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SYSTEMATIC REVIEW

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Systematic review: Association of cardiovascular health and periodontitis

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ABSTRACT

Periodontitis is a chronic inflammatory disease characterized by the destruction of periodontal tissues, primarily caused by pathogenic bacteria and a dysregulated immune response. Recent research has established a significant link between periodontitis and cardiovascular disease (CVD), highlighting the systemic implications of oral health. This systematic review critically evaluates existing literature on the association between periodontitis and cardiovascular health, focusing on underlying mechanisms, epidemiological evidence, and clinical implications. A comprehensive search was conducted using databases such as PubMed, Scopus, and Web of Science, following PRISMA guidelines, resulting in the inclusion of 25 studies published until October 2024. The findings reveal that systemic inflammation, driven by periodontal disease, contributes to endothelial dysfunction and atherosclerosis, increasing cardiovascular risk. Longitudinal and cross-sectional studies demonstrate a clear association between severe periodontitis and elevated risks of coronary heart disease, ischemic stroke, and cardiovascular mortality. Additionally, randomized controlled trials (RCTs) indicate that periodontal therapy can significantly improve systemic inflammatory markers and endothelial function, suggesting potential preventive strategies against CVD. Despite these insights, further research is necessary to elucidate the molecular mechanisms involved and to assess the long-term benefits of periodontal interventions on cardiovascular outcomes. Collaborative care models between dental and medical professionals are recommended to optimize patient management, ultimately improving both oral and cardiovascular health.

KEYWORDS

Periodontitis; Cardiovascular disease; Systemic inflammation; Atherosclerosis; Endothelial dysfunction; Oral health

ARTICLE HISTORY

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Introduction

Periodontitis is a prevalent chronic inflammatory disease that affects the supporting structures of teeth, leading to tissue destruction and eventual tooth loss. It is caused by pathogenic bacteria in the subgingival biofilm and is associated with a dysregulated immune response, resulting in inflammation. Emerging evidence has demonstrated that periodontitis is not only a localized oral disease but is also implicated in several systemic health conditions, including cardiovascular disease (CVD). Cardiovascular disease remains one of the leading causes of morbidity and mortality worldwide, and its association with periodontitis has garnered significant attention in recent years [1-6].

This systematic review aims to critically evaluate and synthesize available research on the association between periodontitis and cardiovascular health, examining the underlying mechanisms, clinical implications, and future research directions.

Methodology

This systematic review was meticulously conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which provide a structured framework for reporting systematic reviews and meta-analyses. Adhering to these guidelines ensures transparency and reproducibility, enhancing the credibility of the review process.

Database search

A comprehensive search strategy was implemented across multiple databases, including PubMed, Scopus, and Web of Science. These databases were selected for their extensive coverage of biomedical literature and their relevance to the fields of dentistry, cardiology, and public health. The search focused on articles published from the inception of each database up until October 2024, ensuring the inclusion of the most current research findings.

Search strategy

The search employed a targeted selection of keywords, including:

- Periodontitis
- Cardiovascular disease
- Systemic inflammation
- Oral health
- Atherosclerosis

These keywords were strategically chosen to encompass the core aspects of the review, reflecting the interrelationship between periodontal health and cardiovascular conditions. The search strategy was designed to retrieve articles that provided insights into both clinical and pathophysiological mechanisms linking these two fields.

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Selection criteria

From the initial search results, a total of 25 articles were selected based on predefined inclusion criteria. The selection process focused on:

- **Relevance:** Articles that directly addressed the relationship between periodontitis and cardiovascular disease were prioritized.
- **Study Design:** Preference was given to clinical studies and RCTs, as these designs provide robust evidence regarding causal relationships and treatment efficacy.
- **Quality of Evidence:** Studies were critically assessed for methodological rigor, sample size, and relevance to the review's objectives.

