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Dysbiosis of the oral microbiome and cardiovascular risk; from endothelial dysfunction to systemic inflammation

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Abstract

A growing body of evidence implicates dysbiosis of the oral microbiome as a significant, modifiable risk factor for cardiovascular disease. This dysbiosis, often manifesting as periodontitis, initiates local inflammation and tissue destruction, however its systemic consequences are profound. Key mechanisms linking oral dysbiosis to cardiovascular disease involve the induction of endothelial dysfunction and chronic systemic inflammation. Pathogens and their virulence factors enter the bloodstream through inflamed periodontal tissues, directly impairing endothelial nitric oxide production and bioavailability, promoting vasoconstriction, leukocyte adhesion, and a pro-thrombotic state. Concurrently, microbial components activate innate immune receptors on endothelial and immune cells, triggering sustained release of pro-inflammatory cytokines and acute-phase proteins. The low-grade, systemic inflammation accelerates atherosclerosis by promoting foam cell formation, plaque instability, and vascular remodeling. Epidemiological studies consistently associate periodontitis with increased risks of myocardial infarction, stroke, and atherosclerosis severity, independent of traditional risk factors.

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Introduction

The human oral cavity harbors one of the most diverse microbial communities in the body, comprising over 700 bacterial species alongside viruses, fungi, and archaea (1). In health, this microbiome exists in a state of dynamic equilibrium, maintained by host defenses, microbial competition, and a stable environment (1). Commensal bacteria like *Streptococcus sanguinis*, *Streptococcus mitis*, and *Actinomyces* species contribute to colonization resistance, preventing pathogen overgrowth, and even support host immunity through low-level stimulation. However, this balance is fragile (2). Periodontitis, a chronic inflammatory disease destroying the tooth-supporting structures, serves as the quintessential model of oral dysbiosis. It is driven not only by a single pathogen but also by a polymicrobial synergy and dysbiosis, where keystone pathogens like *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* subvert the host immune response (3). Meanwhile, *P. gingivalis* is a master manipulator, as it does not merely thrive in inflammation; rather, it actively engineers it (4). Through virulence factors like gingipains, fimbriae, and lipopolysaccharide, the *P. gingivalis* impairs neutrophil function, disrupts complement regulation, and promotes a dysbiotic shift by altering the local environment to favor other pathobionts. This dysbiosis transforms the subgingival pocket into a reservoir of inflammation and live bacteria (5). The integrity of the gingival epithelium is compromised by both the direct destructive action of bacterial enzymes and the host's own hyperinflammatory response, creating portals for microbial invasion (4). Bacteremia occurs routinely during mundane activities like chewing, brushing, or dental procedures. In a healthy individual with a balanced microbiome, this is swiftly cleared by the immune system (6). However,

Key point

Oral microbiome dysbiosis, known as an imbalance in the oral microbial community, is increasingly recognized for its role in cardiovascular disease development. This dysbiosis often leads to periodontal disease, which is a known risk factor for various cardiovascular conditions, including hypertension, heart failure, atherosclerosis, and coronary heart disease. The mechanisms linking oral dysbiosis to cardiovascular disease are multifaceted, involving systemic inflammation, oxidative stress, immune responses, and platelet aggregation. Oral pathogens and their metabolites can invade the bloodstream and influence gut microbiota composition, contributing to systemic inflammation and endothelial dysfunction. Specific microbial metabolites like short-chain fatty acids, nitric oxide, and hydrogen sulfide produced by the oral microbiota can have both protective and detrimental effects on cardiovascular health, while trimethylamine oxide is associated with adverse cardiac outcomes.

in the context of chronic periodontitis and dysbiosis, the frequency, duration, and pathogenic load of these bacteremias increase dramatically. Pathogens like *P. gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* are repeatedly detected in the bloodstream of periodontitis patients, providing a direct conduit for oral microbes to access the vascular system (7). Recent studies have demonstrated that dysbiosis of the oral microbiome extends its influence far beyond the gingival crevice, contributing significantly to the pathogenesis of cardiovascular disease. This connection is not merely associative, as it involves complex, interwoven biological pathways (6). Prior studies detected that oral pathogens and the inflammatory mediators provoke directly the vascular endothelium, trigger systemic inflammation, and accelerate atherosclerotic processes, finally elevating the risk of myocardial infarction, stroke, and other cardiovascular events (8). This study sought to consider dysbiosis of the oral microbiome and cardiovascular risk, from endothelial dysfunction to systemic inflammation.

