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Interdisciplinary Approaches to Understanding and Managing Oral Microbiome Dysbiosis in Relation to Cardiovascular Disease Pathophysiology and Outcomes

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Abstract

Background: The global prevalence of cardiovascular diseases (CVD) has significantly increased over the past three decades, with a notable rise in morbidity and mortality rates. Recent research highlights a potential link between oral health, specifically oral dysbiosis, and cardiovascular outcomes.

Methods: This review synthesizes current literature on the relationship between the oral microbiome and cardiovascular diseases, focusing on atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF). We analyzed epidemiological studies, clinical trials, and mechanistic research to elucidate the pathways through which oral dysbiosis may influence cardiovascular health.

Results: Evidence suggests that periodontal infections contribute to systemic inflammation and bacteremia, facilitating atherogenesis and exacerbating cardiovascular conditions. Notably, specific oral pathogens have been identified in atherosclerotic plaques, indicating a direct connection between oral dysbiosis and ASCVD. Furthermore, interventions such as periodontal treatment have shown promise in reducing inflammatory markers and improving cardiovascular outcomes.

Conclusion: The interplay between oral health and cardiovascular disease underscores the need for an interdisciplinary approach in managing CVD, integrating dental care into cardiovascular risk assessment and treatment strategies. Future research should aim to establish causal relationships and explore therapeutic interventions targeting oral microbiota to mitigate cardiovascular risks.

Keywords: **Cardiovascular diseases, oral dysbiosis, periodontal infections, atherosclerosis, systemic inflammation.**

1. Introduction

The worldwide incidence of cardiovascular disease (CVD) almost increased from 271 million in 1990 to 523 million in 2019 [1]. Cardiovascular disease (CVD) fatalities rose from 12.1 million in 1990 to 18.6 million in 2019, with significant increases in worldwide trends for disability-adjusted life-years (DALYs) and years of life lost associated with CVD throughout the same timeframe [1]. The incidence of cardiovascular disease (CVD) is projected to rise significantly in the next decades, especially in Northern Africa, Western Asia, and Latin America, where the aging population is anticipated to result in a doubling of those aged over 65 years from 2019 to 2050 [2,3]. Moreover, the incidence of CVD- related events has escalated, especially in low-income and middle-income nations, where roughly 80% of all CVD-related fatalities have transpired since 2013 [4].

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Over the last 10 years, there has been significant expansion in studies into the human microbiome and its possible influence on cardiovascular disease. Dysbiosis, characterized by alterations in the composition, distribution, function, or metabolic activities of the microbiome, has been linked to many cardiovascular disease-related diseases, including atherosclerosis, hypertension, heart failure, and type 2 diabetes mellitus [5]. The intricate and dynamic community of microorganisms, including bacteria, archaea, viruses, and eukaryotic species, in the human microbiota exhibits variability in abundance and variety. Microorganisms have co-evolved with humans, resulting in symbiotic partnerships that are essential for the proper functioning of human physiology. The genetic material of the human microbiome surpasses that of the host by a factor of 100 [6]. The quantity of bacteria is comparable to the entire number of cells in the human body, with their cumulative mass estimated at about 200 grams. The microbiota's variety is dynamic, with species proportions affected by an individual's genetic composition, birth delivery mode, age, nutrition, comorbidities, and medications. Microbiota variation is significant across people at the species level; but, at higher taxonomic levels, such as phyla, the microbiota exhibit similarities. The microbiome plays a crucial role in human metabolic function, offers protection against infections, and is essential for the proper development of the immune system [7].

In the last ten years, alterations in the oral microbiome, or oralome, have been increasingly associated with cardiovascular inflammation and cardiovascular disease (CVD). This correlation is substantiated by an expanding array of evidence from epidemiological studies, systematic reviews, and both basic science and clinical research [8,9]. Consequently, a comprehensive examination of the existing data connecting the oralome to cardiovascular disease and its rising worldwide incidence is crucial [10].

This Review investigates the correlation between oral dysbiosis and atherosclerotic cardiovascular disease (ASCVD), which includes coronary artery disease (CAD), stroke, peripheral arterial disease (PAD), heart failure (HF), infective endocarditis (IE), and rheumatic heart disease (RHD). We elucidate the pathophysiological pathways via which oral dysbiosis induces cardiovascular disease and examine options for prevention and therapy.

