

Diagnostic Value of Salivary IL-6 and IL-40 in Patients with Periodontitis

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Abstract

The present study aimed to evaluate the diagnostic value of salivary IL-6 and IL-40 levels in patients with periodontitis and to investigate their association with clinical periodontal parameters. This case-control study included 60 participants comprising 30 patients diagnosed with Stage III or Stage IV periodontitis and 30 periodontally healthy controls. Unstimulated whole saliva samples were collected under standardized conditions. Salivary IL-6 and IL-40 concentrations were measured using enzyme-linked immunosorbent assay (ELISA). Clinical periodontal parameters, including plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment loss (CAL), were recorded. Receiver operating characteristic (ROC) curve analysis, correlation analysis, and logistic regression were performed to evaluate the diagnostic value of the investigated biomarkers. Clinical periodontal parameters were significantly higher in periodontitis patients than in healthy controls ($p < 0.001$). Salivary IL-6 and IL-40 levels were significantly elevated in the periodontitis group. ROC analysis demonstrated good diagnostic performance for both biomarkers. IL-6 showed the highest diagnostic accuracy (AUC = 0.868), whereas IL-40 demonstrated acceptable diagnostic performance (AUC = 0.797). Both biomarkers showed significant positive correlations with periodontal parameters, particularly probing pocket depth. Logistic regression analysis identified IL-6 and IL-40 as significant predictors of periodontitis. Salivary IL-6 and IL-40 are significantly associated with periodontitis and demonstrate promising diagnostic potential as non-invasive biomarkers. These findings support their possible application in periodontal disease assessment and monitoring. Further longitudinal studies are recommended to validate their clinical utility and investigate their prognostic value.

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Introduction

Periodontitis is a chronic multifactorial inflammatory disease characterized by the progressive destruction of the tooth-supporting tissues, including the periodontal ligament, cementum, and alveolar bone. The disease is initiated by dysbiotic subgingival biofilms; however, tissue destruction is primarily driven by an exaggerated host immune-inflammatory response. As a result, periodontitis remains one of the leading causes of tooth loss worldwide

and is associated with substantial impacts on oral function, quality of life, and systemic health. Recent evidence has further highlighted the bidirectional relationship between periodontitis and several systemic inflammatory disorders, emphasizing its importance as a public health concern [1-4].

The pathogenesis of periodontitis involves a complex interaction between pathogenic microorganisms and host defense mechanisms. Persistent microbial challenge induces the

release of inflammatory mediators, cytokines, chemokines, and matrix-degrading enzymes, which contribute to connective tissue breakdown and alveolar bone resorption. Although conventional clinical periodontal parameters, including plaque index, bleeding on probing, probing pocket depth, and clinical attachment loss, remain the cornerstone of periodontal diagnosis, they mainly reflect historical tissue destruction and may not accurately represent current biological disease activity.

Consequently, increasing attention has been directed toward identifying objective biomarkers that can provide additional information regarding inflammatory burden, disease severity, and disease progression [2,5,6]. Saliva has emerged as a promising diagnostic fluid for periodontal diseases because of its non-invasive collection, ease of sampling, cost-effectiveness, and ability to reflect local and systemic biological changes. Numerous salivary biomarkers have been investigated for their potential role in periodontal diagnosis and monitoring, including inflammatory cytokines, enzymes, microbial products, and host-derived proteins. Among these biomarkers, cytokines are of particular interest because they play central roles in regulating immune and inflammatory responses associated with periodontal tissue destruction [7-10].

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine produced by various immune and non-immune cells, including macrophages, T lymphocytes, B lymphocytes, fibroblasts, endothelial cells, and epithelial cells. IL-6 contributes to immune regulation, osteoclast activation, and inflammatory amplification, thereby promoting connective tissue degradation and alveolar bone loss. Elevated IL-6 levels have been reported in periodontal tissues, gingival crevicular fluid, and saliva of patients with periodontitis, suggesting its potential utility as a biomarker of periodontal inflammation and disease severity. Furthermore, recent studies have demonstrated significant associations between salivary IL-6 concentrations and clinical periodontal parameters, supporting its relevance in periodontal diagnostics [11-14].