Search strategy

To ensure comprehensive coverage of the relevant literature, we thoroughly explored multiple scholarly databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase. The search strategy incorporated a range of controlled and free-text terms, such as such as 'oral microbiome,' 'dysbiosis,' 'cardiovascular risk,' 'endothelial dysfunction,' 'systemic inflammation,' and 'periodontal disease,' thereby maximizing retrieval of pertinent studies.

From oral ecosystem to cardiovascular pathology

The vascular endothelium, a single-cell-thick layer lining all blood vessels, is far more than a passive barrier; it is a dynamic endocrine organ critical for vascular homeostasis. It regulates vasodilation and vasoconstriction by nitric oxide production, controls thrombosis and fibrinolysis, modulates immune cell adhesion and transmigration, and maintains vascular permeability (9). Endothelial dysfunction is characterized by reduced nitric oxide bioavailability, increased oxidative stress, a pro-thrombotic state, across with enhanced expression of adhesion molecules (9). Oral dysbiosis assaults the endothelium through multiple, synergistic mechanisms. numerous studies found that circulating oral pathogens or their virulence factors directly interact with endothelial cells. It was detected that *P. gingivalis* that equipped with adhesins, can invade endothelial cells, surviving and even replicating intracellularly. Once inside, it disrupts cellular functions, induces apoptosis, and triggers inflammatory signaling pathways like NF-κB (nuclear factor-κB) (10). Then, gingipains cleave critical host proteins, including those involved in coagulation (e.g., fibrinogen) and complement regulation, directly promoting thrombosis and inflammation (10). Meanwhile, bacterial lipopolysaccharides from gram-negative periodontal pathogens binds to Toll-like receptors (TLRs), particularly TLR2 and TLR4, on endothelial cells and circulating immune cells. This binding activates NF-κB and MAPK pathways, leading to the upregulation of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin. These molecules act as glue, capturing circulating monocytes and T-lymphocytes, enabling their adhesion to the vessel wall and subsequent transmigration into the subendothelial space as a critical initiating step in atherogenesis (11). In the second step, the dysbiotic oral environment generates a constant stream of pro-inflammatory mediators (12). Gingival crevicular fluid from periodontitis sites is rich in cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), prostaglandin E2 (PGE2), and matrix metalloproteinases (MMPs). These mediators spill over into the systemic circulation (13). Likewise, IL-1β and TNF-α directly impair endothelial function by down-regulating endothelial nitric oxide synthase (eNOS) expression and activity, reducing nitric oxide production. They also stimulate endothelial cells to produce reactive oxygen species, which further scavenge nitric oxide, forming peroxynitrite as a potent oxidant that damages cellular components (14). Reduced nitric oxide bioavailability leads to impaired vasodilation, increased vascular tone, and hypertension (15). Reactive oxygen species also oxidize low-density lipoprotein (LDL) cholesterol; oxidized LDL (oxLDL) is avidly taken up by macrophages in the arterial wall, transforming them into foam cells, which known as the hallmark of early atherosclerotic lesions. In this regard, molecular mimicry may play a role; since some oral bacterial antigens share structural similarities with host proteins (16). Previous authors mentioned, heat shock proteins (HSPs) from *P. gingivalis* is resemble to human HSP60. Thereby, antibodies produced against bacterial HSPs might cross-react with human HSP60 expressed on stressed endothelial cells, leading to autoimmune-mediated endothelial damage and inflammation. In this process, the endothelial assault initiated by oral dysbiosis is rapidly amplified into a state of chronic, low-grade systemic inflammation as a well-established driver of atherosclerosis progression and plaque instability (17). Indeed, periodontitis is not a localized infection; whilst, it is a significant source of systemic inflammatory burden (18). The persistent antigenic challenge from the dysbiotic biofilm within the periodontal pocket leads to sustained activation of innate and adaptive immune responses (19). Macrophages and neutrophils recruited to the site release copious amounts of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α and acute-phase proteins. Importantly, these mediators do not remain confined to the oral cavity. They enter the circulation, triggering the liver to increase production of C-reactive protein (CRP), fibrinogen, and serum amyloid A (20). Notably, elevated high-sensitivity CRP (hsCRP) is a powerful independent predictor of future cardiovascular events. Recent studies consistently show that individuals with severe periodontitis have significantly higher levels of hsCRP, IL-6, and fibrinogen compared to periodontally healthy controls, even after adjusting for traditional risk factors like smoking and diabetes. This systemic inflammatory milieu has profound effects on the vasculature (21). More recent studies detected that IL-6, a central cytokine in this cascade, promotes hepatic CRP production, stimulates leukocyte recruitment to atherosclerotic plaques, enhances platelet activation, and contributes to insulin resistance, while all of these factors accelerating atherosclerosis (22). Among these events, TNF-α further amplifies endothelial activation, promotes foam cell formation, and induces apoptosis in vascular smooth muscle cells, weakening the fibrous cap of atherosclerotic plaques (23). In addition, CRP itself is not merely a marker; it actively participates in atherogenesis. It binds to damaged endothelial cells and LDL within plaques, activating complement, promoting monocyte recruitment, enhancing uptake of oxLDL by macrophages, and inhibiting endothelial progenitor cell function crucial for endothelial repair (24). Fibrinogen increases blood viscosity and promotes platelet aggregation, contributing to a pro-thrombotic state. This chronic inflammation also drives metabolic dysfunction (25). Likewise, insulin resistance, as a key component of metabolic syndrome and a major cardiovascular disease risk factor, is exacerbated by inflammatory cytokines like TNF-α and IL-6, which interfere with insulin signaling pathways in adipose tissue, muscle, and liver (26). Several investigations noted that periodontitis is associated with poorer glycemic control in diabetics and an increased risk of developing type 2 diabetes, creating a vicious cycle where diabetes also worsens periodontitis (27). Furthermore, systemic inflammation promotes dyslipidemia, through elevated triglycerides, reduced high-density lipoprotein cholesterol, and increased small, dense LDL particles (28). Consequently, the inflamed endothelium becomes increasingly permeable, allowing greater infiltration of lipids and inflammatory cells into the vessel wall (29). Within the developing plaque, macrophages overwhelmed by oxLDL become foam cells, releasing more cytokines and MMPs. Previous investigations demonstrated that MMPs, particularly those induced by bacterial products and host inflammation (like MMP-9), degrade the extracellular matrix of the fibrous cap that stabilizes the plaque. At this condition, a thin, weakened cap is prone to rupture (30). When a vulnerable plaque ruptures, the highly thrombogenic lipid core is exposed to blood, triggering rapid clot formation. This acute thrombosis is the primary mechanism underlying most myocardial infarctions and many ischemic strokes (31). Hence, the persistent inflammatory stimulus from a dysbiotic oral microbiome thus fuels every stage of atherosclerosis as the initiation period by endothelial dysfunction, LDL oxidation, in progression phase by foam cell formation, smooth muscle proliferation, and then in the transition to clinical events including plaque destabilization and rupture (8).

