



Evaluating Specific Salivary Biomarkers including Interleukin-1 (IL-1) as Potential Indicators of Systemic Inflammation in known Diabetic Patients with Periodontitis: An Original Research Study

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(Received: 27 September 2025 Revised: 05 October 2025 Accepted: 18 November 2025)

KEYWORDS

Biomarkers, Interleukin-1 (IL-1), Diabetic Mellitus, Periodontitis, Inflammation

ABSTRACT:

Aim: This study evaluates specific salivary biomarkers, particularly interleukin-1 (IL-1), in diabetic patients presenting with periodontitis as potential indicators of systemic inflammation.

Materials and Methods: This study explored the link between severe periodontal inflammation and diabetes mellitus by enrolling 80 patients with significant periodontal issues. Of these, 60 diabetic individuals expressed interest in treatment. Participants, aged 35 to 60, included both genders and were carefully selected to eliminate confounding factors such as mental instability, smoking, or pregnancy. After obtaining informed consent and conducting comprehensive evaluations, the final cohort comprised 60 patients divided into three groups: Group 1: 20 diabetic patients with periodontitis (DWP), Group 2: 20 healthy individuals with periodontitis (WoP), and Group 3: 20 diabetic patients without periodontitis (DWPo). This allowed for a detailed analysis of diabetes and periodontal disease. Peri-implant crevicular fluid (PICF) samples were collected and analysed for interleukin-1 (IL-1) levels using an ELISA test, aiming to establish these biomarkers as indicators of systemic inflammation and inform future treatment strategies.

Statistical Analysis and Results: This study analysed a cohort of 60 participants—31 males and 29 females—as shown in Table 1. The participants were divided into three groups based on health conditions: Group 1 (Diabetic Patients with Periodontitis, DWP) included 20 individuals with both diabetes and periodontitis; Group 2 (Individuals with Periodontitis Only, WoP) comprised 20 healthy individuals with periodontitis but no diabetes; and Group 3 (Diabetic Patients without Periodontitis, DWPo) featured 20 diabetic patients without periodontitis. Salivary interleukin-1 (IL-1) levels were measured using ELISA, revealing significant elevations in Group 1, mixed responses in Group 2 (with 10 showing no inflammation), and stable levels in Group 3, indicating that diabetes alone does not lead to inflammation without periodontitis. One-way ANOVA results summarised in Table 5 highlight the interactions between diabetes, periodontitis, and salivary biomarkers, enhancing understanding of the inflammatory processes and their implications for patient management and public health research.

Conclusion: The study found that diabetic patients with periodontitis (DWP) have significantly higher IL-1 levels compared to healthy individuals, patients with periodontitis alone (WoP), and diabetic patients without



periodontitis (DWP). This increase in IL-1 in the DWP group is due to the combined effects of diabetes and periodontitis, resulting in a stronger inflammatory response. While IL-1 levels in the WP group are elevated compared to healthy individuals, they remain lower than in the DWP group. DWP patients have IL-1 levels similar to healthy individuals.

Introduction

Diabetes mellitus (DM) has become a critical global health issue, with its occurrence rising among different demographics and age groups. This long-term metabolic disorder is marked by elevated blood sugar levels, referred to as hyperglycemia, and can present various early warning symptoms. Frequently observed signs include polydipsia (excessive thirst), polyuria (increased urination), cephalalgia (headaches), blurred vision, ongoing fatigue, unexpected weight loss, and slow wound healing.^{1,2} The emergence of these symptoms can greatly affect quality of life and highlights the need for early diagnosis and treatment. Diabetes is divided into four main types, each characterised by unique pathophysiological processes.³ Type 1 diabetes arises when the body's immune system incorrectly targets and destroys the insulin-producing β -cells in the pancreas. This autoimmune reaction results in a complete lack of insulin, necessitating lifelong insulin treatment for survival. Type 2 diabetes is marked by a gradual reduction in insulin secretion combined with insulin resistance, wherein the body's cells become less responsive to insulin. This type is often linked to lifestyle factors like obesity, lack of physical activity, and poor dietary habits, and generally emerges in adulthood, though it is increasingly seen in younger individuals as well. Gestational diabetes occurs during pregnancy, with hormonal fluctuations leading to insulin resistance. This condition poses risks for both the expectant mother and the developing fetus, requiring careful management to reduce potential complications. Other specific types of diabetes arise from various causes, including genetic abnormalities in insulin function or secretion, pancreatic diseases, or conditions triggered by certain medications.⁴⁻⁶ A notable discovery in diabetes research is the bidirectional interaction between diabetes and periodontitis, a prevalent inflammatory disease that affects the supporting tissues of the teeth. Chronic systemic inflammation serves as a crucial link between these two conditions; periodontitis can impair glycemic control and heighten insulin

