Journal of Chemical Health Risks

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JCHR (2025) 15(5), 2868-2876 | ISSN:2251-6727

Estimation of the Relationship between Periodontal Inflamed Surface Area (PISA) and Macrophage Inflammatory Protein-1α (MIP-1α) in Type 2 Diabetic and Non-Diabetic Patients with Chronic Periodontitis

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(Received: 25 August 2025 Revised: 27 September 2025 Accepted: 14 October 2025)

KEYWORDS

PISA, MIP-1α, chronic periodontitis, diabetes mellitus, salivary biomarkers, HbA1c, systemic inflammation

ABSTRACT:

Background: Chronic periodontitis (CP) and type 2 diabetes mellitus (T2DM) are chronic, multifactorial diseases that influence and exacerbate one another through systemic immunoinflammatory pathways. Periodontal Inflamed Surface Area (PISA) provides a quantitative assessment of the inflamed periodontal surface, which may contribute to systemic inflammatory burden. Macrophage Inflammatory Protein-1α (MIP-1α), a key salivary chemokine, reflects monocyte/macrophage activation and plays a crucial role in local and systemic immune responses. Understanding the interplay between PISA and MIP-1α in diabetic and non-diabetic individuals could provide deeper insights into the shared pathophysiology of periodontal and metabolic disorders.

Aim: The study aimed to evaluate and correlate PISA and salivary MIP-1α levels in chronic periodontitis patients with and without type 2 diabetes and to investigate their relationship with glycemic control, as indicated by glycated hemoglobin (HbA1c) levels.

Methods: Sixty patients aged between 25 and 80 years, clinically diagnosed with chronic periodontitis, were selected and categorized into two groups (n=30 each): Group A (non-diabetics with CP) and Group B (T2DM patients with CP). Standard periodontal parameters—probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP)—were recorded. PISA values were computed using CAL and BOP. Salivary MIP-1α concentrations were analyzed via ELISA, and HbA1c levels were evaluated to assess glycemic status.

Results: Patients in Group B exhibited significantly higher PISA and MIP-1α levels than those in Group A. Correlation analysis revealed strong positive relationships: PISA vs. MIP-1α ($r = 0.62$), PISA vs. HbA1c ($r = 0.68$), and MIP-1α vs. HbA1c ($r = 0.59$). These findings underscore the bidirectional influence of periodontal inflammation and glycemic control.

Conclusion: Salivary MIP-1α and PISA are robust, non-invasive markers for assessing periodontal inflammation and may serve as adjuncts in evaluating systemic disease status, particularly in T2DM.

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Their significant association with glycemic parameters supports the integration of periodontal evaluation into diabetes management protocols.

1. Introduction

Periodontal diseases represent a spectrum of inflammatory conditions affecting the supporting structures of the teeth. Chronic periodontitis (CP), the most prevalent form, results from prolonged host-microbial interaction, leading to progressive attachment loss and alveolar bone resorption.[1] Globally, it affects approximately 35–50% of the adult population and contributes significantly to tooth morbidity and edentulism. While microbial biofilm is the primary etiologic factor, host immune response, influenced by systemic and behavioral variables, plays a pivotal role in disease severity and progression.[2,3]

Among systemic conditions, **type 2 diabetes mellitus (T2DM)** has emerged as one of the most important and modifiable risk factors for **chronic periodontitis (CP)**. It is well-established that poorly controlled diabetes not only increases susceptibility to periodontitis but also accelerates its **severity, extent, and progression**.[4,5] The biological mechanisms underlying this association are multifactorial. Persistent **hyperglycemia** promotes the formation of **advanced glycation end-products (AGEs)**, which accumulate in periodontal tissues and interact with their receptors (RAGEs), thereby amplifying local inflammatory responses.[6] In addition, **heightened oxidative stress**, **impaired neutrophil chemotaxis and phagocytosis**, and **exaggerated cytokine production** (including interleukin-1β, interleukin-6, and TNF-α) create a hyper-inflammatory milieu that compromises periodontal tissue integrity and repair mechanisms.[7]