1. Periodontitis and bacteremia

Periodontal infections are a significant source of oral and systemic inflammation, induced by bacterial biofilm (dental plaque) on teeth and gums. In gingivitis, the illness is confined to the gingiva and may be reversed via proper dental care [11,12]. In periodontitis, inflammation penetrates more profoundly into the tissues, impacting the attachment mechanism of the teeth. Periodontitis serves as a reservoir for various bacteria that enter the bloodstream via ulceration of inflamed crevices and pocket epithelium into the surrounding gingival microcirculation. Invasive dental treatments and routine activities, such as mastication and teeth brushing, facilitate the introduction of microorganisms into the circulation. Microorganisms or their byproducts in the bloodstream may exacerbate local vascular inflammation, leading to a procoagulant condition [13].

Bacteraemia arising from the oral cavity is induced by a diverse array of bacteria, particularly Gram-negative anaerobes and viridans group streptococci (VGS). In individuals with chronic periodontitis, the extent of bacteraemia is strongly correlated with the degree of gingival inflammation [14,15]. Smoking elevates the frequency and extent of periodontal infections, hence enhancing an individual's vulnerability to bacterial proliferation. Smokers with chronic periodontitis have increased loss of the tooth attachment apparatus and bone, heightened furcation involvement, and deeper pockets, indicating that smoking might aggravate periodontal bacteraemia [16].

2. The oral microbiota in cardiovascular disease

Atherosclerosis denotes the abnormal development of fibrofatty defects in the arterial intima, and its sequelae—coronary artery disease, acute myocardial infarction, stroke, and peripheral artery disease—constitute a primary cause of morbidity and death globally [17,18]. In 2019, there were 9.14 million deaths from coronary artery disease globally, resulting in 182 million disability-adjusted life years (DALYs). In that year, there were 6.55 million fatalities, and 143 million Disability-Adjusted Life Years (DALYs) attributed to stroke [19-23].

Chronic inflammation is exacerbated over time through a complex interplay of genetic predisposition and environmental factors, including tobacco use, physical inactivity, obesity, and poor diet, leading to cholesterol accumulation in the intima of arterial walls, accompanied by macrophage infiltration [24-27]. An ongoing and harmful immune response is initiated and perpetuated, causing increased smooth muscle cell proliferation, growth of connective tissue elements, and oxidation of LDL, which leads to plaque split, thrombus formation, and subsequent blockage of downstream blood vessels, resulting in tissue ischemia and necrosis [28,29] (Figure 1).

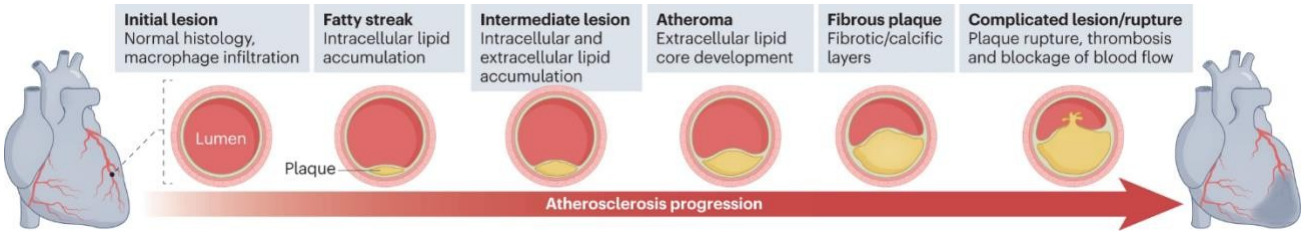

Figure 1. Advancement and evolution of atherosclerotic heart disease.