resistance, while diabetes increases the risk of developing and progressing periodontitis due to overlapping inflammatory pathways. This connection underscores the importance of integrated care approaches that concurrently address both conditions to enhance overall health outcomes.^{7,8} Biomarkers are instrumental in medicine, acting as measurable indicators of biological processes or disease states that can be detected in blood or other bodily fluids. These markers are essential for disease detection, diagnosis, and the continuous monitoring of health status. For example, increased levels of prostate-specific antigen (PSA) in blood may suggest the presence of prostate cancer, while hemoglobin A1c (HbA1c) has become the recognized biomarker for diagnosing diabetes mellitus, indicating long-term glycemic control over weeks to months.^{9,10} The enzyme-linked immunosorbent assay (ELISA) is a widely used laboratory method for detecting and quantifying various biomarkers. This technique utilizes enzyme-linked antibodies that bind to specific antigens, generating a measurable signal that reflects the presence and concentration of the target substance. ELISA is crucial in diagnosing numerous medical conditions, offering reliable results that assist in clinical decision-making.¹¹ Interleukin-1 (IL-1) is a crucial cytokine primarily produced by macrophages, which are key players in our immune system. This signalling molecule is vital in orchestrating the body's inflammatory response and regulating various aspects of immunity. IL-1 participates actively in recruiting other immune cells to sites of infection or injury, thereby amplifying the body's defence mechanisms. Additionally, it is responsible for inducing fever, a common physiological response that helps to create an environment less favourable for pathogens.¹² Beyond its role in typical inflammatory processes, IL-1 is implicated in the pathology of numerous inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. Its significant involvement in such conditions has positioned IL-1 as an attractive target for therapeutic strategies. By focusing on this cytokine, researchers are exploring innovative interventions aimed at mitigating the detrimental effects of



inflammation, ultimately improving patient outcomes and quality of life for those suffering from these disorders.¹³ This study evaluates specific salivary biomarkers, particularly interleukin-1 (IL-1), in diabetic patients presenting with periodontitis as potential indicators of systemic inflammation.

Materials and Methods

This study was designed to explore the relationship between severe periodontal inflammation and diabetes mellitus by initially enrolling a cohort of 80 patients who displayed significant periodontal issues. Among these participants, 60 individuals who had been diagnosed with diabetes mellitus expressed a keen interest in receiving treatment for their oral conditions. The study established detailed inclusion criteria, specifying that participants must be aged between 35 and 60 years. Both males and females were welcomed to ensure a representative sample of the population, with all participants required to have a confirmed diagnosis of diabetes mellitus, thereby establishing a clear focus on the relationship between diabetes and periodontal health. Meticulous exclusion criteria were also implemented to safeguard the integrity of the research findings. Individuals demonstrating signs of mental instability, those who are current smokers and pregnant women were systematically excluded from the study. This decision was made to avoid any confounding factors that might obscure the results and lead to inaccurate conclusions regarding the impact of diabetes on periodontal disease. Before the commencement of any clinical procedures within the study, informed consent was diligently obtained from all participants. This process encompassed a thorough explanation of the study's purpose, procedures, potential risks, and benefits, ensuring that participants were fully aware and agreeable to the terms. Furthermore, comprehensive clinical evaluations were conducted for each participant. These evaluations included detailed medical histories, where past health issues and current conditions were noted, as well as comprehensive physical examinations designed to assess overall health. Radiological assessments were performed to accurately document the severity of periodontal disease and identify any other pertinent health conditions that could influence the study's outcomes, thereby providing a robust foundation for analysing the interplay between diabetes and periodontal health. The final analytical