Data analysis

A thorough analysis was conducted on the selected articles, emphasizing the following aspects:

- **Relationship Between Periodontitis and Cardiovascular Health:** The review explored how periodontal disease contributes to systemic inflammation, potentially exacerbating cardiovascular conditions.
- **Mechanisms of Action:** The review examined underlying biological mechanisms, such as the role of bacterial lipopolysaccharides (LPS) in promoting atherosclerosis and systemic inflammation.
- **Clinical Implications:** Findings were discussed in the context of clinical practice, highlighting the importance of periodontal care in managing cardiovascular health and the potential for interdisciplinary approaches to patient care.

Pathophysiological Mechanisms

Inflammation and systemic spread

The most widely accepted mechanism linking periodontitis and cardiovascular disease is systemic inflammation. Periodontitis is a chronic inflammatory condition, and the inflammatory mediators produced locally in the periodontal tissues can enter the bloodstream, potentially contributing to a systemic inflammatory burden. These inflammatory markers include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which have been implicated in the pathogenesis of atherosclerosis and coronary artery disease (CAD) [6-8].

Moreover, pathogenic bacteria from the oral cavity, particularly *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, have been identified in atherosclerotic plaques, suggesting a possible direct bacterial dissemination from the oral cavity to the arterial walls. This bacterial translocation might contribute to endothelial dysfunction, a hallmark of cardiovascular disease.

Endothelial dysfunction and atherosclerosis

Endothelial dysfunction is a key early event in the development of atherosclerosis. Studies have suggested that periodontitis may contribute to this dysfunction by enhancing oxidative stress and promoting the formation of reactive oxygen species (ROS). The bacteria involved in periodontitis have been found to increase the expression of adhesion molecules on the endothelial surface, facilitating the infiltration of inflammatory cells and accelerating the formation of atherosclerotic plaques [9,10].

Furthermore, periodontal pathogens like *P. gingivalis* have been shown to trigger platelet aggregation, contributing to thrombus formation, which increases the risk of cardiovascular events such as myocardial infarction and stroke. These findings underline the multifactorial nature of the association between periodontitis and cardiovascular disease [11].

Epidemiological Evidence

Cross-sectional and longitudinal studies

Numerous observational studies have shown a significant association between periodontitis and cardiovascular disease. A notable longitudinal study by Kelly et al. (2013) followed over 10,000 participants for 17 years and reported that individuals with severe periodontitis had a 25% increased risk of developing coronary heart disease (CHD) [9]. Another study conducted by Larvin et al. (2021) demonstrated that periodontitis was associated with an elevated risk of ischemic stroke and peripheral arterial disease (PAD) [3].

In addition, a meta-analysis conducted by Blaizot et al. (2009) reviewed 15 cohort studies and found a significant association between periodontitis and cardiovascular mortality, with an adjusted hazard ratio of 1.14 for CVD-related deaths in individuals with severe periodontal disease [2].

Randomized controlled trials

While observational studies provide compelling evidence of an association, RCTs have been essential in examining the effects of periodontal treatment on cardiovascular outcomes. A landmark RCT by Tonetti et al. (2007) investigated the effect of periodontal therapy on endothelial function in patients with periodontitis and found that intensive periodontal treatment improved endothelial function, as measured by flow-mediated dilation (FMD) of the brachial artery, within six months of therapy [4].

Another RCT by Montero et al. (2020) explored the impact of non-surgical periodontal treatment on systemic inflammation and cardiovascular biomarkers in patients with periodontitis [5]. The study reported a significant reduction in systemic inflammatory markers, including CRP and IL-6, following periodontal treatment, suggesting that managing periodontal inflammation may positively influence cardiovascular health [12].

Genetic and Environmental Factors

Genetic predisposition

Genetic factors may play a role in the susceptibility to both periodontitis and cardiovascular disease. Studies have identified common genetic variants, such as polymorphisms in the IL-1 gene cluster, that are associated with an increased risk of periodontitis and coronary artery disease (Table 1) [13,14]. Moreover, twin studies have shown a shared heritability between periodontitis and atherosclerosis, further supporting the genetic link between these conditions (Table 2) [15].