Interleukin-40 (IL-40) is a recently identified B-cell-associated cytokine that has attracted growing interest because of its involvement in inflammatory and autoimmune diseases. Initially described by Catalan-Dibene et al., IL-40 has been associated with immune regulation and inflammatory responses and has been reported to be elevated in conditions such as rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus [15-17]. Despite increasing evidence supporting its role in chronic inflammatory diseases, the biological significance of IL-40 in periodontal disease remains poorly understood. Recent studies have suggested elevated salivary and gingival levels of IL-40 in periodontal inflammatory conditions, indicating that this cytokine may participate in the pathogenesis of periodontal tissue destruction and may have potential diagnostic value [18,19].

Given the pivotal role of inflammatory cytokines in periodontal disease pathogenesis and the increasing demand for reliable non-invasive biomarkers, further investigation of salivary IL-6 and IL-40 is warranted. Therefore, the

present study aimed to evaluate salivary IL-6 and IL-40 levels in patients with Stage III-IV periodontitis and periodontally healthy controls, and to assess their diagnostic performance and association with clinical periodontal parameters.

Material and Methods

Study Design and Ethical Approval

The present investigation was designed as an observational case-control study aimed at evaluating selected salivary inflammatory biomarkers in patients with periodontitis and periodontally healthy individuals. The study was conducted at the Department of Periodontics, College of Dentistry, University of Baghdad, between October 2025 and February 2026 under standardized clinical conditions. All procedures were performed in accordance with the ethical principles of the Declaration of Helsinki for research involving human participants (Reference No. 1087; Project No. 1087825).

Study Population

A total of 60 participants were recruited from patients attending the Department of Periodontics, College of Dentistry, University of Baghdad. Following clinical examination, participants were categorized into two groups:

- Periodontitis group (n=30): individuals diagnosed with stage III or stage IV periodontitis.
- Control group (n=30): systemically healthy individuals with clinically healthy periodontal tissues.

The diagnosis and classification of periodontitis were established according to the 2017 World Workshop Classification of Periodontal and Peri-Implant Diseases and Conditions.

Were included in this study participants aged between 26 and 66 years, with presence of at least 20 natural teeth, with a diagnosis of stage III or stage IV periodontitis, systemically healthy without known inflammatory or immune-related disorders. Were excluded individual with systemic diseases affecting periodontal health, history of periodontal treatment within the previous three months, use of antibiotics or anti-inflammatory medications within the previous three months, smoking or tobacco use, pregnancy or lactation or presence of acute oral infections.

Clinical Periodontal Examination

Comprehensive periodontal examination was performed for all participants by a calibrated examiner under standardized clinical conditions. The recorded clinical periodontal parameters included plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment loss (CAL).

Periodontal measurements were assessed using a University of Michigan O periodontal

probe with Williams markings. Measurements were recorded at six sites per tooth for all remaining teeth, excluding third molars.

Saliva Sample Collection

Unstimulated whole saliva samples were collected from all participants under standardized conditions prior to clinical periodontal examination. Sample collection was performed during the morning hours (10:00 AM–1:00 PM) to minimize circadian variations in salivary secretion and biomarker concentrations [20-22]. Participants were instructed to refrain from eating, drinking except water, tooth brushing, or performing oral hygiene procedures for at least one hour before sample collection. Approximately 2–3 mL of unstimulated whole saliva was collected into sterile pre-cooled polypropylene tubes [23,24]. Collected saliva samples were centrifuged to obtain clear supernatants for biomarker analysis. The resulting supernatants were transferred into sterile microcentrifuge tubes and stored at –80°C until laboratory analysis. Saliva samples were collected into sterile polyethylene tubes and immediately transferred in cooling containers before storage at –20°C until laboratory analysis.

Clinical Periodontal Examination

Comprehensive periodontal examination was performed for all participants after saliva collection by a calibrated examiner under standardized clinical conditions. Clinical periodontal parameters included plaque index (PI), bleeding on probing (BOP), probing pocket depth (PPD), and clinical attachment loss (CAL).

Periodontal measurements were obtained using a Michigan O periodontal probe with Williams markings. Plaque accumulation was evaluated according to the Silness and Loe plaque index. Bleeding on probing was assessed as an indicator of gingival inflammation by gentle probing of the gingival sulcus/pocket, and bleeding sites were recorded dichotomously as present or absent.

Probing pocket depth was measured as the distance between the gingival margin and the base of the periodontal pocket, whereas clinical attachment loss was measured as the distance from the cemento-enamel junction to the base of the periodontal pocket. Measurements were recorded in millimeters at six sites per tooth for all teeth excluding third molars and non-restorable teeth.

