Original Article

The Association of Serum Levels of T-helper-2 (IL-13) Cytokine with Periodontitis

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Abstract

Background: Periodontitis is a chronic inflammatory disease affecting the supporting structures of teeth. Cytokines have a dynamic role in both starting and regulating the inflammatory process associated with periodontitis. A powerful anti-inflammatory cytokine called interleukin-13 has been found to inhibit the production of pro-inflammatory cytokine, prevents the creation of osteoclasts, and may prevent bone resorption in periodontitis. **Objective:** The scope of the current investigation was to discover the association of serum levels of T-helper-2 (IL-13) cytokine with periodontitis. **Materials and Methods:** The study involved 88 Iraqi participants who were categorized into two distinct groups: a periodontitis group (44 individuals) and a control group (44 subjects). Clinical periodontal parameters were measured, alongside the collection of venous blood samples from each participant, which were then analyzed to determine the levels of IL-13 serum. **Results:** The serum level of IL-13 was found to be nonsignificantly lower in the periodontitis group (2.78 ± 0.79 [pg/mL]) compared to the control group (3.22 ± 1.31 [pg/mL]). Additionally, no significant association was observed between the serum level of IL-13 and the clinical periodontal parameters. **Conclusion:** Even though a nonsignificant association was detected between IL-13 and periodontitis, IL-13 levels were reduced in periodontitis patients compared to healthy controls. Suggesting its role as an inhibitory factor in inflammation associated with periodontitis.

Keywords: Anti-inflammatory, cytokines, IL-13, immune response, inflammation, periodontitis

Introduction

One of the most widespread chronic inflammatory illnesses, periodontitis affects the soft tissues and alveolar bones that support teeth, leading to tooth loss. In addition to its influence on a person's oral health and quality of life.[1-5] Periodontal disease is caused by a complex combination of multiple factors, including pathogenic microorganisms, host immunological responses, genetics, and environmental factors.[6-8] Although bacterial infection is the main factor that initiates periodontal disease, the disease development and progression are affected by the generation of immune mediators in response to the bacteria and their metabolic products.[3] As periodontal pathogens and inflammatory processes interact, a cytokine network regulates whether tissue responses to periodontal pathogenesis are amplified or suppressed.[9]

In reaction to microbial chemicals, inflammatory cells, particularly T lymphocytes, produce proteins called cytokines in injured tissues. Through the stimulation and differentiation of osteoblasts, fibroblasts, and collagen synthesis, these cytokines and prostaglandins performed a dynamic role in the beginning and guideline of the inflammatory process of periodontitis.[10,11] Subsequently, the overproduction of pro-inflammatory cytokines or insufficient production of anti-inflammatory cytokines that are appropriate can both initiate and perpetuate periodontitis.[12]

Interleukins including TNF-, IL-1, IL-2, IL-12, and IFN are released by T-helper-1 cells and cause the cellular

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immune response.[13] While, others such as IL-4 and IL-13 are produced by T-helper-2 cells, and these molecules trigger the humoral immune response.[14]

An immunoregulatory protein called interleukin-13 is a powerful anti-inflammatory cytokine that prevents the synthesis of potent inflammatory cytokines like interleukin-1. IL-13 is produced primarily by activated T-helper-2 cells and may be also produced by the gingival epithelial cells.[15] It has an essential part in the growth and differentiation of B cells[16] and it is accountable for a variety of biological processes since it inhibits osteoclast formation and might play an inhibitory effect in periodontitis' inflammation-induced bone resorption.[17]

Many investigations study the presence of IL-13 in periodontal lesions.[18-21] As well, others only found IL-13 in people with healthy periodontal tissue and patients with gingivitis.[22] It has been suggested that the transition from gingivitis to periodontitis may be brought on by an imbalance between Th1 and Th2 cells.[23,24] So, the current paper was issued to investigate the association of IL-13 with severe periodontitis.

