

Evaluation of Serum Interleukin-33 Level in Iraqi Patients with and without Periodontal Disease

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Objective: Periodontitis is a multifactorial inflammatory illness characterized by periodic tissue support deterioration. Interleukin-33 has recently been discovered as a new pro-inflammatory cytokine implicated in the pathogenesis of periodontitis. The objective of this case control study is to compare IL-33 levels among periodontitis patients and healthy volunteers using serum samples and investigate the potential association with clinical periodontal parameters.

Materials and Methods: A total of 100 subjects (50 patients with periodontal disease and 50 healthy individuals) were included in this case control study. Clinical plaque index (PLI), gingival index (GI), bleeding on probing (BOP), probing pocket depth (PPD) and clinical attachment loss (CAL) were assessed. Serum was extracted from the venous blood that was collected. Serum IL-33 values were measured using an enzyme-linked immunosorbent assay (ELISA).

Results: Serum levels of interleukin-33 showed considerably elevated level in the patient's group than in the healthy control group ($P < 0.01$). There was a strong correlation between the blood levels of IL-33 and PLI, GI, and BOP ($P \leq 0.05$). While PPD and CAL demonstrated a non-significant relationship ($P > 0.05$).

Conclusion: The results of this study suggested that IL-33 may be used as a potential indicator of the inflammation associated with periodontitis and might have a role in the development of the disease. Further studies with large sample sizes are needed to improve knowledge about the role of IL-33 in periodontal health and disease.

Clinical Significance: Owing to the noticeable role that IL-33 plays in the pathogenicity of periodontitis as a local warning clue for the periodontal tissue breakdown, tissue-specific therapeutic strategies may improve.

Keywords: periodontitis, interleukin, serum, ELISA, pathogenesis, periodontal parameters

Introduction

Periodontal disease is classified as an infectious condition characterized by the presence of pathogenic microorganisms. These microorganisms have been identified as the key causative agents in the development of inflammatory periodontal disease. The aforementioned condition impacts the periodontal tissues around the teeth, resulting in their gradual breakdown and eventual loss of the affected teeth. The influence of immune response on the advancement of periodontitis implies that the activation of bacterial markers triggers an immune-pathogenic response and the host's reaction to the infection is pivotal in defining the severity and aggressiveness of the disease.¹⁻³

During the host-bacterial interaction, an extensive collection of molecular mediators, including cytokines, prostaglandins, and matrix metalloproteinases, are released into the environment. This release ultimately results in periodontal tissue destruction. Such destruction can be attributed to the excessive synthesis, dysregulation, or insufficient suppression of these mediators.⁴

Cytokines are a class of soluble proteins that function as mediators, facilitating the transmission of commands between cells. Cytokines, including interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α , have been known for their significant involvement in the deterioration of periodontal tissue.⁵ IL-33 is shown to be generated by a variety of cell types inside the periodontium, including endothelial cells, epithelial cells, fibroblasts, and osteoblasts. Additionally,

immune cells such as monocytes, neutrophils, basophils, eosinophils, T helper cells (Th2), osteoclasts, dendritic cells, and mast cells have also been observed to express IL-33.⁶

IL-33 has a double function. Under normal physiological circumstances, IL-33 is shown to be expressed as a nuclear factor, contributing to the preservation of tissue integrity by its ability to induce collagen synthesis. Additionally, IL-33 serves a protective role against infections.⁷ By enhancing the Th2 response, it elicits an anti-inflammatory reaction. Nevertheless, during periods of cellular injury or stress, it actively engages in the synthesis of numerous pro-inflammatory mediators and has a damaging effect in various inflammatory disorders.⁸

The multifunctional nature of IL-33 has been recognized in the context of periodontal disease, where it demonstrates characteristics of an alarmin, chemoattractant, and central cytokine.⁶ In the progression of necrosis, the pro-inflammatory cytokine IL-33 is discharged into the extracellular environment and assumes the role of an alarming cytokine, so provoking the breakdown of various cell populations, such as fibroblasts and cells of epithelial tissue. Interleukin-33 has the capacity to be generated by viable cells subsequent to the application of mechanical force. In cell culture experiments, the upregulation of IL-33 is stimulated by cytokines such as tumor necrosis factor-alpha and IL-10.⁹ The occurrence of many inflammatory mediators in periodontal disease enhances the probability of IL-33 acting as a pro-inflammatory signaling protein, leading to bone resorption. IL-33 promotes the differentiation of monocytes into pro-inflammatory cells, triggers the degranulation process in mast cells, and leads to an increase in osteoclastogenic factors such as receptor activator of nuclear factor kappa-B ligand (RANKL).⁶

In the literature, the number of studies examining the correlation between IL-33 and periodontal disease was inadequate. The purpose of this investigation is to compare IL-33 levels between individuals with chronic periodontitis (CP) and those with good periodontal health. In addition, the study intends to investigate the potential relationship between IL-33 levels and periodontal parameters.