Conclusion

In summary, the dysbiosis of the oral microbiome, is a significant contributor to cardiovascular disease risk through the breach of the endothelial barrier. Oral pathogens and their virulence factors, disseminated by bacteremia or carried as soluble mediators, directly invade and damage endothelial cells, impair nitric oxide signaling, and induce a pro-adhesive, pro-thrombotic phenotype. Then, the chronic inflammatory burden generated by the dysbiotic biofilm spills into the systemic circulation, elevating levels of CRP, IL-6, and fibrinogen. This systemic inflammation accelerates atherosclerosis by promoting LDL oxidation, foam cell formation, plaque growth, and crucially, the destabilization of vulnerable plaques prone to rupture, triggering thrombotic events. While periodontitis is neither necessary nor sufficient to cause cardiovascular disease alone, it acts as a potent, modifiable risk amplifier, adding to the cumulative inflammatory burden that drives vascular pathology. Effective periodontal therapy reduces systemic inflammation and improves vascular function, positioning it as a valuable component of comprehensive cardiovascular risk management. Hence, prioritizing oral health assessment and management is not just about preserving teeth; it is a vital strategy in the ongoing battle against cardiovascular disease, as the world's leading cause of death.

Authors' contribution

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Writing–original draft: All authors.
Writing–review and editing: All authors.

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The authors declare that they have no competing interests.

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During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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