Review Article

CHANGES IN THE ORAL MICROBIOTA AND THEIR ASSOCIATIONS WITH CARDIOVASCULAR DISEASES

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ABSTRACT

The oral microbiota constitutes a complex and dynamic microbial ecosystem within the human body and is increasingly recognised as an important contributor to systemic health beyond the oral cavity. Dysbiosis of the oral microbiota has been associated with a broad spectrum of cardiovascular diseases (CVDs), including atherosclerosis, coronary artery disease, heart failure and hypertension. Growing evidence supports several interconnected mechanistic pathways linking oral microbial imbalance to cardiovascular pathology. These include translocation of oral bacteria into the bloodstream during transient bacteremia, activation of systemic inflammatory and immune responses, and the production of microbial metabolites such as trimethylamine-N-oxide, short-chain fatty acids, nitric oxide and hydrogen sulfide, which can influence vascular tone, endothelial function and atherogenesis. In addition, disruption of nitrate-reducing oral commensals may impair nitric oxide bioavailability, contributing to endothelial dysfunction. This review summarises current evidence on the composition and functional roles of the oral microbiome in cardiovascular disease, highlights key microbial taxa implicated in cardiovascular risk, and discusses recent diagnostic and research advances, including sequencing and metabolomic approaches. Potential preventive and therapeutic implications, such as oral hygiene optimisation and microbiome-modulating strategies, are also considered. Although causality has not been fully established, the oral microbiota represents a promising and biologically plausible target for future cardiovascular research and risk stratification strategies.

Key words: Oral microbiota, Dysbiosis, Cardiovascular diseases, Microbial metabolites, Endothelium, Inflammation.

Introduction

Cardiovascular diseases (CVDs) remain the foremost cause of morbidity and mortality worldwide and arise from multifactorial interactions among genetics, metabolic status, inflammation and environmental exposures [1, 2]. The human oral microbiome — an anatomically proximal, diverse microbial community comprised of bacterial, fungal, viral and archaeal members — is increasingly recognised as a contributor to systemic inflammation and cardiometabolic risk [3-6]. Periodontal disease, tooth loss, and chronic oral dysbiosis correlate with adverse cardiovascular outcomes in multiple cohorts, while mechanistic and interventional data suggest biologically plausible links mediated by bacteremia, immune activation, and microbial metabolites [7-13]. This review synthesises recent evidence on composition, mechanistic pathways, clinical associations, diagnostics, and therapeutic implications of the oral microbiota in cardiovascular disease.

Composition and ecology of the oral microbiota

The oral cavity contains discrete ecological niches (supragingival plaque, subgingival biofilm, tongue dorsum, saliva, and mucosal surfaces) with characteristic microbial assemblages. Dominant bacterial phyla include Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria and Fusobacteria; common genera include Streptococcus, Veillonella, Actinomyces, Neisseria, Haemophilus and Prevotella [3, 4, 14]. Homeostatic functions include maintenance of mucosal barrier integrity, colonisation resistance, and nitrate reduction that supports systemic nitric oxide (NO) biology [11, 15]. Perturbations from poor oral hygiene, tobacco, diet, medications (including antibiotics and antiseptic mouthwashes), systemic disease and ageing can shift community structure toward pathogenic consortia (periodontopathogens and anaerobic gram-negative microbes), promote biofilm maturation, and increase local inflammatory burden [4, 16-18].

Epidemiologic links between oral disease and CVD

Large observational cohorts, systematic reviews and pooled analyses report associations between periodontitis and incident atherosclerotic events, coronary artery disease, stroke and cardiovascular mortality after adjustment for traditional risk factors [7, 12, 19-22]. The strength of association varies by population, periodontitis severity, and residual confounding; nevertheless several consensus bodies have concluded that the association is biologically plausible and likely independent in part from shared risk factors [2, 7, 12]. Recent randomized interventional evidence indicates that intensive periodontal therapy can attenuate progression of carotid intima-media thickness (cIMT) and improve endothelial function — findings that strengthen the causal argument though do not yet constitute definitive proof of prevented hard cardiovascular outcomes.

Epidemiologic links between oral disease and CVD

1. Bacterial translocation and local vascular invasion

Transient bacteremia occurs frequently after routine oral activities (toothbrushing, chewing) in patients with periodontitis and provides a route for oral microbes to reach distant vascular sites. Oral bacterial DNA and viable organisms (e.g., Streptococcus spp., Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum) have been detected in atheromatous plaques, valvular tissue and thrombi, supporting direct microbial involvement in lesion biology [8, 23-26]. Animal models demonstrate that chronic exposure to periodontal pathogens accelerates atherogenesis and destabilises plaques via local immune activation [27-36].

2. Systemic inflammation and immune modulation

Chronic periodontal inflammation increases systemic markers such as C-reactive protein, IL-6 and TNF-α, and promotes monocyte activation and endothelial adhesion molecule expression, thereby facilitating lipid infiltration, foam cell formation and plaque progression [9, 16, 37-39]. Molecular mimicry and cross-reactive immune responses (e.g., heat-shock proteins) may further link oral infection to vascular immune pathology.