Subjects Materials and Methods

One hundred individuals participated in this case-control investigation. They were patients seeking treatment at periodontal department. The participants were provided with comprehensive details regarding the study and the protocols entailed; this study complies with the Declaration of Helsinki.

The research included two distinct groups of subjects: group I, referred to as the control group, and group II, consisting of individuals diagnosed with chronic periodontitis (CP).

The study included a group of healthy volunteers who were precisely matched to a group of patients comprising 50 persons, based on their ages and genders (36 male and 14 females with age range 30–50 years) who were considered as controls with healthy intact periodontium: had no clinical attachment loss (CAL), and probing pocket depth (PPD) ≤ 3 mm, with bleeding on probing (BOP) less than 10%.¹⁰ Patients included those with chronic periodontitis who had not had periodontal treatment in the preceding three months; all people with CP had at least 20 teeth. The patient group consists of 50 people (39 men and 11 women ranging in age from 30 to 50). Individuals with CP were diagnosed using the clinical criteria outlined in the World Workshop on Periodontitis consensus report.¹⁰ The study's inclusion criteria encompassed patients that had four teeth in each jaw, with a probing depth of 5 mm or more and a clinical attachment loss of 4 mm or more. These people also experienced bleeding on probing more than 80% of the proximal areas. All individuals should exhibit good overall health and lacked any prior systemic illnesses and required to possess a minimum of 20 teeth. Conversely, the exclusion criteria were the presence of chronic systemic diseases that could potentially impact the advancement of periodontitis, additionally, a smoking background or alcohol consumption. Pregnant and menopausal women were also excluded, along with individuals who had taken any medication within the preceding three months.

The clinical assessment of periodontal health parameters, including plaque index (PLI), gingival index (GI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment level (CAL), was conducted using a William probe. The examination included all surfaces of the teeth, specifically at six distinct locations: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual. However, the third molars were excluded from this analysis.

Participants provided informed approval by completing a consent form accepted by the ethical committee of the College of Dentistry under reference number of REC143 and study number MUOSU-202112.

Blood Sampling

Aseptic approach was employed to obtain 3 mL of venous blood from each patient. The blood specimens were placed in tubes containing serum separating gel and allowed to coagulate for a duration of 30 minutes. Subsequently, centrifugation was conducted at a speed of 3500 revolutions per minute (rpm) for a period of 10 minutes. Following centrifugation, the serum samples were separated and transferred into eppendorf tubes. These tubes were then stored in plastic containers within a deep freezer set at a temperature of -40°C . The purpose of this storage was to facilitate subsequent analysis of serum IL-33 levels. Prior to the assay, the serum samples were promptly thawed.

ELISA Detection of Serum IL-33

Interleukin-33 levels in serum were tested using two commercial human enzyme-linked immunosorbent assay (ELISA) Kits (Diaclone SAS, France), following the instructions provided by the manufacturer. The lower threshold for identification of IL-33 was determined to be 31.25 pg/mL. A spectrometric measurement was conducted using a wavelength of 450 nm. Serum IL-33 values were calculated using a standard curve.

Statistical Analysis

The data analysis was conducted with commercially accessible software, specifically IBM SPSS Statistics 27. The Shapiro–Wilk test was used in order to determine if the data were normally distributed, which indicated that the periodontal parameters and ELISA data did not follow a normal distribution. For descriptive statistics, the numbers were given as a frequency, a percentage, a mean, a standard deviation. Differences across study groups were examined using the Mann–Whitney *U*-test. Additionally, Spearman’s association test was used to investigate the possible links between IL-33 and clinical periodontal measures. *P* -values lower than 0.05 were used to indicate statistical significance.

Results

Clinical Findings

The study participants’ demographic features, including patients and healthy controls, were presented in [Table 1](#). The average age of the CP group was 43.74 years with a standard deviation of 4.448, whereas the average age of the healthy controls was 41.82 years with a standard deviation of 6.42. The male-to-female ratio in the CP group was 39:11, whereas it was 36:14 in the control group. Regarding age and gender, there were no statistically significant differences ($P>0.05$) between the two research groups. The patients had substantially higher periodontal parameter scores than the controls ($p<0.001$) as shown in [Table 2](#).

Biochemical Findings and Correlations

The analysis of serum IL-33 revealed a notable elevation in the patient group, with average IL-33 concentrations measured at (56.32 ± 15.604 pg/mL) in the CP group and (40.68 ± 4.111 pg/mL) in the control group of healthy individuals, as presented in [Table 3](#).