cohort was composed of 60 patients, meticulously categorised into three distinct groups to facilitate a comprehensive comparative analysis. Group 1 consisted of 20 patients diagnosed with diabetes who were also experiencing periodontitis, referred to as Diabetic Patients with Periodontitis (DWP). Group 2 included 20 healthy individuals, all of whom presented with periodontitis, and are designated as Individuals with Periodontitis only (WoP). Lastly, Group 3 comprised 20 diabetic patients who did not show any signs of periodontitis, referred to as Diabetic Patients without Periodontitis (DWoP). This careful stratification of the participants was essential for gaining insights into the complex relationship between diabetes and periodontal disease, highlighting the variances in clinical outcomes and disease mechanisms across the different groups. To investigate the biomarkers associated with periodontal health, specifically the levels of the cytokine interleukin-1 (IL-1), samples of peri-implant crevicular fluid (PICF) were meticulously collected from each implant site across all patient groups. This sample collection process was carried out with great precision using calibrated microcapillary pipettes to ensure accuracy. Cotton rolls were systematically utilized during the procedure to maintain a sterile environment, thereby minimizing the risk of contamination. The collected samples were promptly transferred to a phosphate-buffered saline solution to preserve their biochemical integrity, and they were subsequently frozen at -70°C for further analysis. Any samples that exhibited signs of contamination were discarded to ensure the reliability and validity of the study outcomes. For the evaluation of IL-1 levels, an ELISA test kit was employed, which are widely recognized in the scientific community for its high sensitivity and specificity in quantifying cytokine concentrations. This study was to investigate the presence and levels of salivary biomarkers, particularly IL-1, in diabetic patients with periodontitis. The hypothesis posited that these biomarkers could serve as potential indicators of systemic inflammation, contributing valuable insights into the intricate relationship between diabetes and periodontal disease and potentially guiding future therapeutic strategies.

Statistical Analysis and Results

In this study, we employed SPSS software version 29.0 for all statistical analyses, leveraging its capabilities for



statistical computing and data analysis within the social sciences. To assess the significance of our findings, we utilised the chi-square test, a method well-suited for exploring differences in proportions among various groups. This approach enabled us to conduct a thorough and rigorous comparison of categorical data, ensuring that our results accurately represent the underlying trends and relationships in the dataset.

Results

This study involved a diverse and well-characterised cohort of 60 participants, comprising both male and female individuals. As summarised in Table 1, the demographic information provides an extensive statistical overview of the age and gender distribution among the participants, which is crucial for understanding the interplay of these variables in relation to the health conditions being studied. Additionally, Graph 1 visually represents this demographic data, showcasing a near equilibrium in gender representation, with 31 males and 29 females included in the analysis. The participants were classified into three distinct groups based on their specific health conditions, thereby facilitating targeted comparisons across different patient profiles. Group 1, titled Diabetic Patients with Periodontitis (DWP), comprised 20 individuals who had been diagnosed with diabetes and were also exhibiting signs of periodontitis. This group's identification is particularly significant as it allows for an exploration of the interactions between metabolic dysregulation (diabetes) and periodontal disease. Group 2, designated Individuals with Periodontitis Only (WoP), included another cohort of 20 healthy individuals who were diagnosed with periodontitis but did not have diabetes. This classification serves to highlight the differences in inflammatory responses and salivary biomarkers between those with and without diabetes. Finally, Group 3 encompassed Diabetic Patients without Periodontitis (DWoP), consisting of 20 diabetic patients who did not exhibit any signs of periodontal disease. This group allows for a clearer understanding of how diabetes may affect inflammatory processes in the