Epidemiological as well as mechanistic data connects periodontitis with atherosclerosis as well as thromboembolic events [30]. In 1993, individuals with periodontitis were shown to have a 25% elevated likelihood of atherosclerotic plaque development [31]. A reliable, affirmative association has been shown between many indicators of periodontal illness and the onset of incident ASCVD [32]. An examination of 10,362 healthy people from the Atherosclerosis Risk in Communities (ARIC) project, monitored over a 15-year period, revealed a substantial association between periodontal disease and stroke incidence. Consistent dental care was protective, correlating with a decreased risk of stroke (HR 0.77) [33]. In a separate analysis of the ARIC trial cohort, tooth loss due to periodontal disease was linked to a 30% heightened likelihood of venous thromboembolic events. A meta-analysis of prospective cohort research indicated that periodontal disease and tooth loss elevate the risk of coronary artery disease by 24% and 34%, respectively. Since the late 1980s, periodontal disease has been linked to a heightened risk of acute myocardial infarction. Periodontitis is correlated with peripheral artery disease (PAD), resulting in a fivefold increase in risk for those diagnosed with concomitant periodontitis [34]. The risk of peripheral artery disease (PAD) is greatest in those with increased blood concentrations of interleukin-6 (IL-6) and tumor necrosis factor (TNF) [35,36]. Short research (n = 30) conducted in Mexico found that severe periodontal disease correlated with a sixfold elevation in the incidence of peripheral artery disease (PAD), and tooth loss was much greater in patients with PAD compared to control subjects [37]. Periodontitis has been linked to elevated circulating fibrinogen levels, indicating a heightened risk of thrombosis, and to disrupted lipid metabolism leading to hyperlipidaemia, another significant risk factor for ASCVD [38-40].

Research from in vitro, animal, and human research indicates that some oral infections have a role in atherosclerotic thromboembolism by influencing platelet aggregation. *Streptococcus sanguinis* produces platelet aggregation-associated protein (PAAP) , whereas serotype k of *Streptococcus mutans* synthesizes collagen-binding adhesins and may persist in the bloodstream for extended durations [41-44]. Porphyromonas gingivalis not only expedites atheroma plaque development but also provokes fatty streaks in the aorta of rabbits, whereas apolipoprotein E-deficient animals subjected to intraoral challenge with S. Sanguinis have a significant elevation in pro-inflammatory cytokine expression and the production of atherosclerotic plaques [45]. Researchers discovered 23 distinct oral commensal bacteria in the atherosclerotic plaques of patients having interventional procedures, based on data from 63 trials involving 1,791 patients. Among the 23 bacteria, five (*Porphyromonas endodontalis*, *P. gingivalis*, *Campylobacter rectus*, *Prevotella nigrescens,* and *Prevotella intermedia*) were exclusive to coronary artery plaques, whereas the other 18 were found in non-cardiac organs and linked to over 30 non-cardiac conditions [46,47]. The researchers discovered 36 secretory proteins from these microorganisms that are linked to bacterial pathogenesis, enhanced virulence, and the control and modulation of host immunity, potentially contributing to the development of ASCVD [48].

Multiple different pathways have been suggested regarding the function of oral dysbiosis in the progression of ASCVD. A mechanism includes bacteraemia from pathogenic oral microbiota originating from periodontitis foci, which infiltrates the artery wall and facilitates plaque development. Oral inflammatory lesions produce pro-inflammatory cytokines into the circulation, facilitating plaque development via the amplification of inflammatory cascades (Figure 2) [49-52]. Furthermore, autoimmunity, induced by the host's humoral immune response that targets self-proteins resembling oral pathogenic antigens, facilitates plaque development. Additionally, oral pathogenic bacteria secrete particular bacterial toxins that have pro-atherogenic actions. Patients with chronic or severe periodontitis have raised blood levels of LDL and triglycerides, and decreased serum levels of HDL, both of which correlate with an increased risk of ASCVD [53-55].