Conversely, chronic untreated periodontal inflammation does not remain localized. Periodontal pockets serve as a reservoir of microbial products such as **lipopolysaccharides (LPS)** and **peptidoglycans**, which translocate into the systemic circulation.[8] These, in turn, upregulate the release of systemic pro-inflammatory mediators including **IL-6, TNF-α, and C-reactive protein (CRP)**, thereby contributing to **insulin resistance** and worsening glycemic control. This bidirectional interaction between diabetes and periodontitis has been aptly described as a **"two-way street" relationship**, wherein each condition exacerbates the other, creating a vicious cycle.[9,10]

While traditional periodontal parameters—such as probing pocket depth (PPD), clinical attachment level (CAL), and bleeding on probing (BOP)—are invaluable for clinical diagnosis, they do not provide a quantitative estimate of the **systemic inflammatory burden** imposed by periodontal disease. Recognizing this gap, **Nesse et al. (2008)** introduced the concept of the **Periodontal Inflamed Surface Area (PISA)**. PISA is calculated by combining **CAL** and **BOP** scores across all periodontal sites to estimate the total area of **ulcerated pocket epithelium** (expressed in mm^2). This ulcerated epithelial surface represents the "portal of entry" through which periodontal pathogens and inflammatory mediators can access the bloodstream. By translating clinical periodontal data into a **numerical measure of inflammatory burden**, PISA serves as a bridge between localized periodontal disease and its potential **systemic implications**.

Thus, PISA not only complements traditional indices but also enhances our understanding of the potential role of periodontitis in systemic conditions such as diabetes, cardiovascular disease, and chronic kidney disease. This innovative concept allows researchers and clinicians to objectively quantify the **extent of inflammatory exposure** to systemic circulation, thereby offering a more precise tool for exploring the **periodontal-systemic link**.[11]

Concurrently, research on salivary diagnostics has gained momentum. Saliva, due to its ease of collection, reflects both oral and systemic health.[12] Among the numerous biomarkers, Macrophage Inflammatory Protein-1α (MIP-1α)—a chemokine involved in leukocyte recruitment and activation—has shown promise in periodontal disease assessment. Elevated levels of MIP-1α have been found in gingival crevicular fluid and saliva of periodontitis patients, indicating active inflammation.[13] In diabetic individuals, this chemokine

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may also be upregulated due to systemic immune dysregulation.[14]

The present study investigates whether PISA and MIP-1α are significantly elevated in type 2 diabetics with CP and whether these biomarkers correlate with HbA1c, an established indicator of long-term glycemic control. Establishing such relationships could reinforce the role of periodontal health in systemic disease monitoring and management.

2. Materials and Methods

Materials and Methods

This cross-sectional analytical study was conducted in the Department of Periodontology at NIMS Dental College and Hospital, Jaipur. Prior to commencement, ethical clearance was obtained from the Institutional Ethics Committee (IEC), and all study procedures adhered to the ethical standards of the Declaration of Helsinki. The study protocol was approved under the reference number NIMS/Dent/2023/EC45. All participants were briefed about the study objectives, and written informed consent was obtained from each subject before any clinical or laboratory procedure was undertaken.

Study Population

A total of 60 individuals diagnosed with chronic periodontitis were recruited for the study. The participants were divided into two groups based on their glycemic status. Group A comprised non-diabetic individuals with chronic periodontitis, defined by glycated hemoglobin (HbA1c) levels of less than 6.0%. Group B included patients with type 2 diabetes mellitus and chronic periodontitis, with HbA1c values equal to or greater than 6.5%. This stratification allowed for the evaluation of periodontal inflammatory burden and its association with systemic glycemic control.

The inclusion criteria for participation were: (1) age between 25 and 80 years, (2) presence of at least 20 natural teeth, and (3) clinical diagnosis of chronic periodontitis with probing depth (PD) ≥ 5 mm, clinical attachment loss (CAL) ≥ 3 mm, and bleeding on probing (BOP) present in 30% or more of periodontal sites. The exclusion criteria were established to eliminate confounding variables and included the presence of systemic diseases other than diabetes mellitus (e.g., cardiovascular disorders, autoimmune diseases), history of periodontal therapy in the past six months, current use of antibiotics or anti-inflammatory medications within the last three months, pregnancy or lactation, and current tobacco use in any form, including both smoking and smokeless tobacco.