absence of periodontitis. To investigate the salivary levels of the inflammatory biomarker interleukin-1 (IL-1), the study employed the Enzyme-Linked Immunosorbent Assay (ELISA) across all three groups. The findings for Group 1 (DWP) indicated significant inflammatory responses, with all 20 patients showing elevated levels of this biomarker. Statistical analysis performed via the Pearson Chi-Square test underscored the strong correlation between diabetes and periodontitis in this specific cohort, suggesting a heightened risk and severity of inflammatory responses in patients with co-existing conditions. In stark contrast, the analysis of Group 2 (WoP) revealed a more complex picture. Among the 20 participants analyzed, 10 exhibited no observable changes in the salivary levels of the IL-1 biomarker, with none showing indicators of inflammation. This finding suggests that periodontitis may manifest differently in healthy individuals compared to those with diabetes, indicating a potential differential pathway of inflammation and immune response. Similarly, the evaluation of Group 3 (DWoP) found that 11 of the patients showed no significant changes in salivary interleukin-1 levels, reinforcing the idea that diabetes alone does not predispose individuals to the inflammatory consequences associated with periodontitis in the absence of the disease. Furthermore, Table 5 compiles and details the results obtained from a one-way ANOVA, providing an intricate examination of the differences among the three groups studied. This statistical analysis is pivotal in elucidating the complex relationships between diabetes, periodontitis, and salivary biomarker levels, thereby offering valuable insights into the ways these health conditions may interact and influence each other. Such a comprehensive examination greatly contributes to the understanding of the underlying inflammatory processes involved in these health issues, highlighting their implications for patient management and therapeutic interventions. Ultimately, this study serves to enhance the existing body of knowledge on the multifaceted relationships between chronic diseases and suggests pathways for future research in this critical area of public health.

Table 1: Age & gender based statistical description of contributing patients

Age Group (Yrs)	Male	Female	Total	P value
35-40	8	9	17	0.05*



41-45	6	6	12	0.40
46-50	8	5	13	0.02*
51-55	4	4	8	0.60
56-60	5	5	10	0.40
Total	31	29	60	*Significant
*p<0.05 significant				

Graph 1: Patients demographic distribution and associated details

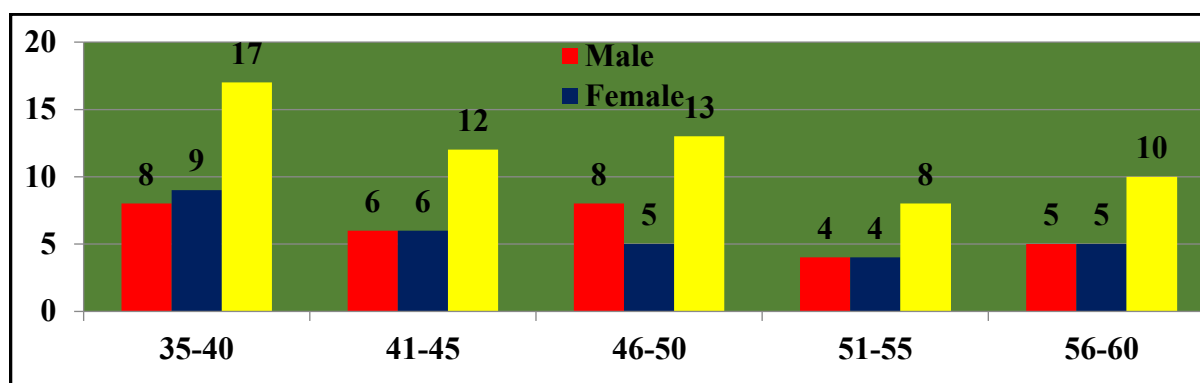


Table 2: Group 1 (n=20) diabetic patients diagnosed with periodontitis, referred to as Diabetic Patients with Periodontitis (DWP). We assessed the salivary biomarker interleukin-1 (IL-1) utilising the ELISA assay. Statistical significance of the results was determined using the Pearson Chi-Square test

