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The Periodontal-Cardiovascular Axis: Molecular Mechanisms, Clinical Evidence, and Therapeutic Perspectives

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ABSTRACT

Periodontitis, a chronic inflammatory disease of the supporting tooth structures, affects nearly 10-12% of the global population and represents a significant public health concern. Beyond localized oral pathology, periodontitis is strongly associated with cardiovascular diseases-including atherosclerosis, coronary artery disease, stroke, and heart failure-through converging mechanisms of chronic inflammation, immune dysregulation, microbial translocation, and epigenetic modifications. Key molecular mediators include NLRP3 inflammasome activation, oxidative stress, asymmetric dimethylarginine-driven endothelial dysfunction, and vascular smooth muscle cell phenotypic modulation. Clinical studies demonstrate that individuals with periodontitis exhibit elevated systemic inflammatory biomarkers, impaired endothelial function, and increased risk of cardiovascular events. Importantly, periodontal therapy-ranging from behavioral interventions to subgingival instrumentation-reduces systemic inflammation and cardiovascular risk, particularly in high-risk populations such as patients with metabolic disorders or on hemodialysis. This mini-review synthesizes current evidence connecting periodontitis and cardiovascular disease, integrates molecular and clinical insights, and highlights the potential for interdisciplinary preventive and therapeutic strategies.

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Periodontitis is a chronic inflammatory condition initiated by a dysbiosis of the Biofilm wich affect root surfaces of the periodnatl teeth. It is characterized by inflammation and destruction of the supporting tooth structures, which can lead to tooth loss, with a lot of different patterns [1]. It is a multifactorial chronic disease and represents the 6th most prevalent condition in the world, affecting about 10-12 percent of the population [2,3]. Almost half of American adults aged ≥30 ys. are affected by periodontitis and in 2010 about 743 millions of people was affected from Periodontal disease all around the world [1].

Periodontitis is not merely a localized oral condition but is strongly associated with systemic diseases such as cardiovascular disease, diabetes mellitus, respiratory disorders, thyroid dysfunction, and obstructive sleep apnea. These associations are primarily mediated through shared pathophysiological and immunological mechanisms, including chronic inflammation, immune dysregulation, and microbial translocation [5].

Cardiovascular diseases are a group of disorders affecting not only the the heart but also blood vessels, leading to coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other related conditions. Cardiovascular disease is a broad category that includes different pathologies such as ischemic heart disease, stroke, hypertension, rheumatic heart disease, cardiomyopathies, atrial fibrillation, atherosclerosis, coronary heart disease, cerebrovascular disease, and peripheral vascular disease [4,6,7]. The risk of cardiovascular disease is increased by socioenvironmental, metabolic, and behavioral risk factors such as smoking, hypercholesterolemia, hypertension, diabetes, a sedentary lifestyle, abdominal obesity, and psychosocial disorders [4].

Cardiovascular disease is responsible for 17.9 million deaths globally annually, accounting for a third of total mortality, and 3.9 million deaths in Europe [4]. In 2020, the WHO estimated that cardiovascular disease was responsible for almost 18 million deaths worldwide [4].

There is limited but consistent evidence that individuals with periodontitis have a higher prevalence and incidence of peripheral artery disease [4]. Patients with periodontitis exhibit significant endothelial dysfunction, increased arterial stiffness, greater carotid intima media thickness, and elevated calcification scores. An association has also been reported between periodontitis and heart failure. Furthermore, a positive association exists between periodontitis and cerebrovascular disease [4]. Scientific literature suggests that one of the worse side effects of the presence of periodontal pathogens in the blood vessels comes from the fact that all this negative condition lead to a gradual and complete hardening of the musculature surrounding arterial blood vessels.

At molecular level, three principal converging pathways mediate the periodontal cardiovascular axis, namely NLRP3 inflammasome activation, oxidative stress, and asymmetric dimethylarginine mediated endothelial dysfunction. NLRP3 activation requires dual signaling through Toll like receptor 4 mediated nuclear factor kappa B transcriptional priming and secondary stimuli including cholesterol crystals, reactive oxygen species, and extracellular adenosine triphosphate, culminating in caspase 1 activation and maturation of interleukin 1 beta and interleukin 18 [4]. Oxidative stress is driven predominantly by NOX2 mediated superoxide generation, leading to hydrogen peroxide, hypochlorous acid, and peroxynitrite formation. Peroxynitrite concentrations increase from physiological levels <0.1 μM to pathological ranges of 0.5 to 1.0 μM, resulting in endothelial nitric oxide synthase uncoupling and reduced nitric oxide bioavailability >85% to pathological reduction. Biomarker profiling demonstrates decreased vitamin C levels from normal 45 to 80 μM, reduced superoxide dismutase activity from 785 to 1570 U per g Hb, elevated C reactive protein >5 mg per L compared to <3 mg per L, increased vascular cell adhesion molecule 1 from 400 to 800 ng per mL to pathological elevation, and impaired flow mediated dilation <7% compared to >10% in healthy individuals. In parallel, asymmetric dimethylarginine levels exceed 0.8 μM compared to physiological 0.4 to 0.6 μM, competitively inhibiting endothelial nitric oxide synthase and perpetuating endothelial dysfunction [4].

