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Review

Salivary RANKL/OPG, MIP-1α and Serum Lipids in Periodontitis: Evidence across Diabetic and Non-Diabetic Populations– A Narrative review

C Divya Naga Teja[1]*, R Sanjay Andrew[2], P Ajay Reddy[3],Ramalaxmi K[4]
[1,3]Department of Physiology, Army College of Dental Sciences, Telangana, India, [2]Physiology, Chettinad Research Institute, Chettinad Academy of Research and Education, Chennai, Tamil Nadu,[4]Public Health Dentistry, Vishnu Dental College, Andhra Pradesh, India

0009-0008-1616-4997[1]
0000-0002-4585-6545[2]
0009-0008-8948-7084[3]
0000-0002-4225-0185[3]

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Address for correspondence:
Dr. R Sanjay Andrew*

e-mail:
physiosan@gmail.com

Abstract

Background: Periodontitis represents a complex inflammatory disease with significant metabolic implications, particularly in type 2 diabetes mellitus patients. Salivary biomarkers offer potential diagnostic insights beyond traditional clinical parameters.
Objectives: This review examines the performance of salivary biomarkers and serum lipid associations in periodontal disease, comparing diabetic and non-diabetic populations while evaluating enzymatic marker profiles.
Methods: We conducted a narrative review using structured searches of PubMed, Embase, and Cochrane Library through August 2024, focusing on bone remodeling markers, enzymatic profiles, and lipid associations.
Results: Macrophage inflammatory protein-1α demonstrated strong diagnostic performance (AUC 0.94, 94.9% sensitivity, 92.7% specificity at 1.12 pg/mL cutoff) with 18-fold elevation in periodontitis patients. RANKL levels and RANKL/osteoprotegerin ratios were significantly elevated in periodontal disease. Meta-analysis of 103,468 participants revealed 15% increased dyslipidemia odds with periodontitis, though with substantial heterogeneity. Matrix metalloproteinases, antioxidant enzymes, and inflammatory proteases demonstrated variable diagnostic utility, accompanied by significant methodological limitations. While small trials demonstrated reductions in inflammatory markers following periodontal therapy, the largest randomized trial, involving 290 type 2 diabetes patients, showed no significant improvements in lipid profiles.
Conclusions: Bone remodeling markers, particularly MIP-1α, show promise as adjunctive diagnostic tools, though extensive standardization and validation across diverse populations remain essential. Enzymatic profiles face substantial technical and interpretive challenges, which limit their clinical utility. Population-specific approaches appear necessary given differential responses in diabetic versus non-diabetic patients, with therapeutic lipid benefits remaining questionable in diabetic populations.
Keywords: Diabetes mellitus, Dyslipidemia, MIP-1α, Periodontitis; RANKL/OPG; Salivary biomarkers

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Introduction

Periodontal disease affects nearly half the adult population worldwide, creating a substantial public health burden. The relationship between periodontal disease and type 2 diabetes mellitus (T2DM) is particularly

concerning each condition worsens the other through shared inflammatory pathways [1,2]. This bidirectional relationship complicates treatment planning and makes traditional clinical assessments insufficient for capturing the full scope of disease impact [3,4].

Researchers have turned to salivary biomarkers as potential solutions to these diagnostic limitations. These non-invasive tests could provide insights that standard clinical measures miss [3,5]. Bone remodeling markers show the most promise in this field. MIP-1α, for instance, achieved impressive diagnostic accuracy in recent studies, with sensitivity and specificity rates above 90% [6,7]. The RANKL/OPG balance offers another window into the inflammatory processes driving both periodontal destruction and systemic metabolic dysfunction [8,9].Beyond bone markers, researchers have investigated various enzymes found in saliva. Matrix metalloproteinases increase during periodontal disease [10, 9, 11], while antioxidant enzymes and inflammatory proteases exhibit complex fluctuations [12, 13, 14]. Unfortunately, these enzymatic markers face serious hurdles. Studies often contradict each other, and many enzymes lack the specificity needed for reliable periodontal diagnosis [10,11,14].

The systemic implications of periodontal disease extend to cardiovascular health through altered lipid profiles. Meta-analyses involving over 100,000 participants reveal a 15% increase in dyslipidemia risk among periodontitis patients [15,16]. Yet when researchers test whether treating periodontal disease improves lipid levels, results vary dramatically. Small trials have shown promising reductions in inflammatory markers [17], but the largest randomized study in diabetic patients found no significant improvements in lipids after intensive periodontal therapy [1].

This disconnect between association and intervention studies highlights a critical gap in our understanding. We need to determine which biomarkers truly predict treatment outcomes and whether diabetic patients respond differently from non-diabetic individuals. This review consolidates current evidence on the performance of salivary biomarkers and lipid associations, with special attention to population-specific differences and the practical challenges facing clinical implementation.

