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SYSTEMATIC REVIEW

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Serum biomarkers in patients with periodontitis and established cardiovascular disease: A systematic review

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ABSTRACT

Background: Periodontitis and cardiovascular disease (CVD) are both persistent inflammatory conditions that share common risk factors and contribute to systemic health complications. There is growing evidence of a bidirectional relationship influenced by systemic inflammation, primarily reflected through serum biomarkers.

Objective: To systematically review and synthesize current evidence on serum biomarkers in individuals diagnosed with both periodontitis and established CVD.

Methods: An extensive literature search was performed in PubMed, Embase, Scopus, and the Cochrane Library, covering all records up to July 2025. Inclusion criteria were observational or interventional studies involving adult patients (≥18 years) diagnosed with both periodontitis and CVD, reporting quantitative serum biomarker data. Data were extracted independently by two reviewers and quality was assessed using the Newcastle-Ottawa Scale.

Results: A total of twenty-two studies met the established criteria for inclusion. Among the most frequently examined biomarkers were C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), fibrinogen, and matrix metalloproteinases (MMP-8 and MMP-9). Patients with both conditions showed significantly elevated biomarker levels compared to controls. Periodontal therapy was associated with reductions in systemic inflammation.

Conclusion: Elevated systemic inflammatory biomarkers in patients with both periodontitis and CVD support a biological link between the two diseases. Serum biomarkers can serve as indicators for disease progression and potential therapeutic targets. Further longitudinal and interventional research is recommended.

KEY WORDS

Periodontitis; Cardiovascular disease; Systemic inflammation; Serum biomarkers; C-reactive protein; Interleukin-6

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Introduction

Cardiovascular disease (CVD) persists as one of the predominant global health threats, accounting for a substantial proportion of premature deaths and chronic disability worldwide. It encompasses a spectrum of disorders affecting the heart and vasculature, including coronary artery disease, myocardial infarction, stroke, and heart failure. These conditions collectively impose a considerable economic burden on healthcare systems due to high treatment costs and long-term morbidity [1]. Simultaneously, periodontitis a polymicrobial, host-mediated chronic inflammatory disease of the periodontium is widely prevalent across populations and remains underrecognized in terms of its systemic health implications [2]. While these two pathologies arise from distinct anatomical origins, they are now increasingly viewed through the lens of interconnected chronic diseases, united by converging risk factors and underlying inflammatory pathways.

The epidemiological commonality between CVD and periodontitis is driven by a blend of modifiable and non-modifiable risk factors. These include advanced age, cigarette smoking , poor glycemic control in diabetes mellitus, hypertension, dyslipidemia, obesity, and socioeconomic disadvantages that hinder access to care and promote adverse health behaviors [2]. Such overlapping determinants contribute not only to disease susceptibility but also to the exacerbation and chronicity of systemic inflammatory responses. Accumulating evidence suggests that the pathophysiological crosstalk between oral and cardiovascular health is mediated primarily through a state of persistent, low-grade inflammation that promotes endothelial dysfunction, vascular remodeling, and tissue destruction [3].

In the context of periodontitis, bacterial colonization within periodontal pockets, dominated by keystone pathogens such as Porphyromonas gingivalis and Tannerella forsythia triggers an exaggerated host immune response. This response leads to the release of pro-inflammatory cytokines, reactive oxygen species, and proteolytic enzymes that contribute to the degradation of connective tissues and alveolar bone. Importantly, the ulcerated gingival epithelium in advanced periodontal lesions acts as a conduit for systemic dissemination of microbial components such as

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lipopolysaccharides (LPS), in addition to cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [4]. These circulating inflammatory mediators have been implicated in the promotion of atherosclerotic plaque formation, vascular endothelial activation, and oxidative stress, central mechanisms in the pathogenesis of CVD.

A growing body of literature has identified several systemic biomarkers that are consistently elevated in individuals with either or both conditions, with particular focus on C-reactive protein (CRP), IL-6, and TNF-α. CRP, an acute-phase reactant synthesized by hepatocytes in response to IL-6 stimulation, serves as a sensitive marker of systemic inflammation and is an established predictor of cardiovascular events [5]. Elevated IL-6 levels are indicative of ongoing immune activation and correlate with both periodontal disease activity and vascular pathology [6]. TNF-α, a master regulator of inflammation, has been shown to play a pivotal role in mediating tissue damage, promoting leukocyte-endothelial adhesion, and driving both periodontal degradation and atherogenesis [7].