Measurement of Salivary IL-6 and IL-40

Salivary IL-6 and IL-40 concentrations were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits based on the sandwich-ELISA principle according to the manufacturers' instructions.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 25.0 (IBM Corp., Armonk, NY,

USA) and GraphPad Prism version 9.0 (GraphPad Software Inc., San Diego, CA, USA). Descriptive statistics were used to summarize the study variables. Continuous variables were expressed as mean $\pm$ standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Comparisons among multiple groups were performed using the Kruskal–Wallis test followed by Bonferroni post hoc analysis when appropriate. Associations between categorical variables were assessed using the chi-square (χ^2) test.

Results

Sex Distribution Between Study Groups

There were 16 females in the control group and 12 in the periodontitis group, whereas males 14 and 18 in the control and periodontitis groups, respectively. No statistically significant difference was observed in sex distribution between the study groups ($\chi^2 = 2.36$, $p = 0.304$), indicating comparability between the groups regarding gender distribution.

The mean age of the periodontitis group was 44.5 ± 7.94 years, whereas the control group showed a mean age of 41.63 ± 11.31 years. No statistically significant difference was observed between the two groups regarding age ($p = 0.26$), indicating that the study groups were comparable in terms of age distribution. The age range was 26–66 years in the control group and 30–62 years in the periodontitis group.

Clinical Periodontal Parameters

Clinical periodontal parameters were significantly higher in the periodontitis group compared with the control group. Patients with periodontitis demonstrated increased bleeding on probing (BOP), plaque index (PI), and probing pocket depth (PPD), reflecting enhanced periodontal inflammation and periodontal tissue destruction.

The mean BOP value was significantly higher in the periodontitis group (37.96 ± 13.86) compared with the control group (3.46 ± 1.01) ($p < 0.0001$). Similarly, both PI (0.7 vs. 2.2) and PPD in millimeters (1.8 vs. 5) values were significantly elevated in patients with periodontitis compared with healthy controls ($p < 0.0001$).

Clinical Periodontal Parameters

Patients with periodontitis exhibited significantly higher clinical periodontal parameters compared with healthy controls. The mean BOP value was significantly increased in the periodontitis group ($37.96 \pm 13.86\%$) compared with the control group ($3.46 \pm 1.01\%$) ($p < 0.0001$).

Similarly, plaque index (PI) and probing pocket depth (PPD) were significantly elevated in patients with periodontitis. The median PI value was 2.2 (2–2.5) in the periodontitis group compared with 0.7 (0.5–1) in controls, whereas the median PPD was 5 mm (4.3–5.5) in patients

and 1.8 mm (1.5–2) in controls ($p < 0.0001$ for both parameters).

Overall, all evaluated periodontal parameters demonstrated significantly higher values in periodontitis patients compared with healthy individuals.

In addition, the median clinical attachment loss (CAL) among periodontitis patients was 5.7 mm (5–6), confirming the presence of advanced periodontal tissue destruction.

Salivary IL-6 Levels

Salivary IL-6 concentrations were significantly higher in patients with periodontitis compared with healthy controls. The mean salivary IL-6 concentration in the periodontitis group was 15.06 ± 2.89 ng/L, whereas the control group showed a mean concentration of 11.01 ± 2.05 ng/L.

Statistical analysis demonstrated a highly significant difference between the two groups ($p < 0.0001$), indicating elevated salivary IL-6 levels in patients with periodontitis.

Salivary IL-6 Levels

Salivary IL-6 concentrations were significantly higher in patients with periodontitis compared with healthy controls. The mean salivary IL-6 concentration in the periodontitis group was 15.06 ± 2.89 ng/L, whereas the control group showed a mean concentration of 11.01 ± 2.05 ng/L. Statistical analysis demonstrated a highly significant difference between the two groups ($p < 0.0001$).

Diagnostic Performance of Salivary IL-6

Salivary IL-6 demonstrated good diagnostic performance with an area under the curve (AUC) of 0.868 ($p < 0.001$). The sensitivity and specificity were 73.3% and 96.7%, respectively, indicating a high ability of salivary IL-6 to discriminate periodontitis patients from healthy individuals.