3. Microbial metabolites and host signalling

Microbial metabolism produces small molecules with vasoactive and immunomodulatory properties:

- *Trimethylamine-N-oxide (TMAO):* Emerging data indicate oral bacteria can influence systemic TMAO synthesis either directly or via effects on gut communities; elevated TMAO associates with atherothrombosis and adverse outcomes in multiple cohorts. Recent experimental work links periodontal pathogens to increased TMAO levels and hepatic FMO3 modulation.
- *Short-chain fatty acids (SCFAs):* SCFAs influence immune cell function and vascular inflammation; their net effect depends on concentration, receptor engagement and tissue context.
- *Nitric oxide (NO) and nitrate-nitrite pathway:* Commensal oral nitrate-reducing bacteria are essential for conversion of dietary nitrate to nitrite and eventual systemic NO availability. Dysbiosis or antiseptic mouthwash use reduces this capacity and may elevate blood pressure and impair endothelial function. Recent studies document impaired oral nitrate reduction in cardiovascular disease and heart-failure cohorts.
- *Hydrogen sulfide (H_2S):* Produced by some oral anaerobes, H_2S has complex dose-dependent vascular effects.

4. Oral–gut axis and secondary seeding

Oral microbes can colonise the gut (fecal–oral/enteral routes), altering gut ecology and permeability, thereby amplifying systemic inflammation and metabolic dysregulation relevant to cardiometabolic risk [14, 18, 40-43]. This oral–gut seeding may be particularly important for taxa such as Fusobacterium and Streptococcus.

5. Thrombosis, endothelial dysfunction and plaque instability

Direct endothelial cell activation by LPS, gingipains (P. gingivalis virulence factors) and microbial extracellular vesicles, along with systemic inflammatory mediators, enhances prothrombotic states, platelet aggregation and matrix metalloproteinase activity, which can destabilise atheromatous plaques and precipitate acute coronary syndromes [16, 44–46].

Key taxa implicated in cardiovascular associations

Repeatedly implicated oral taxa include *Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Treponema denticola,* and certain Streptococcus species (including viridans streptococci and S. mutans). These organisms contribute through endotoxemia, proteolytic virulence factors, platelet-activating properties and metabolic effects; however, they act within complex communities and their effects are modulated by host susceptibility.

Diagnostics and research advances

High-throughput 16S rRNA gene profiling, shotgun metagenomics, metatranscriptomics and metabolomics enable taxonomic and functional characterisation of oral communities [3, 8, 47-49]. Integrative multi-omics can identify microbial signatures and metabolites (e.g., TMAO, nitrate reduction capacity) that correlate with vascular biomarkers (FMD, cIMT) and clinical endpoints. Novel approaches include oral microbiota transplantation in preclinical models, machine-learning classifiers for risk stratification, and targeted functional assays (e.g., nitrate reduction tests) that are closer to clinical application [50-57].

Preventive and therapeutic implications

Primary and secondary prevention

- Oral hygiene and periodontal care: Observational and some interventional data support that improved oral hygiene, professional periodontal therapy and interdental cleaning reduce systemic inflammatory markers and may favourably affect surrogate vascular measures [6, 12, 58-60]. The recent randomized trial showing reduced cIMT progression after intensive periodontal therapy strengthens the rationale for integrated oral–cardiovascular prevention strategies.
- Medication interactions and mouthwash caution: Antiseptic mouthwashes can suppress nitrate-reducing commensals thereby reducing NO bioavailability and increasing blood pressure in some studies — this has practical implications for prescribing and counseling.

Emerging microbiome-modulating strategies

- Probiotics/prebiotics and functional foods aimed at restoring nitrate-reducing commensals or suppressing

pathobionts show promise in early trials and animal models.
- Small-molecule inhibitors of specific virulence factors (e.g., gingipain inhibitors) are in preclinical/early clinical development.
- Host-directed anti-inflammatory therapies (e.g., IL-1β blockade) afford proof of principle that modulating inflammation reduces cardiovascular events, and these intersect conceptually with infection-driven pathways.
- Microbiome engineering and oral bacteriotherapy remain experimental but offer translational opportunities.

Gaps, limitations and future research priorities

1. Causality vs association: Large, well-designed randomized controlled trials with long-term cardiovascular endpoints are scarce; surrogate outcome trials (cIMT, FMD) are encouraging but insufficient. More interventional trials that test periodontal and microbiome-directed therapies for hard cardiovascular outcomes are needed.
2. Mechanistic specificity: The oral microbiome acts as an ecosystem; disentangling individual taxa vs community function requires integrated multi-omics and mechanistic human translational studies.
3. Population heterogeneity: Effects may vary with baseline cardiovascular risk, comorbidities (diabetes, chronic kidney disease), age, medications and socioeconomic factors — stratified analyses are essential.
4. Standardised diagnostics: Harmonised methods for oral sampling, sequencing, metabolite assays, and functional tests (nitrate reduction) will improve reproducibility across studies.
5. Integration into clinical practice: Evidence-based clinical pathways for dental–cardiac collaboration, risk communication and reimbursement will be necessary if oral health interventions are to be adopted for cardiovascular prevention.

Conclusion

The oral microbiota interfaces with cardiovascular biology through microbial translocation, systemic inflammation, metabolite production and modulation of endothelial and immune function. Recent mechanistic work and emerging randomized clinical evidence strengthen the plausibility of causal links and underscore the potential for oral health interventions as adjuncts in cardiovascular prevention. Future research must prioritise high-quality interventional trials, standardised diagnostics, and mechanistic human studies to translate microbiome science into clinical practice.

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