To investigate any possible associations between IL-33 and periodontal clinical indicators, Spearman’s rho correlation test was used. PLI, GI, BOP, and serum IL-33 levels all had a statistically significant association ($P<0.05$). There was no statistically significant relationship ($P>0.05$) between serum IL-33 values and PPD or CAL ([Table 4](#)).

Table 1 Descriptive Statistics of Study Groups

Parameters		Patients N=50	Controls N=50	P- value
Age (Mean \pm SD)		43.74 \pm 4.448	41.82 \pm 6.42	0.226
Gender (N. (%))	Male	39(78%)	36(72%)	0.638
	Female	11 (22%)	14 (28%)	

Abbreviations: N, Number; SD, Standard Derivation; %, Percentage.

Table 2 Descriptive and Statistical Analysis of Periodontal Parameters of Study Groups

Parameters (Mean ± SD)	Patients N=50	Controls N=50	P- value
PLI	2.521 ± 0.430	0.361 ± 0.161	< 0.00001**
GI	1.946 ± 0.221	0.312 ± 0.166	< 0.00001**
BOP	77.52 ± 23.229	0.717 ± 0.34	< 0.00001**
PPD	5.669 ± 0.714	–	–
CAL	5.667±0.646	–	–

Note: **Highly Significant.

Abbreviations: PLI, Plaque Index; GI, Gingival Index; BOP, Bleeding On Probing; PPD, Probing Pocket Depth; CAL, Clinical Attachment Level

Table 3 Comparisons of IL-33 Level Between Study Groups

Parameter	Patients N=50	Controls N=50	Mann-Whitney U-test	P- value
IL-33	56.32±15.604	40.68±4.111	6.62255	< 0.00001**
Mean (min- max)	(36.25–136.32)	(33.74–49.40)		

Note: **Highly Significant.

Abbreviations: Min, Minimum; Max, Maximum,

Table 4 Spearman Correlations Coefficients of IL-33 and Periodontal Parameters in Patients Group

Parameters\ IL-33	Coefficient of Correlation	P-value
PLI	0.276	0.049*
GI	0.373	0.006**
BOP	0.290	0.038*
PPD	0.134	0.345
CAL	0.162	0.255

Notes: *Significant, **Highly Significant.

Abbreviations: PLI, Plaque Index; GI, Gingival Index; BOP, Bleeding On Probing; PPD, Probing Pocket Depth; CAL, Clinical Attachment Level.

Discussion

Periodontitis is a pathological condition characterized by inflammation and subsequent degradation of periodontal tissues, encompassing both the soft and hard structures within the periodontium. The initiation of local inflammation is attributed to dysbiosis of the local microbial community. However, it should be noted that osteoclastic activity, which ultimately results in the loss of alveolar bone, is directly triggered by the excessive activation of the host immunological response. Numerous studies have documented the complex cytokine network associated with periodontitis, highlighting its pivotal role in the recruitment of certain immunocytes, regulation of pathobionts, and modulation of osteoclastic activity. However, the mechanisms by which pathogens are stimulated in the oral cavity, resulting in the formation of the complicated and specific

periodontal cytokine network, remain largely unresolved.¹¹ The goal of this current case-control investigation was to assess and compare the serum levels of IL-33 among periodontally healthy subjects and those with chronic periodontitis.

Based on our current research, it has been observed that there is a notable elevation in serum IL-33 levels among persons who have CP, indicating a statistically significant distinction. Given the inclusion of people who exhibit systemic health, it is plausible that the elevated concentration of IL-33 in the serum of individuals with periodontitis can be attributed to the transfer of this cytokine from the periodontal tissues to the systemic circulation.

Consistent with the findings of the present research, Buduneli et al observed an elevation in plasma IL-33 levels among persons diagnosed with chronic periodontitis (CP). However, it is noteworthy that the differences between the study groups did not attain statistical significance.¹²

The development and advancement of periodontitis are associated with various etiological and risk variables, with the regional microbiom and host-immune response being the most significant contributors.¹³ The significance of cytokines is highly crucial in the development and progression of periodontitis. Cytokines have a crucial role in regulating both homeostasis and inflammation. They are engaged in the initial reaction against pathogens and stimuli at barrier locations, facilitating communication between connective tissue cells, lymphocytes, and accessory cell populations.¹⁴ Most studies done in vitro found that IL-33 was a key factor in periodontal disease. However, studies done on humans have been somewhat unclear.¹⁵