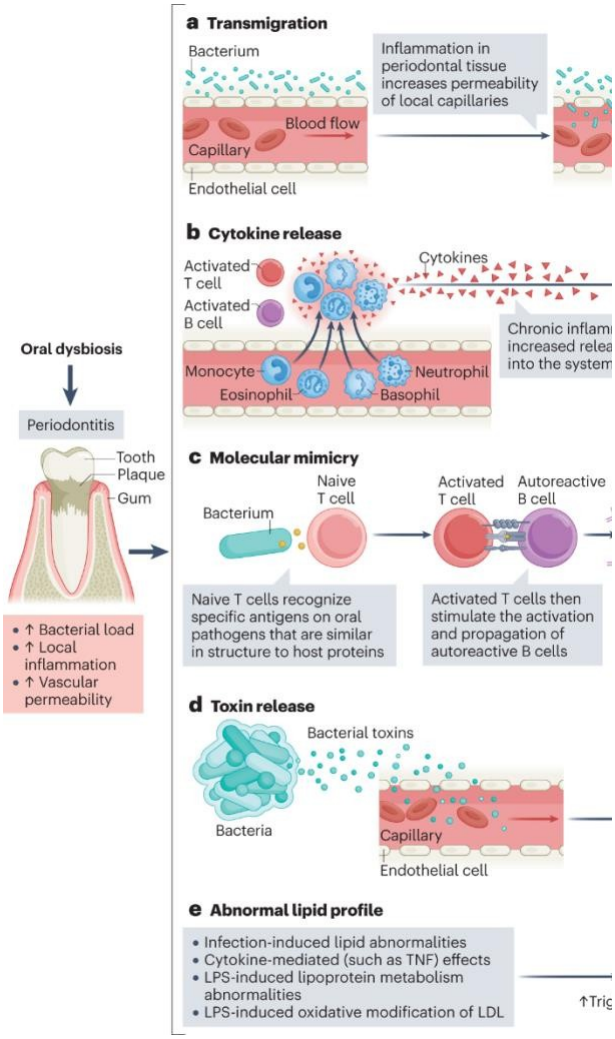

Figure 2. Oral dysbiosis in the etiology of atherosclerotic cardiovascular disease.

Lipid abnormalities associated with persistent low-level inflammation in periodontitis result from associations between bacterial lipopolysaccharides and serum lipoproteins via multiple mechanisms [56]. Infection causes sustained elevations in triglycerides, cholesterol, and phospholipids within VLDL due to simultaneous decreases in lipoprotein lipase and hepatic lipase activity. The persistent secretion of systemic pro-inflammatory cytokines, including TNF, enhances the expression of adhesion molecules on endothelial cells, facilitates the recruitment and activation of inflammatory cells, and directly disrupts the metabolic pathways of triglycerides and cholesterol, thus contributing to the progression of ASCVD [57]. Furthermore, low-dose lipopolysaccharide exposure, characteristic of subclinical endotoxaemia associated with persistent, low-grade periodontal infection, directly stimulates pro-atherogenic lipoprotein profiles by enhancing hepatic synthesis of triglycerides, cholesterol, and finally, VLDL. Lipopolysaccharide influences many HDL-associated apolipoproteins, plasma transfer proteins, and receptors, leading to reduced plasma levels of HDL. Ultimately, lipopolysaccharide promotes the absorption of oxidized LDL via scavenger receptors, facilitating the maturation of lipid-rich macrophages that intensify local inflammation and atheromatous plaque growth [58].

Heart failure (HF) is a clinical disease characterized by exercise intolerance due to left ventricular (LV) malfunction, leading to an excess of fluid and compensatory stimulation of neurohormonal systems. In patients with heart failure, persistently high levels of pro-inflammatory cytokines, including TNF, IL-6, IL-1 receptor-like 1 (ILRL1; also referred to as protein ST2), galectin 3, and C-reactive protein (CRP), signify chronic immune activation and both cardiac and systemic inflammation, serving as indicators of a poor prognosis. Chronic, low-grade inflammation in heart failure is associated with immunological dysregulation (affecting both innate and adaptive immune systems), resulting in maladaptive alterations, such as cardiac fibroblast activation that exacerbates cardiac fibrosis and deteriorates heart failure [59,60].

Oral bacteria may transit via saliva from the oral cavity to the gastrointestinal tract. Certain microorganisms are eradicated by stomach acid, whereas others, like *P. gingivalis,* exhibit acid resistance and therefore provoke local disruptions in gut microbial populations, leading to gut dysbiosis. In patients with heart failure, gut dysbiosis caused by oral bacteria has been associated with heightened gut permeability and the translocation of intestinal bacteria, both of which are catalysts for chronic inflammation [61]. As a result, endotoxins are released from gut bacteria into the bloodstream via compromised membranes, and directly from bacteria that have translocated into the circulation. This condition results in metabolic endotoxaemia, which facilitates cardiovascular disease, left ventricular dysfunction, and heart failure [62]. Microbial dysbiosis may result in inflammation-induced obesity, type 2 diabetes, atherosclerosis, and exacerbation of heart failure. Bacterial translocation significantly exacerbates heart failure due to a detrimental cycle of compromised left ventricular function, which causes intestinal edema and damage to the intestinal microcirculation, culminating in epithelial ischemia and barrier defects in the gut, thereby contributing to progressive cardiac dysfunction [63,64].