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Table 1. Summary of key points.

S/N	Point	Explanation	Reference
1	Genetic Factors in Periodontitis and Cardiovascular Disease	Genetic factors significantly impact susceptibility to periodontitis and cardiovascular disease. Specific gene polymorphisms can affect inflammatory responses, immune functions, and tissue repair mechanisms, influencing the development and severity of these conditions.	Loos and Van Dyke (2020) [16]
2	Role of SIRT1 in Inflammation	SIRT1 is a critical regulator of inflammation and cellular stress responses. Its activation deacetylates key proteins involved in inflammatory pathways, helping to mitigate chronic inflammation associated with both periodontitis and cardiovascular diseases.	Lee et al. (2012) [17]
3	SIRT1 & Cardiovascular Health	SIRT1 is essential for maintaining endothelial function, which is crucial for cardiovascular health. It helps regulate vascular homeostasis and is linked to the prevention of atherosclerosis.	Cantó and Auwerx (2009) and Laky M. et al (2024) [18,19]
4	Environmental Factors Influencing SIRT1	Environmental factors such as diet, exercise, and metabolic conditions significantly influence SIRT1 expression and activity. Specific dietary patterns and physical activity can enhance SIRT1 levels, providing protective effects against both periodontitis and cardiovascular disease.	Radak et al. (2020) [20]
5	Comorbidities and Integrated Management	Addressing comorbidities such as diabetes is crucial since these conditions can exacerbate both periodontitis and cardiovascular disease. Integrated management strategies can improve patient outcomes.	Preshaw et al. (2012) [21]

Table 2. Summary of the elaboration on bacterial lipopolysaccharides (LPS) and their impact on periodontitis and cardiovascular health [22,23].

Aspect	Details
Bacterial Lipopolysaccharides (LPS)	LPS are large molecules found in the outer membrane of gram-negative bacteria. They are potent endotoxins that induce systemic inflammation, contributing to diseases like periodontitis and cardiovascular disease (CVD).
The link between LPS, Periodontitis, and CVD	- **Periodontitis**: Pathogenic bacteria in subgingival biofilms produce LPS, triggering a dysregulated immune response, chronic inflammation, and tissue destruction. Elevated LPS levels correlate with severe periodontitis. - **CVD**: LPS enters the bloodstream during periodontitis, causing systemic inflammation and endothelial dysfunction. Elevated plasma LPS levels are linked to increased CVD risk and promote atherosclerosis.
Measuring Plasma LPS	Measuring plasma LPS levels could serve as a biomarker for diagnosing periodontitis and CVD, providing insights into the severity of periodontal disease and its systemic effects. Further research is required to validate plasma LPS as a diagnostic tool.
Impact of Diet on LPS Levels	Diet influences the microbiome and inflammatory responses, with potential effects on LPS levels: - **Probiotics**: Restore microbial balance, reduce pathogenic gram-negative bacteria, lower systemic inflammation, and improve periodontal health. - **Prebiotics**: Serve as food for beneficial bacteria, enhance gut microbiome diversity, reduce LPS levels, and improve immune responses. - **Dairy Matrices**: Fermented dairy products may modulate inflammation and support oral health, indirectly benefiting cardiovascular health.
LPS and SIRT1 Interaction	LPS represses SIRT1, a key regulator of inflammation and metabolism. SIRT1 activation is associated with anti-inflammatory effects and improved cardiovascular health. By repressing SIRT1, LPS may worsen inflammation and contribute to periodontal disease and cardiovascular complications.

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Environmental risk factors

Environmental and lifestyle factors, such as smoking and diabetes, also modulate the relationship between periodontitis and cardiovascular disease. Smoking is a well-established risk factor for both conditions and is believed to exacerbate the inflammatory response in periodontitis, thereby amplifying its systemic effects. Diabetes, another shared risk factor, has been shown to increase the severity of periodontitis and the risk of cardiovascular complications by promoting a pro-inflammatory state [24-26].