Methods

We conducted a narrative review using structured searches of PubMed, Embase, and Cochrane Library through August 2024. Search terms encompassed "periodontitis," "salivary biomarkers," "RANKL," "osteoprotegerin," "MIP-1α," "dyslipidemia," and "diabetes mellitus" using Boolean operators. Additional searches targeted "metalloproteinases," "antioxidant enzymes," and "neutrophil elastase."

Inclusion criteria required randomized controlled trials, observational studies, or systematic reviews examining salivary biomarkers, enzymatic profiles, or serum lipid associations in periodontal contexts. Studies are needed to report diagnostic performance metrics, concentration differences, or intervention effects on systemic markers. We prioritized studies including T2DM populations.

Data extraction addressed study design, population characteristics, sample sizes, biomarker specifications, and effect estimates. This narrative approach acknowledges methodological diversity across studies and potential selection bias inherent in non-systematic review procedures.

Results

Diagnostic Performance Reveals Marker-Specific Patterns:

MIP-1α demonstrates superior diagnostic capabilities among salivary biomarkers. Al-Sabbagh et al.'s case-control study of 80 subjects achieved an AUC of 0.94 with 94.9% sensitivity and 92.7% specificity at a concentration of 1.12 pg/mL [6]. Nisha et al.'s smaller study reported perfect diagnostic performance, though this likely reflects optimism bias in single-center investigations [7]. Advanced proteomics using SWATH mass spectrometry has identified additional promising biomarkers, though validation in larger populations remains necessary [5]. Systematic review evidence suggests combining multiple biomarkers, particularly IL-6 and MMP-8, may enhance diagnostic accuracy [3]. Comparative diagnostic performance metrics for key salivary biomarkers. (Table 1)

Study	Marker	Population	n	Outcome Type	Key Performance Note
Al-Sabbagh 2012 [6]	MIP-1α	Mixed periodontal	80	AUC 0.94	94.9% sensitivity, 92.7% specificity at 1.12 pg/mL
Nisha 2018 [7]	MIP-1α	Mixed periodontal	75	Sens/Spec	100%/100% (periodontitis vs health)
Nisha 2018 [7]	MIP-1α	Mixed periodontal	75	Sens/Spec	100%/88% (gingivitis vs health)
Kc 2020 [3]	IL-6 + MMP-8	Review synthesis	Multiple	Combined panel	Optimal diagnostic combination

AUC = area under the curve; Sens = sensitivity; Spec = specificity; Mixed periodontal = studies did not specify diabetes status

Table 1. Diagnostic Performance of Salivary Biomarkers in Periodontal Disease

Biomarker Concentrations Show Disease-Specific Elevation Patterns

Al-Sabbagh documented 18-fold higher MIP-1α concentrations in patients with periodontitis compared to healthy controls ($p < 0.001$) [6]. RANKL levels showed significant elevation in generalized aggressive periodontitis patients versus controls (36.46±20.924 vs 12.62±1.068 pg/mL, $p<0.001$), with RANKL/OPG ratios demonstrating corresponding differences ($p<0.01$) [8]. These biomarker elevations reflect underlying inflammatory cascades that connect local periodontal destruction to broader systemic metabolic consequences. The mechanistic pathway linking these biomarker elevations to systemic lipid alterations. (Fig.-1)

Matrix metalloproteinases, particularly MMP-8 and MMP-9, are extensively studied enzymatic markers that demonstrate a neutrophil origin and specific collagenase activity [18,11]. However, diagnostic interpretation requires consideration of tissue inhibitor ratios rather than absolute concentrations [11]. Population-specific variations prove problematic, with T2DM subjects demonstrating altered MMP regulation patterns potentially reflecting hyperglycemic effects rather than periodontal disease severity [10].

Antioxidant enzyme responses show contradictory findings. Some studies report compensatory elevation while others find enzymatic depletion patterns for superoxide dismutase, catalase, and glutathione peroxidase activities [13,14]. Hepatic transaminases appear during periodontal inflammation, although their diagnostic specificity remains questionable, given the elevation in numerous non-oral systemic conditions [19]. The