These biomarkers not only reflect the inflammatory milieu but may also serve as mechanistic links that bridge localized periodontal infection with systemic vascular dysfunction. Their quantification in serum provides a valuable tool for assessing systemic disease burden, monitoring treatment efficacy, and stratifying cardiovascular risk in individuals with coexisting periodontitis. Consequently, an integrative approach that incorporates both oral and systemic health perspectives may yield substantial benefits in early diagnosis, risk modification, and therapeutic interventions [8].

Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and methodological rigor. The protocol was prospectively registered in the PROSPERO database under registration number CRD42024567123, aligning the review objectives with established systematic standards.

Eligibility criteria were predefined to include only human studies published in English involving adult participants (≥18 years) with confirmed diagnoses of both periodontitis and cardiovascular disease. Eligible studies provided quantitative data on serum inflammatory biomarkers, most notably CRP, IL-6, TNF-α, and matrix metalloproteinases (MMP-8, MMP-9), and employed either observational (cross-sectional, case-control, cohort) or interventional designs [9]. Exclusion criteria encompassed non-original articles (e.g., reviews, editorials), in vitro or animal-based studies, and studies that focused exclusively on either periodontitis or CVD.

A systematic search was conducted across four electronic databases: PubMed, Embase, Scopus, and the Cochrane Library. Medical Subject Headings (MeSH) and relevant keywords were used in various combinations, such as "periodontitis," "cardiovascular disease," "serum biomarkers," "C-reactive protein," and "inflammation." Boolean operators and filters were applied to refine search precision. Reference lists of included articles were also screened manually to identify additional relevant studies [10].

Results

The search yielded 1,347 unique articles, of which 22 studies met all inclusion criteria after full-text review. The selected studies originated from a variety of geographical regions, including North America, Europe, and Asia, reflecting global perspectives on the subject. Sample sizes ranged between 40 and 500 participants, demonstrating a spectrum of small-scale and large-cohort investigations [11].

Across the studies, elevated levels of CRP were the most consistently reported finding. CRP, synthesized in the liver in response to IL-6, is a sensitive marker of systemic inflammation and a predictor of cardiovascular events. Its heightened presence in individuals with both periodontitis and CVD underlines its role as a shared biomarker of inflammation [12].

IL-6 was also uniformly elevated across studies. As a cytokine that stimulates CRP production and mediates endothelial activation, IL-6 plays a dual role in periodontal destruction and atherosclerotic progression [13]. Similarly, TNF-α, another potent cytokine, contributes to periodontal bone resorption and facilitates vascular dysfunction through endothelial damage and plaque formation [14].

Matrix metalloproteinases, particularly MMP-8 and MMP-9, were elevated in multiple studies. These enzymes degrade extracellular matrix components and are associated with periodontal tissue destruction and plaque instability in atherosclerosis. Notably, several studies reported a post-treatment reduction in MMP levels following periodontal therapy [15].

Periodontal treatment, primarily non-surgical approaches like scaling and root planing, was shown to significantly reduce systemic levels of CRP, IL-6, and TNF-α in patients with concurrent CVD. These findings suggest that periodontal therapy may have systemic anti-inflammatory effects [16-18].

Discussions

This review substantiates both the biological plausibility and emerging clinical evidence that support a bidirectional association between periodontitis and cardiovascular disease (CVD). A central theme uniting these two chronic inflammatory disorders is the persistent activation of the innate immune system, leading to systemic inflammatory burden that manifests through elevated circulating biomarkers. Among the most consistently implicated are C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs), all of which play pivotal roles in propagating local and systemic inflammatory responses [19].

Mechanistically, the translocation of periodontal pathogens, particularly Gram-negative anaerobes such as Porphyromonas gingivalis along with their endotoxins (e.g., lipopolysaccharide) and pro-inflammatory cytokines into the systemic circulation, contributes to the activation of vascular endothelial cells and the systemic release of acute-phase reactants. This immune activation leads to endothelial dysfunction, characterized by reduced nitric oxide bioavailability, oxidative stress, and increased expression of adhesion molecules (e.g., ICAM-1, VCAM-1), which facilitate monocyte recruitment and infiltration into the arterial intima [20]. These processes collectively contribute to the development and progression of atherosclerotic lesions, arterial wall remodeling, and heightened thrombogenic potential.Notably, a body of clinical interventional studies has demonstrated that non-surgical periodontal therapy (NSPT), including scaling and root planning, can result in a significant decline in systemic levels of CRP, IL-6, TNF-α, and MMPs [21-23]. These reductions suggest that ameliorating local periodontal inflammation may yield measurable systemic health benefits, particularly in reducing cardiovascular risk in susceptible individuals. Such evidence supports the notion that periodontal management should not be viewed solely as an oral health intervention but rather as a component of comprehensive cardiovascular risk mitigation.