Upon cellular insult or death, the production of IL-33 serves as an “alarmin” that functions to warn the immune system about the tissue injury. This event subsequently triggers the development of T helper cells, including Th-2, Th-17, and Treg cells. Additionally, IL-33 has an influence on the process of wound healing in harmed tissues.^{16,17} During the process of periodontal tissue degradation, the deterioration gingival epithelium may lead to IL-33 secretion. This cytokine serves as a signaling molecule, amplifying the Th2 immune response while concurrently exhibiting anti-inflammatory effects.¹³ Nevertheless, the presence of elevated amounts of pro-inflammatory cytokines as a result of bacterial infection triggers the synthesis of IL-33 in periodontal disease, which could contribute to a preference for osteoclastogenesis.^{7,18} Interleukin-33 (IL-33) also induces the recruitment of B and T lymphocytes that express receptor activator of nuclear factor kappa-B ligand (RANKL). This observation may provide an explanation for the elevated levels of IL-33 seen in persons with periodontitis compared to those who are healthy.

According to the results obtained from in vitro and in vivo animal experiments, it has been observed that the expression of IL-33 can be stimulated by gingipain, fimbriae, and lipopeptide derived from *Porphyromonas gingivalis*.^{19,20} This induction of IL-33 expression has the potential to contribute to the deterioration of alveolar bone through a pathway that is dependent on the receptor activator of nuclear factor- κ B ligand (RANKL).^{21,22} The pro-inflammatory characteristics of bone resorption brought on by *Porphyromonas gingivalis* may be revealed by IL-33 levels acting as an extracellular warning signal, according to research done in 2016 by Laperine et al in mild chronic periodontitis.²³

Contrary to our findings, similar levels of IL-33 were observed in gingivitis, healthy gingiva, and chronic and invasive periodontitis by Kursunlu et al. They concluded that IL-33 had no effect on the aetiology of periodontal disease.²⁴ Habeeb and Al-Kaabi in 2021 observed a notable elevation in the level of IL-33 in gingival crevicular fluid (GCF) relative to its amounts in saliva and serum among individuals diagnosed with periodontitis. Additionally, they identified a significant disparity between patients with periodontitis and healthy controls, indicating a substantial involvement of IL-33 in the development of periodontitis. This finding suggests that IL-33 serves as a localized indicator for the onset of periodontal tissue degradation, thereby facilitating the activation of another cytokines in response to the infection site.²⁵ In a different study conducted by Renjith et al, it was shown that patients diagnosed with periodontitis had a salivary IL-33 concentration that was 1.65 times higher compared to that of persons without the condition. Moreover, subsequent to the implementation of nonsurgical intervention, a notable decrease of 16% in salivary interleukin-33 (IL-33) concentrations was found. The results of this study indicate that IL-33 has the potential to be a valuable diagnostic biomarker for periodontal disease and may be used to evaluate periodontal treatment effectiveness.²⁶

There was a strong link between the amount of IL-33 and PLI, GI, and BOP in this study. Although there was an observed increase in PPD and CAL with an elevated IL-33 level, the statistical analysis revealed that these changes were not significant. The data might be accurate to a greater extent if the sample size is larger. The current study's results were in line with the findings presented by Saglam et al, who conducted an investigation to determine the relative concentrations of IL-33 in gingival crevicular fluids (GCF), plasma, and saliva of individuals classified into three groups: chronic

periodontitis, gingivitis, and healthy controls. Elevated levels of (GCF) interleukin-33 (IL-33) were observed in both the gingivitis and chronic periodontitis (CP) groups, relative to the control group. There was a positive link seen between the concentration of IL-33 in (GCF) and the clinical parameters of periodontal inflammation, including (PLI, GI and BOP).²⁷ While Askian et al observed a true association between the IL-33 level and (CAL), while (BOP and PI) did not exhibit a statistically significant correlation. Additionally, their investigation revealed a decrease in IL-33 levels following scaling and root planning. The outcomes of this study indicate that IL-33 may have the potential to be used as a therapeutic target for the treatment of chronic mild periodontitis. The possible impact of IL-33 on the deceleration of inflammatory bone resorption may be attributed to its ability to impede the functioning of pro-inflammatory cytokines.²⁸

The observed disparities between the outcomes of this study and the conclusions drawn from previous investigations could potentially be attributed to variations in several factors, including the nature and extent of periodontal disease, the age of the participants, the type of samples collected (serum, saliva, GCF), the storage temperature of the samples, the methodologies employed, the geographical location of studies, genetic factors, the timing of sample collection, and the size of the sample population.

Conclusion

Taking into account all the limitations of the current investigation, the data revealed that the chronic periodontitis group had higher IL-33 expression levels than the healthy group. In addition, there was an important association between IL-33 expression and periodontal parameters. Thus, it may be inferred that IL-33 plays a pivotal role in the etiology of periodontal disease. Additional research is required to elucidate the underlying mechanism through which IL-33 functions at different stages of periodontitis.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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