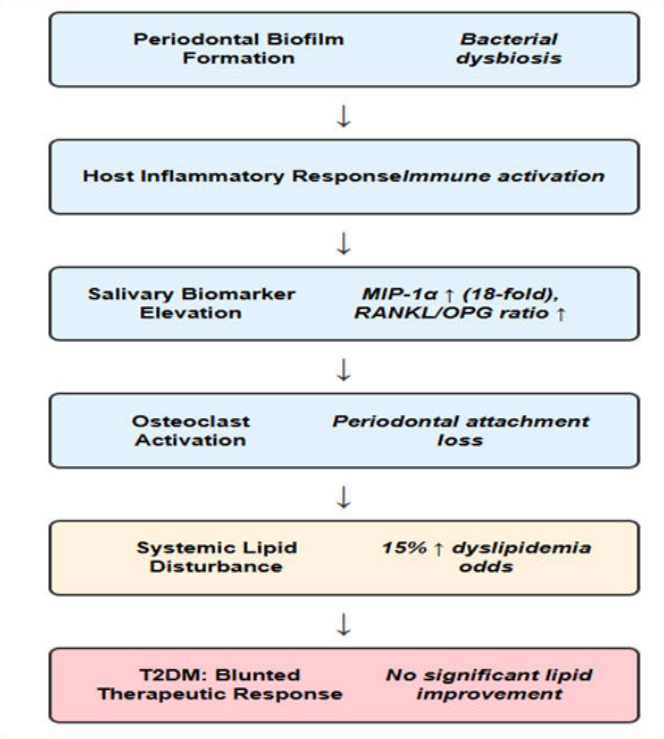

Fig-1: Mechanistic pathway from periodontal biofilm to systemic lipid alterations. Salivary biomarkers (MIP-1α, RANKL/OPG) mediate the pathway from local periodontal inflammation to systemic dyslipidemia, with T2DM patients showing blunted therapeutic responses.

The magnitude and direction of concentration changes for major salivary biomarkers across different disease states. (Table-2)

Lipid Associations Demonstrate Population-Dependent Responses

Mirzaei et al.'s meta-analysis of 34 studies encompassing 103,468 participants demonstrated a 15% increased odds of dyslipidemia with periodontitis (OR: 1.15, 95% CI: 1.04 -1.26) [15]. However, substantial heterogeneity across studies reflects varying periodontitis definitions and

Marker	Direction	Comparator	Effect Magnitude	Reference
MIP-1α	↑	Periodontitis vs healthy	18-fold elevation	[6]
RANKL	↑	GAP vs healthy	36.46±20.924 vs 12.62±1.068 pg/mL	[8]
RANKL/OPG ratio	↑	GAP vs healthy	Significantly higher	[8]
MMP-8	↑	Disease vs healthy	Variable elevation	[9,24]
SOD, Catalase	↑/↓	Disease vs healthy	Paradoxical patterns	[13,14]

GAP = generalized aggressive periodontitis; SOD = superoxide dismutase

Table 2. Salivary Biomarker Concentration Differences in Periodontal Disease

population characteristics.

Intervention studies yield contrasting results. While D'Aiuto et al. demonstrated significant inflammatory marker reductions following intensive periodontal therapy in 40 patients (IL-6 mean change 400 pg/mL, 95% CI: 30-900) [17], the largest randomized controlled trial involving 290 T2DM patients found no significant lipid profile differences following intensive periodontal treatment versus prophylaxis control [1]. This critical negative finding contradicts projections based on smaller studies and suggests that therapeutic responses may be population-dependent. The associations between periodontitis and lipid profiles, as well as the effects of interventions, are summarized in Table 3. Given these complexities and the need for population-specific interpretation of biomarker results, a systematic approach to clinical integration becomes essential. A clinical framework for integrating these population-specific findings into biomarker-guided decision-making. (Fig-2)

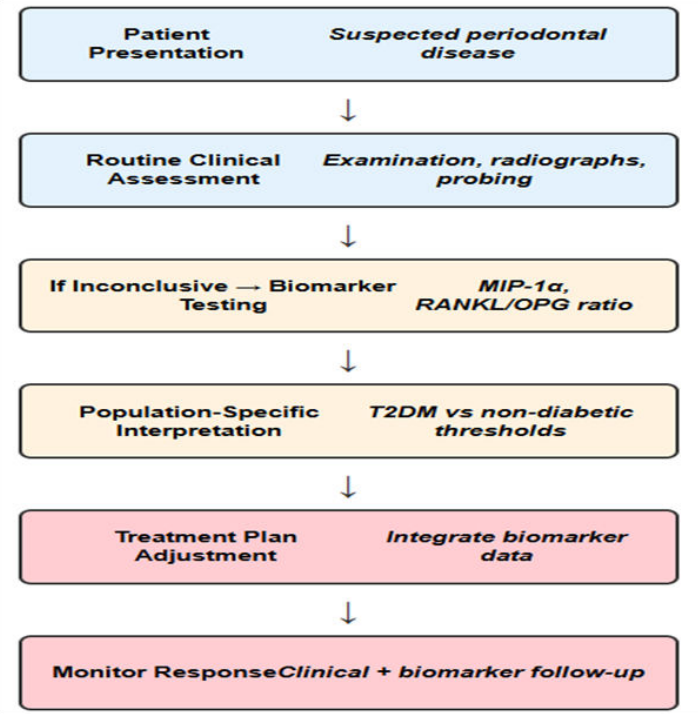

Fig. 2: Clinical decision-making framework for salivary biomarker integration. Biomarker testing is considered when routine assessment is inconclusive, with population-specific threshold interpretation guiding treatment decisions.