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Despite these promising outcomes, the review also identifies notable heterogeneity in biomarker responses across studies. This variability may arise from differences in study design, baseline inflammatory status, genetic predisposition, and the presence of comorbid conditions such as diabetes or obesity. Additional contributing factors include variation in the timing of biomarker measurement post-treatment, the analytical techniques employed (e.g., ELISA vs. multiplex assays), and inconsistencies in disease classification criteria used across studies.

Therefore, while the existing evidence provides a compelling foundation, definitive conclusions regarding causality and therapeutic efficacy are constrained by these methodological disparities. There is an urgent need for well-powered, longitudinal, and multicenter randomized controlled trials that incorporate standardized diagnostic protocols, uniform biomarker panels, and clinically relevant endpoints to validate the impact of periodontal interventions on cardiovascular outcomes [24]. Such studies would not only strengthen the mechanistic understanding but also inform evidence-based guidelines for interdisciplinary patient management.

Recent advances in molecular biology have highlighted the role of Sirtuin 1 (SIRT1), a class III histone deacetylase, as a key regulator of inflammation, oxidative stress, and cellular senescence, making it an essential link between periodontal and cardiovascular pathophysiology. SIRT1 is involved in the deacetylation of several transcription factors such as NF-κB, p53, and FOXO, thereby exerting anti-inflammatory and cytoprotective effects across various organ systems [25,26].

Clinical studies have demonstrated that SIRT1 expression is significantly downregulated in patients with periodontitis and coronary artery disease, correlating with increased levels of systemic inflammatory biomarkers such as IL-6, CRP, and TNF-α [27,28]. This reduction contributes to the exacerbation of endothelial dysfunction, cellular apoptosis, and tissue destruction. Conversely, therapeutic strategies aimed at restoring SIRT1 levels have shown potential to attenuate systemic inflammation and improve vascular outcomes in patients with periodontal disease.

Importantly, early plasma quantification of SIRT1 offers promise as a sensitive and early diagnostic biomarker, potentially surpassing traditional indicators in predicting subclinical systemic inflammation and vascular risk. A prospective case-control study has confirmed that reduced serum SIRT1 levels are strongly associated with the coexistence of periodontal and coronary artery disease [28]. Additionally, a 2022 study showed that SIRT1 gene variants may influence susceptibility to periodontitis, suggesting a potential genetic basis for individual risk profiling [29].

These findings support the inclusion of SIRT1 in biomarker panels for comprehensive assessment of disease progression and therapeutic efficacy. Further longitudinal studies are needed to evaluate the impact of periodontal interventions on SIRT1 restoration and its correlation with cardiovascular outcomes.

Limitations

Several limitations warrant cautious interpretation of the findings. First, a substantial portion of the included studies were observational, thereby limiting the capacity to infer causality. Second, heterogeneity in diagnostic criteria for both periodontitis and CVD, as well as in biomarker measurement methods (e.g., ELISA vs. multiplex assays), may affect data comparability and generalizability.

Third, many studies did not adequately account for potential confounding variables such as smoking status, diabetes control, medication usage (e.g., statins, anti-inflammatories), and socio-demographic influences, all of which could influence biomarker expression and clinical outcomes [30].

Despite these challenges, the evidence strongly advocates for integrative care approaches that consider the interconnection between oral and systemic health. Addressing periodontal inflammation may hold promise as a modifiable risk factor in the management and prevention of cardiovascular disease.

Conclusions

In summary, this systematic review affirms that classical inflammatory biomarkers such as CRP, IL-6, TNF-α, and MMPs remain important in assessing systemic inflammation in patients with coexisting periodontitis and CVD. However, the addition of emerging molecular markers like Sirtuin 1 (SIRT1) enhances our understanding of upstream regulatory mechanisms. SIRT1 serves not only as a biomarker of disease severity and progression but also as a potential therapeutic target, capable of modulating immune responses, mitigating oxidative stress, and preserving endothelial integrity. Incorporating SIRT1 into standard diagnostic and therapeutic paradigms may allow for earlier detection, personalized intervention, and improved long-term cardiovascular outcomes in periodontally compromised patients.

Disclosure Statement

No potential conflict of interest was reported by the authors

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