Lipopolysaccharide is a cell wall component of Gram-negative bacteria, and blood levels of lipopolysaccharide are elevated in patients with HF73. The breakdown of lipopolysaccharide in heart failure is elevated during congestion and decreased after diuretic administration [65]. In patients with heart failure, lipopolysaccharide triggers dysregulated systemic inflammation through various inflammatory pathways, such as Toll-like receptor 4 (TLR4)-mediated macrophage activation, increased production of pro-inflammatory cytokines, heightened nuclear factor-κB (NF-κB)-dependent inflammation, and activation of the ubiquitin–proteasome pathway. Patients experiencing the most severe congestion and edema in heart failure have elevated blood levels of LPS, TNF, and soluble TNF receptor 1 [66-68].

3. Pathways of cardiovascular disease resulting from oral dysbiosis

Whole-metagenome information about the oral microbiome of healthy persons has been compared with that of patients suffering from periodontitis and exhibiting a prevalence of dental biofilms. The results indicate that the pathological microbiome is enriched in metabolic processes associated with parasitism, marked by the presence of nutrients obtained from the breakdown of host tissues. These processes include fatty acid metabolism and acetyl coenzyme A degradation, aromatic amino acid breakdown, and the formation of hazardous metabolites, including the lipid A molecule of lipopolysaccharide [69]. The oral microbiome is connected with cardiovascular disease via dental biofilm, which consists of a dynamic microbial population linked to chronic, low-grade immune activation and systemic inflammation, frequently exhibiting acquired resistance to environmental stressors, including antibiotics. Biofilm microbial communities emerge from dysbiotic alterations in the oral microbiome, marked by significant proliferation of pathogenic bacterial strains on the biofilm surface, which contribute to the onset of periodontitis [70,71].

Biofilms endure via many processes that enable the microbial population to undermine the human immune response. The keystone periodontal pathogen, *P. gingivalis*, inhibits polymorphonuclear leukocytes by the release of lipopolysaccharide, which attaches to adhesion molecules including IL-8, intercellular adhesion molecule 1, and E-selectin, therefore obstructing leukocyte recruitment. Moreover, activated complement receptor type 3 engages with *P. gingivalis* fimbriae and prompts the downregulation of IL-12p70, a cytokine essential for intracellular bacterial clearance [72]. Biofilms have immunomodulatory effects in chronic periodontal disease via the synthesis of the signaling molecule autoinducer 2, which modifies the transcription of immune mediators in epithelial cells. Numerous oral infections linked to dental biofilms, such as *P. gingivalis*, produce autoinducer 2, which stimulates the release of IL-8 in oral epithelial cells [73].

Bacterial persistence, coupled with a regulated human immune response, creates a pathogenic loop whereby dysbiosis and inflammation exacerbate one another. Consequently, biofilms function as resilient structures from which harmful bacteria may provoke systemic illness. The protease gingipain R, released by *P. gingivalis*, promotes cardiovascular disease by stimulating factor X, prothrombin, and protein C, hence boosting thrombotic propensity and intravascular clot formation [74-76]. Moreover, pro-inflammatory cytokines generated by activated macrophages or T cells in periodontal lesions might

exacerbate inflammatory cascades, promoting atherosclerotic alterations in remote locations [77].

The oral microbiota negatively impacts the vasculature via the migration and inoculation of bacteria. Periodontitis leads to a substantial bacterial accumulation in the gingival sulcus, provoking chronic local inflammation and boosting the permeability of adjacent blood vessels [78]. Bacterial invasion of endothelial cells may result in endothelial dysfunction, a critical factor in the progression of atherosclerosis as well as vascular impairment. Endothelial dysfunction correlates with heightened pro-coagulant characteristics, mononuclear cell adhesion, elevated expression of cell adhesion molecules, and higher levels of pro-inflammatory cytokines and chemokines (including IL-6, IL-8, and MCP1), all of which are stimulated by *P. gingivalis* [79].

The oral microbiome contributes to cardiovascular disease (CVD) by generating metabolites, such as lipopolysaccharides from bacteria, which operate as immunostimulators or immunomodulators that enter the bloodstream from the mouth cavity, resulting in endotoxaemia and endothelial dysfunction. Individuals with periodontitis have ongoing endotoxaemia, resulting in chronic, low-grade inflammation that fosters oxidative stress, hence accelerating atherogenesis, heightening vascular inflammation and permeability, and increasing the risk of thrombosis [80-82]. Endothelial dysfunction furthermore plays a role in the onset of hypertension.