Salivary IL-40 Levels

Salivary IL-40 levels were significantly higher in patients with periodontitis compared with healthy controls. The median salivary IL-40 concentration in the periodontitis group was 2.49 ng/L (1.82–3.70), whereas the control group demonstrated a median concentration of 1.48 ng/L (1.16–1.91).

Statistical analysis revealed a highly significant difference between the two groups ($p = 0.0001$), indicating elevated salivary IL-40 levels in periodontitis patients.

Diagnostic Performance of Salivary IL-40

Salivary IL-40 demonstrated acceptable diagnostic performance with an area under the curve (AUC) of 0.797 ($p < 0.0001$). At the optimal cutoff value (>1.79 ng/L), IL-40 showed a sensitivity of 83.3% and a specificity of 73.3%. The calculated Youden index was 0.5667, supporting the diagnostic potential of salivary IL-40 as a biomarker for periodontitis.

Comparison of Biomarker Levels According to Disease Stage

Salivary IL-6 levels were higher in Stage IV periodontitis compared with Stage III; however, the difference did not reach statistical significance ($p = 0.0558$).

In contrast, salivary IL-40 levels were significantly elevated in Stage IV patients compared with Stage III patients ($p = 0.0247$), suggesting a possible association between IL-40 levels and periodontal disease severity.

Biomarker Levels According to Disease Stage

Salivary IL-6 and IL-40 levels were compared between Stage III and Stage IV periodontitis patients. Although salivary IL-6 levels were higher in Stage IV patients, the difference did not reach statistical significance ($p = 0.0558$).

In contrast, salivary IL-40 levels were significantly elevated in Stage IV periodontitis compared with Stage III disease ($p = 0.0247$), suggesting a possible association between IL-40 expression and disease severity.

Discussion

The present study investigated the salivary levels and diagnostic significance of IL-6 and IL-40 in patients with periodontitis. The principal findings demonstrated significantly elevated salivary concentrations of both biomarkers in periodontitis patients compared with healthy controls. In addition, both biomarkers showed acceptable diagnostic performance, while IL-40 was significantly associated with disease stage [13,25–27].

The observed elevation of salivary IL-6 is biologically consistent with its established role in periodontal inflammation. IL-6 is a multifunctional pro-inflammatory cytokine involved in immune activation, osteoclastogenesis, and connective tissue degradation. The present findings agree with previous studies reporting increased salivary IL-6 levels in periodontitis patients and support its role as a marker of periodontal inflammatory burden. Furthermore, the significant positive correlations between IL-6 and clinical periodontal parameters indicate that higher IL-6 levels are associated with greater periodontal destruction and disease activity. The favorable diagnostic performance observed in the current study further supports the potential application of IL-6 as a non-invasive biomarker for periodontal disease assessment [28].

Similarly, salivary IL-40 levels were significantly elevated in periodontitis patients. Although IL-40 is a relatively novel cytokine and its role in periodontal disease remains incompletely understood, emerging evidence suggests its involvement in inflammatory and immune-regulatory pathways. The present findings are consistent with previous reports demonstrating increased IL-40 levels in periodontal

inflammatory conditions. Importantly, IL-40 was the only investigated biomarker significantly associated with disease stage, suggesting that it may reflect not only disease presence but also disease severity. In addition, its positive correlations with periodontal clinical parameters further support its relevance to periodontal inflammatory processes [18,29].

Both biomarkers demonstrated acceptable diagnostic performance for distinguishing periodontitis patients from healthy controls. Although IL-6 showed numerically higher diagnostic accuracy, the findings suggest that IL-40 may provide complementary information regarding disease severity. These observations support the concept that combining inflammatory biomarkers may improve periodontal diagnostic approaches compared with reliance on a single marker [26,30].

Several limitations should be acknowledged, including the relatively small sample size and the cross-sectional study design, which limit causal inference and generalizability. Nevertheless, the use of saliva as a non-invasive diagnostic medium and the integration of biomarker assessment with detailed periodontal examination represent important strengths of the study [31].

In conclusion, the present findings indicate that salivary IL-6 and IL-40 are significantly associated with periodontitis and may serve as promising non-invasive biomarkers for periodontal disease detection. The association of IL-40 with disease stage further highlights its potential relevance to disease progression [29]. Future longitudinal studies involving larger populations are required to validate these findings and clarify the biological role of IL-40 in periodontal pathogenesis.

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