Clinical Implications

The clinical implications of the association between periodontitis and cardiovascular disease are profound. Given the shared inflammatory pathways, it is recommended that clinicians assess cardiovascular risk in patients with severe periodontitis. The American Academy of Periodontology (AAP) and the American Heart Association (AHA) have both issued statements recognizing the potential link between periodontitis and cardiovascular health and advocating for collaborative care between dental and medical professionals [27,28].

Periodontal therapy as a preventive strategy

Given the established association, periodontal therapy has been proposed as a potential preventive measure for reducing cardiovascular risk. Regular dental check-ups, oral hygiene practices, and the management of periodontal inflammation are essential components of cardiovascular risk reduction in individuals with periodontitis. However, more RCTs are needed to definitively establish the long-term benefits of periodontal therapy on cardiovascular outcomes [25-27].

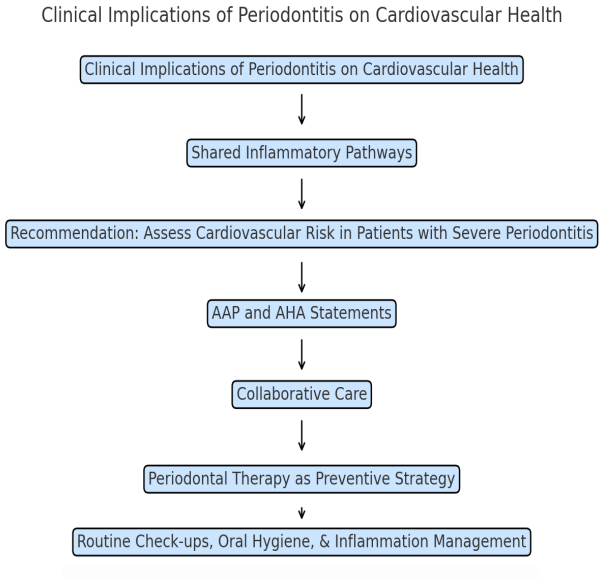

Figure 1. Flowchart illustrating the clinical implications of the association between periodontitis and cardiovascular health. It shows shared inflammatory pathways, recommendations for cardiovascular risk assessment, statements from AAP and AHA, and the role of collaborative care and periodontal therapy as a preventive strategy.

Future Directions and Research Gaps

Despite substantial evidence supporting the association between periodontitis and cardiovascular disease, several research gaps remain. Future studies should aim to:

1. Elucidate the precise molecular mechanisms linking periodontal pathogens to cardiovascular pathology.
2. Investigate the long-term effects of periodontal therapy on cardiovascular outcomes in large-scale, multi-center RCTs.
3. Explore the role of novel biomarkers, such as microRNAs, in the diagnosis and management of both periodontitis and cardiovascular disease.
4. Assess the cost-effectiveness of integrated periodontal and cardiovascular care.

Moreover, public health initiatives should focus on raising awareness of the oral-systemic health connection and promoting preventive strategies to reduce the burden of both periodontitis and cardiovascular disease [15,24-28].

Conclusions

The association between periodontitis and cardiovascular health is well-established, with inflammation serving as a critical link between the two conditions. Periodontal pathogens, systemic inflammatory markers, and endothelial dysfunction all contribute to the increased cardiovascular risk seen in patients with periodontitis. While periodontal therapy has shown promise in reducing systemic inflammation and improving cardiovascular biomarkers, further research is needed to confirm its long-term impact on cardiovascular outcomes. Clinicians should consider periodontal health as part of the comprehensive management of cardiovascular risk, emphasizing the importance of collaborative care between dental and medical professionals.

Disclosure Statement

No potential conflict of interest was reported by the author.

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