Clinical Examination

All clinical evaluations were conducted by a single, calibrated examiner to ensure consistency and minimize measurement variability. Calibration was achieved through repeated measurement exercises until intra-examiner reliability exceeded a kappa value of 0.85. A UNC-15 periodontal probe was employed for all periodontal measurements.

The clinical assessment for each participant included the evaluation of several key periodontal parameters to establish a comprehensive profile of their periodontal health. **Probing Depth (PD)** was measured in millimeters at six sites around each tooth—namely, the mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual surfaces—using a UNC-15 periodontal probe. **Clinical Attachment Level (CAL)** was determined at the same six sites per tooth by measuring the distance from the cementoenamel junction to the base of the periodontal pocket, providing insight into the cumulative loss of periodontal support. **Bleeding on Probing (BOP)** was recorded as a dichotomous variable, indicating the presence or absence of bleeding within 15 seconds after probing, which serves as a marker of active inflammation. (Fig 1) The **Plaque Index (PI)** was assessed using the criteria established by Silness and Löe to quantify the thickness of dental plaque on tooth surfaces. Additionally, the **Gingival Index (GI)** was recorded following the Löe and Silness method, evaluating the severity of gingival inflammation based on tissue color, consistency, and bleeding response to gentle probing. Collectively, these clinical measurements provided a detailed and objective evaluation of each subject's periodontal condition.

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Fig 1: MEASUREMENT OF CLINICAL ATTACHMENT LEVEL, POCKET DEPTH, BLEEDING ON PROBING.

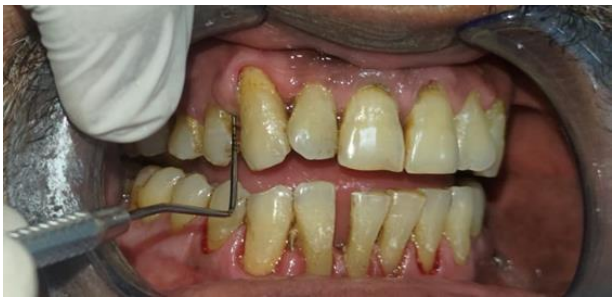

Fig A: Measurement of CAL

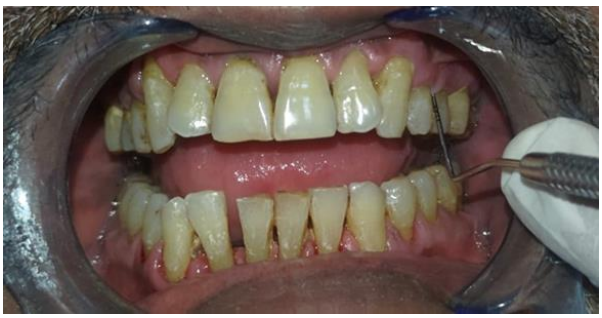

Fig B: Measurement of Pocket Depth

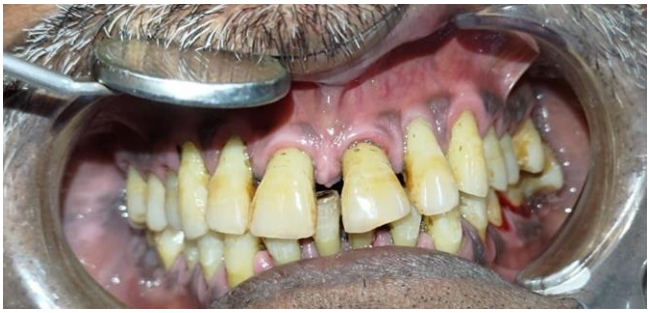

Fig C: Bleeding on Probing

Fig 1: Examination and Measurement of patient findings. Fig a: Measurement of clinical attachment Loss, Fig B: Measurement of Pocket Depth, Fig C: Measurement of Bleeding on Probing

PISA Calculation

To quantify the periodontal inflammatory burden more precisely, the **Periodontal Inflamed Surface Area (PISA)** was calculated. This parameter estimates the surface area of bleeding pocket epithelium in square millimeters and allows for a standardized comparison of inflammation levels across different patients and populations.