Materials and Methods

The current study was a self-funded observational case–control study which received approval from the ethical committee of the University of Baghdad, conducted between January 2022 and June 2022. A total of 88 male volunteers were selected from patients seeking periodontal therapy at the Periodontics Department of the College of Dentistry, University of Baghdad, Iraq. These individuals were fully informed about the purpose and objectives of the study and they signed informed consent, acknowledging their understanding of the study's objectives and their freedom to withdraw at any time. Detailed medical and dental histories of the participants were obtained through the use of a questionnaire. The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of the College of Dentistry, University of Baghdad approved this study (Ref. 733, December 1, 2021, Project # 733522). All participants entered the study after they were fully informed of the process and signed written consent.

The volunteers were divided into two groups:

- Periodontitis group: which included (44) patients with periodontitis, according to the updated classification of periodontitis by the American Academy of Periodontology and European Federation of Periodontology in 2017.[25]
- The control group: 44 subjects who were systemically healthy and with clinically healthy periodontium.

The subject with clinically healthy intact periodontium was selected according to the criteria proposed by Chapple *et al*.[25], and periodontitis patients were well-defined rendering to the criteria of Tonetti *et al*.[26]

Assessment of periodontal status was carried out for all participants by using a UNC-15 probe. Six areas of each tooth were examined to assess the plaque index (PlI),[27] bleeding on probing (BOP),[23] probing pocket depth (PPD), and clinical attachment level (CAL). Moreover; all periodontitis patients were generalized and exhibited an unstable state having at least 20 teeth.

Inter and intra-examiner calibration were done with expert periodontitis until they reached 75% agreement for all clinical parameters.

Participants who had systemic conditions, received extensive periodontal treatment, or were currently undergoing periodontal therapy were excluded from the study. Additionally, individuals who had been on immunosuppressant or antibiotic therapy within the past 3 months, pregnant or nursing women, and those who had experienced recent acute illness symptoms were also excluded from the study.

Following the completion of the periodontal examination, a volume of 3 mL of venous blood was drawn from each participant and collected in a gel-separating tube. The mixture of serum and cells was then separated through centrifugation at 3300 rpm for 10 min. The collected blood serum was subsequently stored in sterile Eppendorf vials at a temperature of −40°C until it was ready for analysis.

The serum levels of IL-13, a biomarker of interest, were determined using the Enzyme-Linked Immuno-Sorbent Assay (ELISA) technique. The samples were thawed and left for a few minutes to reach room temperature. Salivary IL-13 protein levels were measured using commercially available ELISA kits (MyBioSource, San Diego, California). The process was carried out by each kit's manufacturer's instructions. A microtiter plate reader (HumanReader HS; HUMAN Society for Biochemica and Diagnostica mbH) was used to measure optical density (OD). All OD values were exported to spreadsheets and converted to concentrations using a linear regression method tailored for biomarkers.

Statistical analysis was conducted on the collected data using Graph pad Prism 9. Both descriptive and inferential analyses were performed to evaluate and assess the statistical hypotheses. The normality of distribution was examined using the Kolmogorov–Smirnov and Wilk Shapiro tests.

For continuous variables, such as biomarker levels, the mean values and standard deviations were calculated. The *t* test was utilized to compare the mean values of biomarkers between different groups. Furthermore, parametric correlation analysis between clinical periodontal measures and IL-13 was conducted using the Pearson correlation coefficient. All statistical tests were conducted with a significance level of $\alpha \leq 0.05$, indicating a confidence level of 95%.

Table 1: Statistics of demographic, periodontal parameters, and salivary biomarker

Parameters	Group	Mean	Minimum	Maximum	Sig
Age	Periodontitis	43 ± 19	19	50	0.32
	Control	42 ± 22	20	48	NS
PII	Periodontitis	2.58 ± 0.35	1.8	3	0.04
	Control	0.475 ± 0.06	0.3	0.5	S
BOP	Periodontitis	46%	23%	70%	0.03
	Control	7%	5%	9%	S
PPD	Periodontitis	5.19 ± 0.57	4	6.25	0.03
	Control	2.21 ± 0.5	1	3	S
CAL	Periodontitis	6.4 ± 0.68	5	7.85	–
IL-13	Periodontitis	2.78 ± 0.79	1.51	5.11	0.43
	Control	3.22 ± 1.31	1.51	6.38	NS

