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Opinion article

Mouth-heart axis: contribution of oral dysbiotic bacteria in the initiation and development of cardiovascular conditions

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Abstract

The oral microbiota begins to establish at birth and develops over time under the influence of genetic factors, environmental exposures, diet, and individual oral health behaviors. In a healthy state, these microorganisms exist in a balanced ecosystem; however, disruption of this balance, known as oral dysbiosis, can promote oral diseases such as dental caries and periodontitis (PD). Growing scientific evidence indicates that the impact of oral microbial imbalance may extend beyond the oral cavity. With advances in molecular detection techniques, oral bacterial species have been identified in distant body sites, including heart valves, suggesting a possible association between oral dysbiosis and cardiovascular disease. Chronic periodontal inflammation and microbial imbalance may allow bacteria or their inflammatory products to enter the bloodstream, leading to bacteremia via direct invasion or immune-mediated mechanisms. These processes may contribute to systemic inflammation and potentially influence the development and progression of cardiovascular disease. This study aims to review and summarize current evidence on the relationship between oral dysbiosis and cardiovascular disease, with particular focus on the mechanisms by which chronic oral inflammation and microbial imbalance may contribute to bacteremia and systemic inflammatory pathways that influence cardiovascular health.

Keywords: Bacteremia, Infective endocarditis, Inflammation, Mouth-heart axis, Oral dysbiosis, Oral microbiome, Periodontal pathogens

Introduction

The oral cavity is a complex ecosystem composed of approximately 1,000 species of bacteria, viruses, fungi, and protozoa. Commensal bacteria and other naturally occurring microorganisms coexist to maintain the health of the mouth microbiome [1]. Ongoing research explores the connection between the oral microbiota and systemic health [2, 3, 4]. Dysbiosis is characterized by several key features, including decreased microbial community diversity, loss of benefits provided by "healthy" microorganisms, and an increased abundance of pathogenic microbes. Loss of diversity disrupts interspecies connections, which can be collaborative, signaling, or antagonistic, leading to oral dysbiosis [5]. A damaged natural microflora can weaken immunity and increase the risk of opportunistic infections, which occur when commensal microorganisms switch to pathogenic states in response to environmental changes [6]. This article aims to examine oral dysbiosis and its link to cardiovascular conditions, serving as an initial basis for subsequent studies on oral health preservation in cardiovascular disease and the development of new treatments that may be sensitive to biomarkers. Figure 1 shows the potential effect of the unbalanced oral microbiome (Dysbiosis) on the cardiovascular system.

Mechanisms of cardiovascular disease (CVD) from oral dysbiosis

Inflammation caused by bacterial infections that affect the gums and the tooth's supporting tissues is the primary cause of periodontal disease. There are two primary phases: periodontitis, which is more severe and advanced, and gingivitis, which is milder and reversible [7]. With prompt and proper dental treatment, gingivitis can be controlled and even reversed; if ignored, it can progress to periodontitis, which is characterized by bone loss, deep pockets around the teeth, and degeneration of connective tissue. Addressing the early symptoms of the condition is essential to minimize long-term damage to oral health [8, 9]. *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola*, collectively known as the "red complex" bacteria, are the primary bacterial species associated with periodontal disease. The body's immune response to these germs involves the release of inflammatory mediators, including prostaglandins, interleukins, and cytokines [10]. Although this initial reaction aims to combat infection, persistent inflammation can become chronic and lead to systemic