The PISA values were derived using an Excel-based computational model introduced by Nesse et al.(Fig:2). This calculator integrates data from CAL, gingival recession, and the presence of BOP at individual sites. The result is a numeric representation of the area of inflamed periodontal tissue, which is more informative than conventional indices in evaluating systemic inflammatory load due to periodontitis.

Fig 2: Spreadsheet for Calculating the PISA

Fig 2: Spreadsheet for Calculating the PISA

Saliva and Blood Sample Collection

Biological sampling was performed to investigate the expression of a key inflammatory biomarker—**Macrophage Inflammatory Protein-1 alpha (MIP-1α)**—in saliva and to determine systemic glycemic control via HbA1c.

SalivaCollection:

Unstimulated whole saliva samples (5 ml) were collected from each subject between 9:00 AM and 11:00 AM to minimize the effects of diurnal variation. Participants were instructed to refrain from eating, drinking (except water), brushing teeth, or using mouthwash for at least one hour prior to sample collection. Saliva was collected by passive drooling into sterile containers while the participant sat in an upright position. The collected samples were immediately placed on ice, centrifuged at 3,000 rpm for 10 minutes to remove debris, and the

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supernatant was stored at –80°C until laboratory analysis.

BloodCollection:
A 2 ml venous blood sample was drawn from the antecubital vein using sterile techniques. The blood samples were analyzed for HbA1c using **high-performance liquid chromatography (HPLC)**, which is considered the gold standard for glycemic assessment due to its high sensitivity and specificity.

Biochemical Analysis

To assess local inflammatory activity, **salivary MIP-1α levels** were measured using a **commercially available enzyme-linked immunosorbent assay (ELISA)** kit (FineTest, Wuhan, China). (Fig 3)

Figure 3: ELISA KIT

Brand name: Fine test

Specifications: 96T

Application in quantitative determination of MIP-1α concentrations in Serum, plasma, cell culture supernatant, cell lysate or tissue lysate, other biological fluid samples. Reactivity Human Detection Method Sandwich ELISA, Double Antibody Range 23.438-1500pg/ml Sensitivity 14.063pg/ml Detection Duration 120 minutes (excluding balancing and sample preparation) Samples needed for single well (Max) Serum: 50ul, Plasma: 50ul, Cell Culture Supernatant: 50ul, cell or tissue lysate: 50ul, Other liquid samples: 50ul Specificity Specifically recognize MIP-1α, no obvious cross reaction with other analogues Storage 2-8°C (for sealed box).
The analysis was performed according to the manufacturer's instructions . All samples were processed by process of pipetting (Fig 4) and followed by instruction given in the kit in duplicate to ensure accuracy and reproducibility of the results using Elisa machine (fig 5). The final concentrations were expressed in picograms per milliliter (pg/ml). The laboratory personnel conducting the assays were blinded to the group allocations to avoid any potential bias in result interpretation.

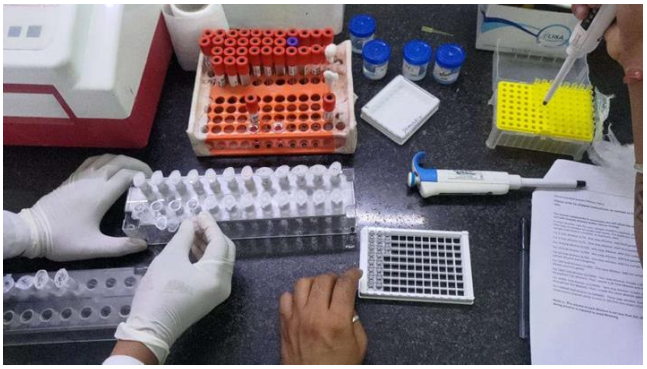

Fig 4: PROCESS OF PIPETTING

Fig 5: ELISA MACHINE

Fig 5: The ALTA ELISA Reader (ADX-110) is a user friendly 96-well micro plate reader.

Product Specifications:

It is intended for diagnostic use to measure and interpret enzyme immunoassay results, both monochromatically and dichromatically.