PII: plaque index, PPD: probing pocket depth, CAL: clinical attachment loss, BOP%: bleeding on probing percentage, NS: nonsignificant at *P* value ≤ 0.05, S: significant at *P* value ≤ 0.01

The comparison was done using a *t* test for all parameters

Results

Demographic and clinical parameters

The study included exclusively male participants, with an average age of 43 ± 19 years in the periodontitis group and 42 ± 22 years in the control group, which consisted of individuals with a healthy periodontium. There was no significant difference in age between the two groups. The periodontal parameters (PII, BOP, PPD, and CAL) were considerably higher in the periodontitis group compared to the control group. Concerning the Serum level of IL-13, the control group exhibited a higher IL-13 serum level (3.22 + 1.31 [pg/mL]) compared to the periodontitis group (2.78 + 0.79 [pg/mL]), although the difference was not statistically significant ($P = 0.18$). The maximum IL-13 level observed in the control group was 6.38 (pg/mL), while in the periodontitis group, it was 5.11 (pg/mL). Both groups had a minimum IL-13 level of 1.51 (pg/mL). as demonstrated in Table 1 and Figure 1.

Moreover, Figure 2 illustrates that no significant association was observed between the serum level of IL-13 and any of the periodontal parameters (PII, BOP, PPD, and CAL).

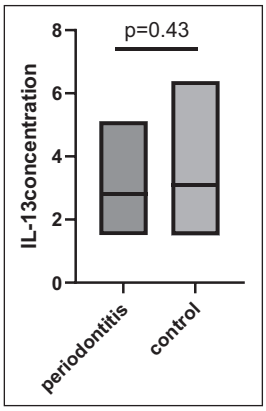

Figure 1: Comparison of IL-13 concentration in periodontitis and control group. NS: nonsignificant at *P* value ≥ 0.05

Discussion

The current study aimed to investigate the association between serum levels of IL-13 and periodontitis. IL-13 is known for its anti-inflammatory properties and its potential role in inhibiting pro-inflammatory cytokine production and preventing bone resorption in periodontitis. The present results showed that although there was no statistically significant difference, the serum level of IL-13 was slightly lower in the periodontitis group compared to the control group with nonsignificant association between salivary IL-13 and clinical periodontal parameters.

The finding of a non-significant decrease in IL-13 levels in periodontitis patients is consistent with previous studies that have reported similar trends.[28,29] One possible explanation for this observation is the dynamic and complex nature of the cytokine network in periodontal tissues. The local production and regulation of IL-13 may be influenced by factors other than serum levels, such as tissue-specific responses and the presence of other cytokines and immune cells. In periodontitis, type 2 helper T lymphocytes (Th2) secrete IL-13 with other cytokines which encourage the B cell humoral immunity and recover the symptoms of inflammation as IL-13 can inhibit the secretion of TNF-α and attain some anti-inflammatory effects that activate transforming growth factor-β1 producing fibrosis. Furthermore, IL-13 can inhibit bone resorption that is, caused by the inflammation associated with periodontitis.[18] This inhibition is achieved by affecting the bone protection factor system and can directly promote IgE and thus cytokine synthesis in humans.[30]

It is worth noting that the existing study focused on serum levels of IL-13 rather than local levels within periodontal tissues. Previous studies have shown the presence of IL-13