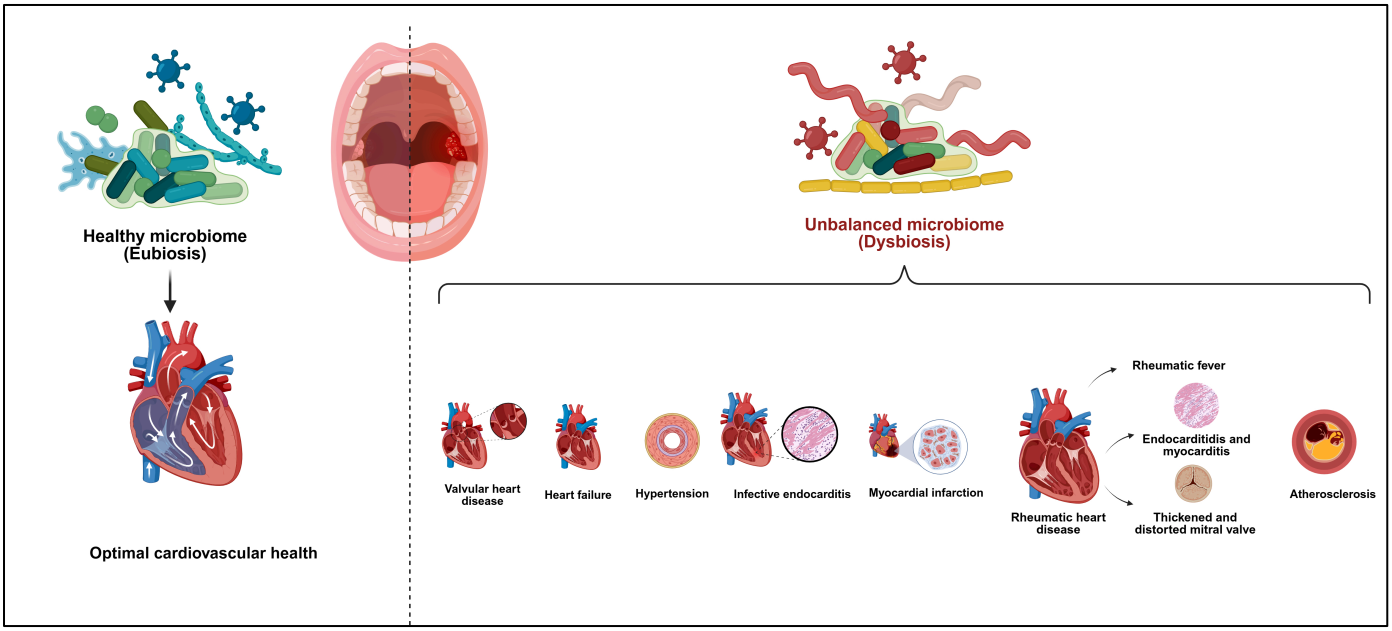

Figure 1: A diagram illustrating the potential effect of the unbalanced oral microbiome (Dysbiosis) on the cardiovascular system.

effects. Oral germs can enter the circulation and cause systemic inflammation in individuals with periodontal disease. Oral pathogens can enter the bloodstream when the gums are injured or ulcerated, especially in severe periodontitis [11, 12, 13]. Once in circulation, these bacteria can spread to other parts of the body, such as the cardiovascular system, where they may contribute to the development of atherosclerotic plaques and increase the risk of stroke and cardiac events by further damaging cardiovascular tissues [14, 15]. These findings demonstrate the impact of gum disease on overall health, particularly cardiovascular disorders. Bacterial endotoxins, including LPS, are released into the circulation, serving as another significant mechanism. Gram-negative bacteria such as *Porphyromonas gingivalis* are the primary producers of lipopolysaccharide (LPS), which can trigger systemic inflammation by inducing the release of pro-inflammatory molecules, including IL-6, TNF-α, and interleukin-1β (IL-1β) [16]. Subsequently, these cytokines travel through the body's tissues, causing widespread inflammation. This process illustrates how oral bacterial activity might influence broader systemic responses beyond oral health. Locally released cytokines in response to chronic gingival disease can enter the circulation, worsening systemic inflammation [17]. Among these are IL-1β, a potent pro-inflammatory cytokine that intensifies tissue damage, enhances immune responses, and accelerates the development of inflammatory diseases. In periodontal disease, TNF-α, an inflammatory cytokine produced by immune cells, plays a major role in the breakdown of bone and connective tissue. It also contributes to vascular inflammation, which can impact circulation throughout the body [18]. IL-6 is well-known for its role in stimulating the liver [19]. C-reactive protein (CRP), a marker of systemic inflammation and a potential predictor of cardiovascular events, is produced in response to IL-6. The persistent elevation of these mediators highlights the crucial link between systemic disorders and oral health. This underscores the importance of properly managing periodontal disease to reduce broader health risks and improve overall well-being [20].

The oral microbiome in cardiovascular conditions

Dental disorders are increasingly understood to result from disturbances in the normally stable oral microbiome [21]. Frequent carbohydrate intake or reduced saliva flow can contribute to the development of caries, and extensive plaque accumulation increases the risk of periodontal disease. However, while these factors act as "disease triggers," some individuals are more susceptible, whereas others show resistance or apparent immunity to harmful changes in their oral microbial communities [22]. The intricate metabolic and functional interactions between biofilms and the host illustrate a system that promotes oral health by mitigating the effects of pathogenic agents [23].