Ability to read plate within 15 seconds

Digital light control with unique circuit for long lamp life 4 standard wavelengths (405nm, 450nm, 492nm & 630nm) & 2 free positions; Single and dual wavelength readings

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Statistical Analysis

The collected data were compiled and analyzed using **IBM SPSS Statistics software, version 26.0**. Continuous variables such as PD, CAL, PISA, MIP-1α levels, and HbA1c were expressed as **mean ± standard deviation (SD)**. The **Shapiro-Wilk test** was used to assess normality of the data distribution. Intergroup comparisons between Group A (non-diabetics) and Group B (diabetics) were conducted using **independent samples t-tests** for normally distributed data, while the **Mann–Whitney U test** was employed for non-normally distributed data.

To evaluate the association between periodontal inflammation, glycemic control, and biomarker levels, **Pearson's correlation coefficient** was calculated for normally distributed variables, and **Spearman's rank correlation coefficient** for non-parametric variables. A **p-value < 0.05** was considered statistically significant for all tests.

To further explore potential interactions, **multivariate linear regression analysis** was considered to adjust for confounding variables such as age, gender, and oral hygiene practices, though the primary analysis focused on un adjusted relationships.

3. Results

Demographic Characteristics

The two groups were comparable in terms of gender distribution and age. Group A had a mean age of 48.2 ± 7.6 years, while Group B averaged 52.5 ± 8.3 years. Gender differences were not statistically significant.

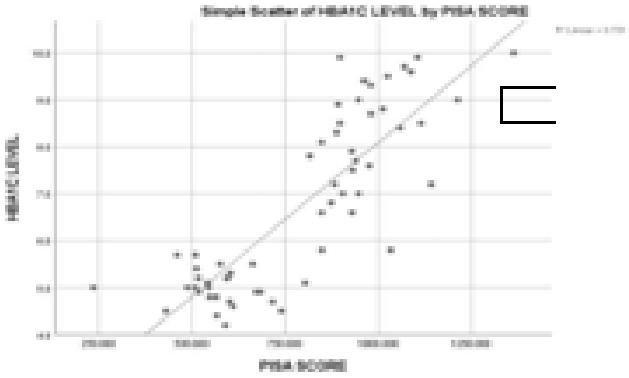
Clinical and Biochemical Findings

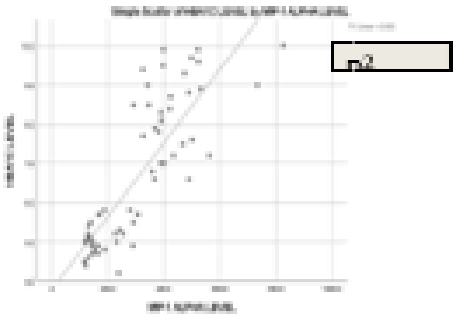
Parameter	Group A (Non-diabetic)	Group B (Diabetic)	p-value
Probing Depth (mm)	4.7 ± 0.6	5.8 ± 0.7	< 0.01
CAL (mm)	4.3 ± 0.5	5.5 ± 0.6	< 0.01
BOP (%)	38.2 ± 8.4	52.7 ± 10.3	< 0.01
PISA (mm²)	670.4 ± 115.7	980.6 ± 142.3	< 0.001
MIP-1α (pg/ml)	82.3 ± 15.6	134.5 ± 19.2	< 0.001
HbA1c (%)	5.5 ± 0.7	8.4 ± 1.2	< 0.001

Correlation Analysis

- **PISA vs. MIP-1α:** r = 0.62, p < 0.01
- **PISA vs. HbA1c:** r = 0.68, p < 0.01
- **MIP-1α vs. HbA1c:** r = 0.59, p < 0.01

These results confirm significant positive correlations between periodontal inflammation, systemic glycemic control, and inflammatory chemokine expression.





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4. Discussion

The current study investigated the relationship between local periodontal inflammation and systemic metabolic status through the dual lens of PISA and salivary MIP-1α. Our findings corroborate earlier studies suggesting that periodontal inflammation is more severe in patients with type 2 diabetes.