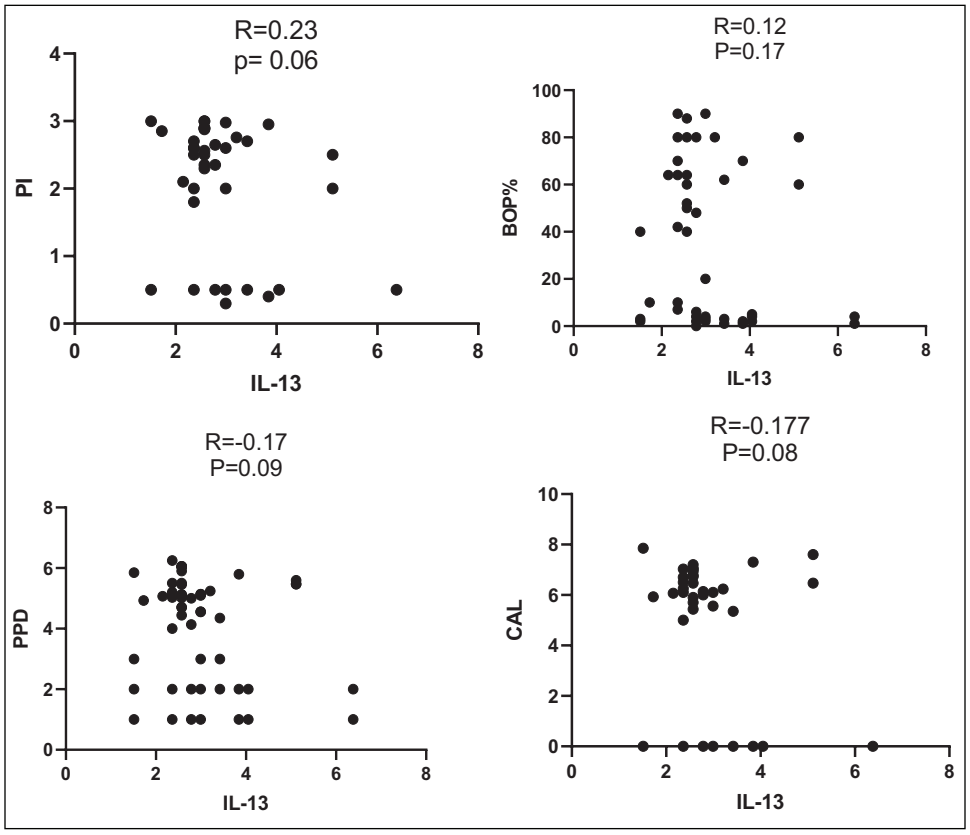

Figure 2: Correlation of IL-13 with clinical periodontal parameters. The correlation was done using the Pearson correlation (*r*); *p*: *P* value at significance level 0.05; PII: plaque index, BOP: bleeding on probing index, PPD: probing pocket depth, CAL: clinical attachment loss

in periodontal lesions, suggesting its involvement in the inflammatory response at the tissue level.[31,32] Therefore, future studies should consider analyzing IL-13 levels in gingival crevicular fluid or tissue samples to provide a more comprehensive understanding of its role in periodontitis.

The influence of genetic and environmental factors on IL-13 production and signaling cannot be ignored. Genetic polymorphisms and epigenetic modifications may affect IL-13 expression and function,[30,33,34] leading to individual variations in its levels and impact on periodontal health. Future studies could explore the genetic profiles and environmental factors that may influence IL-13 levels and their association with periodontitis. Also, the secretion of IL-13 was lowered in the current study since the included periodontitis cases had unstable status favoring the prominence of pro-inflammatory cytokine.

Several limitations to the current study should be acknowledged. Firstly, the sample size was relatively small, which may have limited the statistical power to detect significant differences in IL-13 levels. Additionally, the study design was cross-sectional, preventing us from establishing a cause-and-effect relationship between IL-13 and periodontitis. Longitudinal studies and functional analyses are required to provide more comprehensive insights into the role of IL-13 in the development and progression of periodontitis. Lastly, we focused on serum levels of IL-13, neglecting the local levels in periodontal tissues, which could have provided additional valuable information. In conclusion, the present investigation indicates that there was a decrease in IL-13 levels among individuals with periodontitis compared to healthy controls, although the difference was not statistically significant. This suggests that IL-13 may have an inhibitory role in the inflammatory processes associated with periodontitis. However, additional investigations are required to better comprehend the complex interactions between IL-13 and other cytokines, as well as their specific effects within the periodontal tissues. Advancing our understanding of IL-13 regulation and its involvement in periodontal disease could open up possibilities for targeted therapeutic interventions in the future.

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Conflicts of interest
The authors announce no conflict of interest.

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