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Association/Intervention	Study Design	No. od patients	Direction/Magnitude	Key Finding
Periodontitis-dyslipidemia association	Meta-analysis	103,468	↑ 15% odds	OR 1.15 (95% CI: 1.04-1.26) [15]
Periodontal therapy → IL-6	RCT	40	↓ inflammatory	Mean reduction 400 pg/mL [17]
Periodontal therapy → CRP	RCT	40	↓ inflammatory	Mean reduction 0.4 mg/L [17]
Periodontal therapy → lipids (T2DM)	RCT	290 (T2DM)	No change	No significant lipid differences [1]

OR = odds ratio; CI = confidence interval; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus

Table 3. Serum Lipid Associations and Periodontal Therapy Effects

Discussion

The periodontal biomarker landscape presents promising opportunities alongside significant implementation challenges that vary substantially across marker categories.

Enzymatic Markers Face Fundamental Consistency Problems

The most troubling aspect of enzymatic marker literature is its fundamental inconsistency. Antioxidant enzyme findings exemplify this problem: while some studies report compensatory elevation of superoxide dismutase and catalase in T2DM patients with periodontitis [13], others find enzymatic depletion patterns in similar populations [14]. These contradictory findings suggest many enzymatic markers lack the biological consistency required for clinical application. Matrix metalloproteinases present similar contradictions. Kumar et al. demonstrated elevated MMP-8 and MMP-9 levels in diabetic periodontitis patients [10], while Collin et al. found no significant MMP-8 differences between diabetic patients and controls [11]. Studies reporting elevated MMPs often fail to account for tissue inhibitor ratios, potentially misinterpreting compensatory responses as disease markers [11]. Measurement variability approaches 25%—nearly equivalent to reported disease-related changes [20].

Large Negative Trials Challenge Therapeutic Utility

Intervention studies reveal a stark disconnect between cross-sectional associations and therapeutic outcomes. While smaller studies have shown promising reductions in inflammatory markers [17], Rapone et al.'s study of 290 patients with T2DM and generalized periodontitis found no significant improvements in lipid profiles following intensive periodontal treatment [1]. This negative finding represents the most robust evidence available and directly contradicts optimistic projections based on smaller studies. Multiple studies have reported biomarker correlations with disease severity; however, these associations fail to predict treatment responses [21]. This pattern suggests many biomarkers may reflect disease presence without indicating therapeutic responsiveness, limiting their clinical utility for treatment planning and monitoring.

Implementation Barriers Exceed Acknowledged Limitations

The sample collection methodology emerges as a critical limitation, with enzymatic markers demonstrating rapid degradation that potentially occurs within minutes of collection [22,14]. This instability fundamentally undermines measurement reliability. Economic realities present additional barriers, as current biomarker methodologies are considerably more expensive than traditional assessments, while providing diagnostic information of questionable clinical value [23].

Conclusions

Overall, the current evidence supports *selective and context-specific* use of salivary and inflammatory biomarkers rather than broad clinical adoption. Among available candidates, MIP-1α appears most promising for advanced diagnostic applications, particularly in T2DM patients, yet its translation into practice is constrained by the need for population-specific thresholds, rigorous standardization, and validation of clinical relevance. Other biomarkers, including RANKL/OPG ratios and enzymatic markers, add limited incremental value due to issues of specificity,interpretive complexity, stability and cost effectiveness

Significant translational gaps remain, especially regarding periodontal specificity and differential biomarker behavior in diabetic versus non-diabetic populations. Consequently, future research should focus on stability assessment, population-tailored validation, and harmonized analytical frameworks. Until these challenges are addressed, biomarker-based diagnostics should be pursued with cautious optimism, emphasizing targeted implementation strategies over universal clinical application.

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Study conception and design: KRL, PAR

Data collection: CDNT, SAR

Data analysis and interpretation: KRL, SAR

Drafting of manuscript: KRL, CDNT

Critical revision: All authors read and approved the final manuscript.

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Ethics Statement: This narrative review of published literature did not require ethics approval as no human participants were directly involved. All referenced studies were conducted in accordance with relevant ethical guidelines and institutional approvals.

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