Hypertension

Hypertension, or high blood pressure, is a chronic condition in which the force of blood against arterial walls makes the heart work harder. Often called a "silent killer," it may show no obvious symptoms, although very high blood pressure can cause headaches, vision problems, and dizziness. Risk factors include age, genetics, smoking, stress, and high salt intake. Zhan et al. investigated the link between periodontitis severity and hypertension [24]. They found that Stage III and IV periodontitis occurred in

41.4% of individuals with hypertension compared to 28.0% of those with normal blood pressure. Severe periodontitis was more prevalent among hypertensive patients and individuals aged 55–64, but not in those aged 65–74, indicating that the difference in periodontal health between hypertensive and normotensive individuals decreases with age. Both the severity of periodontitis and the number of teeth with probing depths ≥4 mm or ≥6 mm were associated with hypertension. The likelihood of high blood pressure increased with worsening periodontitis, particularly in younger adults. These findings highlight the importance of raising awareness, providing periodontal care education, and promoting preventive strategies, especially for younger individuals at risk of hypertension [24].

In another study conducted by Larvin and colleagues [25], the authors examined both the combined and individual effects of periodontitis and hypertension on the risk of future systemic diseases. Overall, hypertension appeared to have a stronger influence on risk estimates than periodontitis alone. The likelihood of cardiovascular and respiratory diseases was higher in hypertensive patients who also had loose teeth, a marker of more severe periodontitis. This association is likely driven by overlapping inflammatory pathways and endothelial dysfunction. However, the precise biochemical mechanisms linking periodontitis, hypertension, and subsequent systemic conditions remain unclear, highlighting the need for further research [25].

Atherosclerotic cardiovascular disease (ASCVD)

Oral dysbiosis is linked to atherosclerotic cardiovascular disease (ASCVD) through both direct and indirect pathways. The direct pathway involves the translocation of oral bacteria into the bloodstream and their subsequent infiltration into the arterial walls [26, 27]. Periodontal pathogens, including *Streptococcus mutans* and the red complex bacteria, significantly increase the risk of ASCVD [28]. Indirectly, oral dysbiosis promotes ASCVD by stimulating immune responses that trigger chronic inflammation. This persistent inflammatory state can lead to arterial hypertension, imbalances in regulatory T cells (Tregs), recruitment and proliferation of macrophages, and ultimately the erosion and rupture of atherosclerotic plaques [29, 30, 31].

Heart failure (HF)

Heart failure (HF) is a clinical syndrome characterized by reduced physical capacity due to left ventricular (LV) dysfunction, which results in fluid retention and compensatory activation of neurohormonal systems [32]. Chronic, low-grade inflammation in HF is linked to immune dysfunction, leading to maladaptive changes such as activation of cardiac fibroblasts, promoting fibrosis and further deterioration of cardiac function. Oral bacteria can be transported via saliva to the gut, where some are neutralized by gastric acid, while acid-resistant species, such as *Porphyromonas gingivalis*, can disrupt the gut microbiota, causing gastrointestinal dysbiosis. In HF patients, this dysbiosis is associated with increased intestinal permeability and bacterial translocation, promoting systemic inflammation (Figure 2) [33]. Consequently, endotoxins enter the bloodstream through "leaky" intestinal barriers, resulting in metabolic endotoxemia, which contributes to cardiovascular disease, LV dysfunction, and HF progression. Persistent bacterial migration and the resulting chronic inflammation play a key role in the progression of HF by maintaining a cycle of compromised LV function that ultimately leads to chronic heart failure [34].

Infective endocarditis (IE)

Infective endocarditis (IE) is a condition characterized by infection or inflammation of the heart's endocardial membrane. It can affect both natural and prosthetic heart valves, as well as cardiac implantable electronic devices (CIEDs), including pacemakers, defibrillators, and cardiac resynchronization therapy devices [35]. Epprecht et al. reported a link between oral streptococcal IE and moderate-risk patients, particularly following revisions to antibiotic prophylaxis (AP) guidelines [36]. They emphasized the importance of annual dental examinations and a clear, shared understanding of IE prevention for individuals with intermediate risk. However, AP may alter the oral microbiota, contribute to antibiotic resistance, and reduce microbial susceptibility over time. Additionally, the potential for adverse drug reactions and the associated costs should be carefully considered when evaluating the benefits of prophylactic antibiotics [36].