Epigenetic reprogramming and vascular smooth muscle cell phenotypic modulation further consolidate the mechanistic bridge between periodontitis and cardiovascular pathology. Upregulation of DNA methyltransferase 1, increased H3K4me3 promoter enrichment, and elevated microRNA 146a expression contribute to sustained inflammatory gene transcription, while Nrf2 target genes including heme oxygenase 1 and NAD P H quinone oxidoreductase 1 are downregulated under chronic oxidative stress conditions. Quantitative evidence indicates 5 fold higher cell free DNA levels in saliva at 582 ± 1023 ng per mL versus 100 ± 259 ng per mL with $p < 0.001$, detection of citrullinated histone H3 in 60% of periodontal tissues, and adjusted hazard ratios of 1.26 for future cardiovascular events in periodontitis patients. Collectively, these data delineate an integrated molecular network in which polymicrobial dysbiosis, inflammasome activation, oxidative injury, nitric oxide pathway disruption, and epigenetic modifications converge to promote endothelial dysfunction, vascular remodeling, atherosclerosis, hypertension, thrombosis, and heart failure, thereby establishing periodontal disease as a significant modifiable contributor within the cardiovascular disease continuum [4].

Study by Qi J et al. reported that higher orange-blue and yellow-orange cluster scores were associated with reduced all-cause mortality, and the orange-blue cluster was also inversely associated with cardiovascular disease mortality. The orange-blue cluster demonstrated a consistent protective association with both all cause and cardiovascular disease mortality. This cluster comprises antibodies against Eubacterium nodatum and Actinomyces naeslundii. Actinomyces naeslundii is commonly associated with periodontal health, and higher antibody titers to Eubacterium nodatum have been reported in individuals without periodontitis. The yellow-orange cluster includes Campylobacter ochracea, another species linked to periodontal health. These findings suggest that antibodies within the orange-blue and yellow-orange clusters may reflect a health associated oral microbiome profile and could confer protection against periodontal disease, thereby reducing systemic inflammatory burden and mortality risk [1].

In contrast, the red-green cluster includes antibodies to established periodontal pathogens such as Treponema denticola and Tannerella forsythia, members of the red complex strongly implicated in periodontitis. Elevated antibody levels in this cluster likely reflect chronic periodontal infection and systemic inflammatory activation, which may explain the observed positive association with mortality [1].

Periodontal therapy is a standard treatment aimed at disrupting the biofilm to control inflammation in periodontal disease. According to the European Federation of Periodontology, which developed an S3 level guideline using a stepwise approach, the first step consists of behavioral change by motivating the patient to remove biofilm and control risk factors. The second step includes subgingival instrumentation, including subgingival scaling and root surface debridement, with the aim of eliminating calculus and biofilm, with adjunctive therapy if needed. The third step consists of repeated subgingival instrumentation if required or the necessity to proceed with surgical procedures [6,9].

A systematic review by Meng et al reported that non-surgical periodontal therapy decreased CRP, IL 6, and SBP in patients with periodontitis, while there was no difference in outcomes including IL 1β, TNF α, LDL, HDL, TC, TG, DBP, and FMD. Subgroup analyses showed that the effect of non-surgical periodontal therapy on cardiovascular disease risk markers differed according to systemic health status and antiseptic or antibiotics use, with greater benefit observed in patients with periodontitis, cardiovascular disease, or metabolic disorders, and enhanced effects when antiseptics or antibiotics were used adjunctively [6].

Huang et al. demonstrated that hemodialysis patients receiving periodontal therapy exhibited a significant reduction in both all-cause mortality and cardiovascular events compared with untreated patients. Periodontal treatment was associated with a significantly lower overall cardiovascular disease risk than that of the untreated group, and a reduction in all cardiovascular diseases remained evident after competing risk model analysis. The periodontal treatment cohort showed lower risks of developing acute coronary syndrome, acute myocardial infarction, stroke including ischemic stroke and hemorrhagic stroke, congestive heart failure, and sudden cardiac death than the untreated group, both before and after propensity score matching [10]. Furthermore, periodontal treatment was associated with a significantly lower overall mortality risk compared with no treatment, both before and after propensity matching, with aHR = 0.50, 95% CI = 0.47-0.54, $p < 0.001$ before matching and aHR = 0.49, 95% CI = 0.45-

0.54, $p < 0.001$ after propensity matching, suggesting a potential preventive role of periodontal therapy in cardiovascular disease among hemodialysis patients [10].

In addition, a systematic review by Millan et al including ten articles reported that periodontal treatment reduced C reactive protein levels in 77.8% of clinical trials, tumor necrosis factor alpha in 66.7%, interleukin 6 in 100%, and leukocytes in 50%, with fibrinogen levels improving in 66.7%. Effects on lipid parameters were limited, with significant decreases observed only in oxidized low density lipoprotein and very low density lipoprotein cholesterol. Meta analysis showed a statistically significant decrease in C reactive protein and leukocyte values in patients undergoing non surgical periodontal treatment compared with no treatment at all 1.100-1.299, $p < 0.001$ and mean difference 0.79 g per L, 95% confidence interval 0.717-0.879, $p < 0.001$, respectively [11].

Collaboration between cardiologists and periodontists is crucial for developing integrated treatment strategies, particularly since many patients remain unaware of the association between periodontitis and cardiovascular disease [5]. Clinicians should prioritize patient education, emphasizing the connection between oral and cardiovascular health and advocating for both preventive dental care and cardiovascular risk management [5]. Early identification of periodontitis in at-risk individuals may facilitate timely intervention and help prevent systemic complications.

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