEMENT: Conceptualization and design: K.B. and S.G.; Literature review: S.B., S.A. and D.A.; Methodology and validation: K.B. and S.A. ; Investigation and data collection: S.G., S.B. and D.A.; Formal analysis and data interpretation: K.B. and S.B.; Writing-original draft preparation: K.B.; Writing-review and editing: S.G., S.B., S.A. and D.A.; Supervision and project administration: K.B.

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