The enterosalivary nitrate–nitrite–nitric oxide pathway, including nitrogen-reducing oral bacteria, is essential for maintaining nitric oxide homeostasis in a healthy oral microbiome. Furthermore, clinical data indicate that a high prevalence of oral nitrate-producing bacteria correlates with diminished cardiometabolic risk, evidenced by reduced insulin resistance and plasma glucose levels, as well as a relationship with mean systolic blood pressure in normotensive individuals [83]. Consequently, imbalances in oral nitrogen-reducing bacteria, within the framework of dental dysbiosis induced by periodontitis, have been linked to diminished nitric oxide levels, hence fostering endothelial dysfunction and elevating cardiovascular disease risk. Additional clinical data indicate that intensive periodontal treatment correlates with enhanced endothelial function after 6 months, as demonstrated by increased flow-mediated dilation of the brachial artery and a reduction in biomarkers of inflammation, coagulation, and endothelial activation [84].

Although a dysbiotic oral microbiome has detrimental consequences, its total eradication is not preferable, since a eubiotic oral microbiota has health advantages. The following sections will address ways for generating and sustaining a eubiotic condition in the oral cavity, as well as examine both validated and speculative methods to mitigate cardiovascular disease stemming from oral infections. While faecal microbiota transplantation and bariatric surgery have been shown to influence gut dysbiosis, the data about their impact on mouth dysbiosis is scarce and requires additional investigation. Recent results from the last two years indicate that bariatric surgery may modify the oral and salivary microbiota [85]. There is a scarcity of randomized clinical studies addressing appropriate treatment methods for the oralome.

The bacterial load in tooth plaque is correlated with the severity of periodontal disease. Oral hygiene is crucial for managing the microbial burden on the teeth and inside the oral cavity, aiding in the prevention of periodontitis and consequent bacteraemia. Established oral hygiene practices include brushing teeth using fluoride toothpaste to eliminate dental plaque and utilizing chemical antiplaque mouth rinses, which diminish gingival irritation and dental plaque indices [86]. While oral hygiene may only transiently disturb the acidogenic biofilm, consistent practice may maintain dental plaque in an immature condition and in minimal quantities, so substantially reducing the risk of bacteraemia. Fluoride use enhances enamel remineralization. In contrast, clinical evidence suggests that the use of over-the-counter mouthwash, often believed to diminish the prevalence of nitrate-producing bacteria in the oral microbiome, correlates with an elevated risk of hypertension, regardless of significant risk factors and other confounding variables. Small research involving 19 healthy volunteers shown that antiseptic mouthwash decreased oral nitrite generation by as much as 90%, which was associated with a 2.0–3.5 mmHg elevation in systolic blood pressure within one day after application [87]. The ambiguity around whether the hazards of mouthwash use surpass the benefits has prompted some academics to propose that restricting its use to prescription-only might be a prudent solution. Additional clinical research on the hazards and

advantages of mouthwash usage in individuals with periodontitis and cardiovascular disease is essential [88].

Intensive periodontal therapy has shown a reduction in glycated hemoglobin (HbA1c) levels in individuals with type 2 diabetes. HbA1c serves as a dependable indicator for all-cause and cardiovascular mortality, indicating that regular dental health evaluations and treatment of periodontitis are crucial for the proper management of cardiovascular disease. Given the beneficial impacts of periodontal therapy on systemic illness, there is a need for enhanced cooperation between dentists and cardiologists to clarify these pathways and improve therapies for at-risk individuals [89].

4. Conclusions

The persistent increase in cardiovascular disease morbidity and death over the last twenty years, despite continuous research efforts, signifies the need for novel strategies to comprehend cardiovascular disease biology for the development of effective therapeutics. Dysbiosis of the oral microbiome leads to cardiovascular disease via biofilm development, dysfunction of endothelial cells, molecular imitation, platelet aggregation, direct artery invasion, and systemic inflammation. These systems function either synergistically or separately in a complicated way; yet a progressive clarification of these connections may provide significant insights to address the ongoing gaps in our comprehension of cardiovascular disease (CVD) overall. A comprehensive knowledge is required not just from a mechanistic standpoint but also from a medical one, where the opportunity to develop innovative therapeutics targeting these systems exists. Consequently, additional research is necessary to ascertain the biological reliability of the proposed pathophysiological mechanisms outlined in this Review, to evaluate the efficacy and practicality of addressing oral dysbiosis in the avoidance and treatment of cardiovascular disease, and to clarify the intricacies of the connection among human physiology alongside the oral microbiome.

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