Parameters	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Inflammation	5	1.12	1.08	1.60	1.170	1.18	1.17	1.09
Disease severity and progression	4	1.10	1.06	1.030	1.140	1.16	1.16	1.07
Osteoclastic activity	3	1.07	1.04	1.026	1.130	1.13	1.09	1.0
Other systemic health	2	1.04	1.03	1.045	1.210	1.04	1.07	0.02*
Treatment response monitoring	3	1.07	1.04	1.026	1.130	1.13	1.09	1.0
Early detection	3	1.07	1.04	1.026	1.130	1.13	1.09	1.0
No abnormality detected	-	-	-	-	-	-	-	-
*p<0.05 significant								



Table 3: Group 2 (n= 20) Healthy individuals with periodontitis, known as Individuals with Periodontitis only (WoP). We assessed the salivary biomarker interleukin-1 (IL-1) utilising the ELISA assay. Statistical significance of the results was determined using the Pearson Chi-Square test.

Parameters	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Inflammation	3	1.07	1.04	1.026	1.130	1.13	1.09	1.0
Disease severity and progression	2	1.04	1.03	1.045	1.210	1.04	1.07	0.02*
Osteoclastic activity	1	1.03	1.02	1.023	1.022	1.12	1.05	0.01*
Other systemic health	1	1.03	1.02	1.023	1.022	1.12	1.05	0.01*
Treatment response monitoring	2	1.04	1.03	1.045	1.210	1.04	1.07	0.02*
Early detection	1	1.03	1.02	1.023	1.022	1.12	1.05	0.01*
No abnormality detected	10	1.26	1.12	1.78	1.182	1.19	1.18	1.22
*p<0.05 significant								

Table 4: Group 3 (n= 20) diabetic patients without periodontitis, referred to as Diabetic Patients without Periodontitis (DWoP). We assessed the salivary biomarker interleukin-1 (IL-1) utilising the ELISA assay. Statistical significance of the results was determined using the Pearson Chi-Square test

Parameters	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Inflammation	2	1.04	1.03	1.045	1.210	1.04	1.07	0.02*
Disease severity and progression	2	1.04	1.03	1.045	1.210	1.04	1.07	0.02*
Osteoclastic activity	1	1.03	1.02	1.023	1.022	1.12	1.05	0.01*
Other systemic health	2	1.04	1.03	1.045	1.210	1.04	1.07	0.02*
Treatment response monitoring	1	1.03	1.02	1.023	1.022	1.12	1.05	0.01*
Early detection	1	1.03	1.02	1.023	1.022	1.12	1.05	0.01*
No abnormality detected	11	1.28	1.22	1.80	1.190	1.22	1.19	1.26



*p<0.05 significant

Table 5: Estimation amongst all studied groups using one-way ANOVA

Variables	Degree of Freedom	Sum of Squares Σ	Mean Sum of Squares $m\Sigma$	F	Level of Sig. (p)
Between Groups	4	2.440	2.467	1.4	0.02*
Within Groups	17	2.256	2.232		–
Cumulative	131.20	16.364	*p<0.05 significant		

Discussion

Punthakee Z et al reviewed in their study that Diabetes mellitus (DM) is often described as an "iceberg" phenomenon because many people with the condition do not know they have it. This chronic disease happens when the pancreas does not produce enough insulin or when the body cannot use insulin properly. When diabetes is not controlled, it can lead to high blood sugar levels, which can harm important parts of the body, such as blood vessels and nerves. To manage DM effectively, individuals need to monitor their health closely and make lifestyle changes. This includes eating a balanced diet, exercising regularly, maintaining a healthy weight, and limiting sodium and alcohol intake.^{14,15} Karakaya RE et al included in their study that current therapeutic strategies for both type 1 and type 2 diabetes prioritise the reduction of hyperglycemia and the alleviation of symptoms resulting from complications. There is a pressing need to enhance the efficacy of existing pharmacological agents while also exploring innovative multimodal approaches for the management and prevention of diabetes. One notable complication associated with diabetes is periodontal disease (periodontitis), which transcends a mere localized oral infection. The interrelationship between periodontitis and diabetes illustrates how systemic conditions can heighten susceptibility to oral infections, which in turn can exacerbate the underlying diabetic condition. Furthermore, oral infections may pose an increased risk for systemic complications.^{16,17} Kocher T et al showed in their study that to elucidate the cellular and molecular mechanisms underpinning this