Higher PISA scores in diabetic individuals indicate a broader area of ulcerated epithelium in contact with systemic circulation.[15,16] This inflamed surface acts as a conduit for inflammatory mediators, microbial endotoxins, and cytokines, thereby contributing to systemic inflammation and insulin resistance. Similar findings have been reported in other observational studies, which also linked higher PISA values to poor glycemic control.[17]

The elevated MIP-1α levels in Group B align with the current understanding of its role in periodontal pathogenesis.[18,19] As a pro-inflammatory chemokine, MIP-1α facilitates leukocyte trafficking and is upregulated in response to microbial challenge. In diabetics, chronic hyperglycemia can further stimulate macrophage activity, enhancing MIP-1α expression. Studies by Emingil et al. and kristan RM. have consistently shown increased levels of this marker in periodontal disease, which this study reinforces.[20]

Moreover, the correlations between PISA, MIP-1α, and HbA1c illustrate a potential biological feedback loop: periodontitis exacerbates systemic inflammation, impairing insulin sensitivity, while hyperglycemia promotes gingival inflammation and microbial dysbiosis. This bidirectional relationship emphasizes the need for interdisciplinary collaboration between medical and dental professionals.

Importantly, this study also supports the growing emphasis on salivary diagnostics. Non-invasive and convenient, salivary biomarkers such as MIP-1α could supplement conventional assessments and allow for real-time monitoring of both periodontal and systemic disease states.

However, limitations exist. Being cross-sectional, causality cannot be inferred. Confounding variables such as diet, stress, and medication were not fully controlled. Additionally, salivary flow rate and viscosity may influence biomarker concentrations.

5. Conclusion

This study reinforces the intrinsic link between periodontal and systemic health, highlighting the potential of periodontal inflammation as both a local and systemic contributor to chronic disease burden. The findings revealed that individuals with type 2 diabetes mellitus and chronic periodontitis exhibited significantly higher values of both the Periodontal Inflamed Surface Area (PISA) and salivary Macrophage Inflammatory Protein-1 alpha (MIP-1α) compared to non-diabetic individuals. These elevations suggest not only increased local periodontal inflammation but also indicate a systemic inflammatory status that may be closely tied to metabolic dysregulation in diabetes.

The significant positive correlations observed among PISA, salivary MIP-1α levels, and HbA1c values point to a bidirectional relationship between periodontal disease and glycemic control. Inflammation originating from the periodontal tissues, quantified through PISA, may contribute to insulin resistance and impaired glycemic regulation via systemic dissemination of pro-inflammatory cytokines such as MIP-1α. Conversely, poor glycemic control exacerbates periodontal destruction by impairing immune responses and increasing the host's susceptibility to periodontal pathogens. These findings support the growing body of evidence that chronic periodontitis is not merely an oral health issue but a condition with systemic implications, particularly in individuals with diabetes.

Given these insights, there is a strong rationale for incorporating periodontal assessments, including advanced indices such as PISA and non-invasive salivary biomarkers like MIP-1α, into the routine evaluation of patients with diabetes. Such an integrated approach has the potential to facilitate early detection of periodontal inflammation, monitor disease progression, and assess systemic inflammatory status without the need for invasive procedures. It also paves the way for more personalized and interdisciplinary healthcare, wherein dental and medical professionals collaboratively manage patients with comorbid conditions.

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Furthermore, the inclusion of salivary biomarkers in clinical practice offers an accessible, cost-effective, and patient-friendly diagnostic tool. Saliva, being easily obtainable and rich in inflammatory mediators, provides a practical medium for screening and longitudinal monitoring. MIP-1α, in particular, has shown promising potential as a biomarker that reflects both periodontal disease severity and systemic inflammation related to diabetes.

To translate these findings into clinical practice, future longitudinal and interventional studies are warranted. Such research should aim to determine whether periodontal treatment can lead to measurable reductions in salivary and systemic inflammatory biomarkers and improve glycemic control in diabetic patients. Establishing a causal relationship would strengthen the case for routine periodontal care as a component of diabetes management protocols. Additionally, standardized protocols for the use of PISA and salivary biomarkers in routine practice need to be developed to ensure accuracy, reproducibility, and clinical utility.

In conclusion, this study adds to the growing evidence that managing periodontal inflammation is not only essential for oral health but may also play a critical role in systemic disease control. As the burden of diabetes continues to rise globally, adopting a multidisciplinary approach that includes periodontal health screening and intervention could significantly enhance patient outcomes and reduce the broader impact of chronic inflammation-driven diseases.

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