Rheumatic heart disease (RHD)

Rheumatic heart disease (RHD) is a cardiovascular condition in which heart valves are damaged due to an inflammatory response triggered by group A *streptococcus* (GAS) infections. Current management primarily relies on penicillin-based treatment of acute rheumatic fever and surgical replacement of severely damaged valves, as no effective vaccine is yet available [37]. Progress in this field has been limited in recent years, highlighting the need for new strategies to improve RHD prevention and management. The oral cavity hosts the second-most diverse microbial community in the human body, which influences both oral and systemic health. It harbors a large proportion of commensal bacteria that contribute to immune homeostasis, can provoke inflammation, and may translocate to other tissues [38]. Increasing evidence indicates that the human microbiome plays a crucial role in cardiovascular diseases. Periodontal infections can alter the subgingival microbial composition

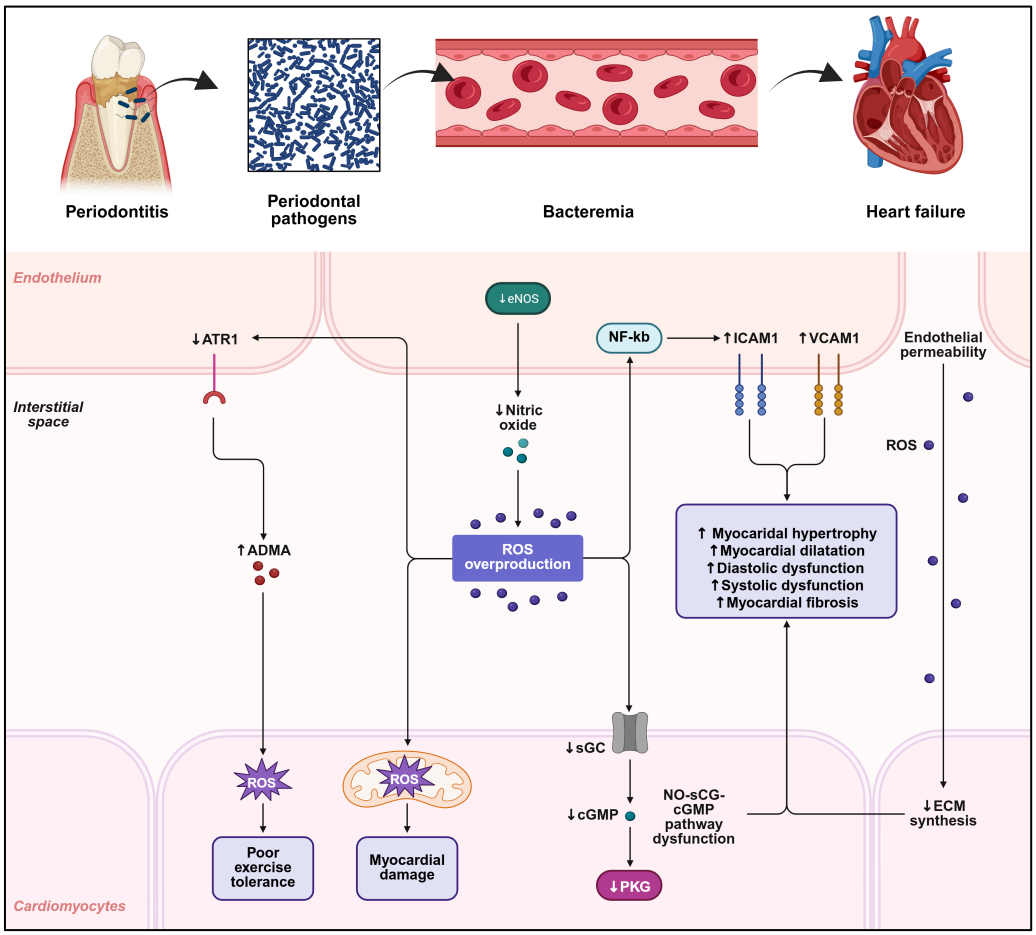

Figure 2: Mechanistic processes of oral dysbiotic bacteria in triggering and development of endothelial heart failure.

and disrupt host-microbe interactions, leading to localized inflammation and loss of periodontal tissue [39]. The presence of periodontal bacterial DNA in cardiac tissues and atherosclerotic plaques suggests a connection between oral infections and cardiovascular disease. Periodontitis, a common inflammatory oral condition, is associated with elevated risks of pregnancy complications, atherosclerosis, stroke, rheumatoid arthritis, diabetes, and other systemic disorders. Despite these findings, the specific role of the oral microbiome in RHD remains poorly understood [40].