bidirectional relationship, it is critical to identify shared physiological alterations linked to both diabetes and periodontitis that engender a synergistic impact when these conditions are coexistent. A potential mechanistic axis revolves around inflammation, particularly concerning immune cell function, serum lipid levels, and tissue homeostasis. Diabetes-related changes in immune cell dynamics contribute to a pro-inflammatory profile, characterised by elevated levels of pro-inflammatory cytokines from monocytes and polymorphonuclear leukocytes, alongside a reduction in growth factors produced by macrophages. This inflammatory milieu predisposes individuals to chronic inflammation, persistent tissue breakdown, and impaired tissue repair capacity. Periodontal tissues are often indicative of these pathological changes, reflecting ongoing damage resulting from microbial biofilm byproducts.^{18,19} Fischer RG et al reviewed in their study that the designation "biomarker," stemming from "biological marker," encompasses a broad array of medical signs—specifically, objective indicators of a pathological state that can be quantitatively measured outside the patient. This differentiates biomarkers from symptoms, which are subjective experiences reported by patients. Various biomarkers detectable in saliva, gingival crevicular fluid (GCF), and blood are employed in the diagnosis of periodontitis, including inflammatory mediators such as IL-1 β , IL-6, and TNF- α , as well as enzymes like MMP-8 and proteins such as haemoglobin and C-reactive protein. These biomarkers facilitate early detection, assessment of disease severity, and monitoring of treatment response, often leveraging



rapid point-of-care methodologies.^{20,21} Gomes AM et al showed in their study that Interleukin-1 (IL-1) is a crucial pro-inflammatory cytokine that plays a significant role in the pathogenesis of periodontitis, a serious gum disease. It contributes to the destructive processes that affect periodontal tissues, leading to the breakdown of soft and hard tissue structures and promoting bone resorption, which can ultimately compromise dental integrity. Research has demonstrated that elevated levels of IL-1 β , a specific form of this cytokine, are closely linked to the severity of periodontitis, suggesting that higher concentrations may correspond with more advanced stages of the disease. Furthermore, genetic variations, or polymorphisms, within the IL-1 gene cluster have been associated with an increased risk of developing severe forms of periodontitis, indicating a genetic predisposition that may enhance an individual's susceptibility to the condition.²²⁻²⁴ Hayrapetyan et al. reviewed in their study that the enzyme-linked immunosorbent assay (ELISA) is a commonly employed analytical technique for measuring and studying these biomarkers due to its ability to detect specific proteins. However, it does have its drawbacks; particularly, its sensitivity threshold of approximately 1 picomolar can limit the detection of low-abundance biomarkers that may be present in the early stages of periodontal disease or infection. This limitation underscores the challenges researchers face in identifying initial biological signals that could lead to earlier diagnostics and interventions.²⁵

Conclusion

In this study, the author investigated specific salivary biomarkers, with a particular emphasis on interleukin-1 (IL-1), in diabetic patients diagnosed with periodontitis, considering them as potential indicators of systemic inflammation. The findings reveal that diabetic patients with periodontitis (DWP) demonstrate significantly elevated levels of the IL-1 biomarker when compared to healthy individuals, patients with periodontitis only (WoP), and diabetic patients without periodontitis (DWoP). The increase in IL-1 levels observed in the DWP group is attributed to the synergistic effects of diabetes and periodontitis, which elicit a pronounced inflammatory response. Patients within this group exhibit the highest concentrations of IL-1 β (a subtype of IL-1). The presence of hyperglycemia associated with diabetes appears to intensify the inflammatory response

to periodontal disease, leading to an increase in IL-1 β levels. Conversely, individuals in the WoP group, who present with periodontitis independent of diabetes, also exhibit elevated IL-1 levels compared to healthy individuals; however, their levels remain lower than those observed in the DWP group. Furthermore, diabetic patients without periodontitis (DWoP) display lower IL-1 levels than the DWP group, which are generally more aligned with the levels seen in healthy individuals. These results underscore the need for further research to elucidate the underlying mechanisms contributing to these observations and to refine clinical practices in periodontology in the future.

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