Myocardial infarction:

Acute myocardial infarction (AMI) is a prevalent cardiovascular emergency associated with significant morbidity and mortality, and it represents a major contributor to cardiovascular failure and cardiac-related deaths worldwide [41]. Increasing evidence suggests a link between the oral microbiome and AMI [42, 43, 44], with several oral pathogens implicated in heightened risk of myocardial infarction (Figure 3) [45, 46, 47]. Hernández-Ruiz et al. explored the role of oral dysbiosis in relation to trimethylamine N-oxide (TMAO) as a distinct risk factor for AMI progression, a relationship not previously reported in human populations. They identified a significant association between TMAO levels and porphyromonas, and observed that peptidiphaga levels were elevated in individuals without systemic risk factors (SRs). Notably, the presence of traditional risk factors did not affect TMAO concentrations in these individuals, highlighting a potential role for oral infections combined with gut dysbiosis in AMI progression, although further studies are needed [48].

In a retrospective cohort study of the Korean population from 2002 to 2015, Cho et al. assessed the causal relationship between periodontitis and the incidence of AMI and stroke while adjusting for multiple variables. Participants were categorized as having healthy periodontium, moderate periodontal disease, or severe periodontal disease (SPD). Individuals with SPD had a higher likelihood of AMI (adjusted hazard ratio [aHR] 1.11; 95% confidence interval [CI], 1.02–1.20), stroke (aHR 1.035; 95% CI, 1.01–1.07), and nonfatal major adverse cardiovascular events (MACEs) (aHR 1.04; 95% CI, 1.01–1.07). The associations between SPD and AMI/MACEs were particularly pronounced in females and adults aged 40–59 years. Overall, SPD contributed to a 4.3% increase in AMI events, a 1.4% increase in stroke events, and a 1.6% increase in MACEs in this population,

demonstrating a direct link between severe periodontitis and the occurrence of new AMI and stroke episodes [49].

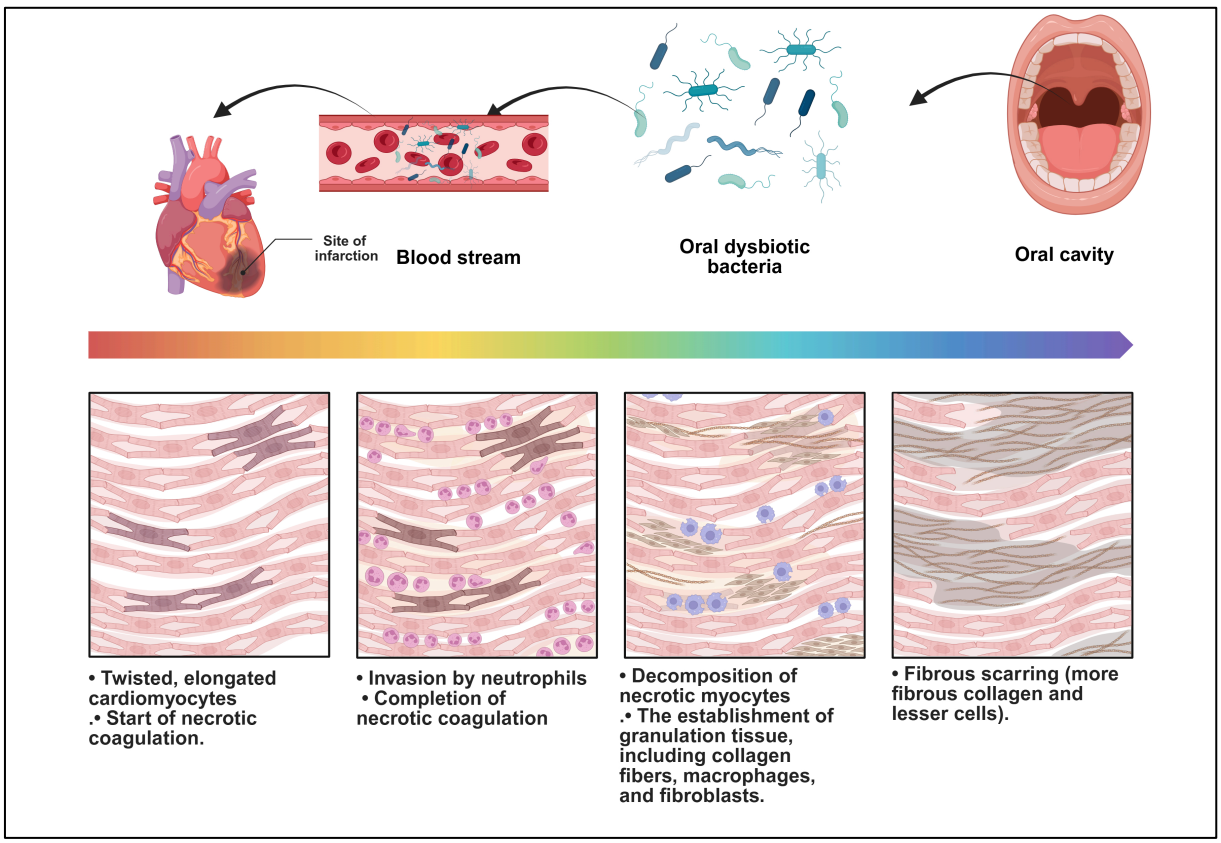

Figure 3: Role of oral dysbiotic bacteria in induction and worsening of myocardial infarction.

Valvular heart disease

Valvular heart disease (VHD) is associated with significant morbidity and mortality worldwide. Advances in diagnostic techniques and medical therapies, along with the development of safer, less invasive treatment options, have prompted updates to VHD management guidelines [50, 51]. Yaguchi et al. employed 16S rRNA metagenomic sequencing to analyze the bacterial composition of resected aortic valves and directly compared these genetic profiles with those found in the oral cavity [52]. The study included 32 patients with aortic stenosis or aortic regurgitation who underwent valve replacement. Analysis revealed that patients with aortic valve disease also had more severe periodontitis based on Socransky's microbial complexes. Bacterial DNA was detected in the aortic valves of 12 patients, and in six cases, the V3–V4 regions of 16S rRNA sequences in valve bacteria closely matched those found in the oral cavity. These findings suggest that bacteria may reach the aortic valve via oral dysbiosis, a disruption in the oral microbiota that increases susceptibility to oral disease, linking oral microbial imbalance and transient bacteremia to the pathogenesis of aortic valve disorders [52].

In contrast, Raffaelli et al. investigated periodontal bacterial DNA in aortic valves and systemic specimens from patients undergoing valve replacement but found no direct correlation between oral infections and valve or blood samples [53]. They proposed that localized aortic valve hypertension may prevent bacterial adhesion and growth, suggesting that bacterial-triggered inflammatory mediators might indirectly contribute to aortic stenosis [53]. Nakano et al. further examined the role of oral pathogens in cardiovascular diseases by analyzing heart valve biopsies and atheromatous plaques, identifying *Streptococcus mutans* and *Aggregatibacter actinomycetemcomitans* as the primary oral bacterial species implicated in cardiovascular pathology [54].

Conclusion

The oral cavity hosts a diverse microbial community that supports host health by inhibiting pathogenic bacteria and modulating immune responses. Oral dysbiosis, an imbalance in this ecosystem, can arise from various factors, including illness, poor oral hygiene, medication use, and diet, and may contribute to both oral and systemic diseases. In systemic disorders, oral dysbiosis alters microbial composition by increasing pathogenic species and reducing beneficial commensals. Disease development results from interactions between microorganisms and host immune responses, with certain infections triggering the release of pro-inflammatory

mediators that promote periodontal disease. However, the precise molecular mechanisms underlying inflammatory signaling and their effects on immune responses remain incompletely understood.

Future research should explore novel therapeutic strategies guided by sensitive biomarkers. Despite ongoing advances, CVD morbidity and mortality have continued to rise over the past two decades, highlighting the need for improved understanding of its pathophysiology. Oral microbial dysbiosis contributes to CVD through multiple mechanisms, including biofilm formation, endothelial dysfunction, molecular mimicry, platelet aggregation, direct arterial invasion, and systemic inflammation. These pathways can act synergistically or independently in a highly complex network. A more comprehensive understanding of these interactions may provide innovative approaches to addressing current gaps in CVD management. Insight is needed not only from a mechanistic perspective but also from a clinical standpoint, as this could facilitate the development of targeted therapies. Consequently, additional studies are required to validate the proposed mechanisms, assess the feasibility and effectiveness of interventions targeting oral dysbiosis, and elucidate the full implications of microbial contributions to human cardiovascular physiology and pathology.

Declarations and supplementary information

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