Association between periodontitis and heart failure: Mechanisms and clinical implications (Review)

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Abstract. Periodontitis, a common oral disease, is increasingly recognized for its potential impact on systemic health, particularly its association with heart failure (HF). HF is a complex clinical syndrome with a multifactorial pathogenesis. Emerging evidence suggests that periodontitis may influence the cardiovascular system and contribute to the onset and progression of HF through mechanisms such as systemic inflammation, microbial shifts, and immune dysregulation. However, current research still faces limitations in establishing causality and elucidating the precise underlying mechanisms. Furthermore, clinical intervention strategies require further investigation. Relevant literature was identified from PubMed, Web of Science, and Scopus using keywords related to periodontitis and heart failure, and screened for relevance to epidemiological evidence, mechanistic insights, and clinical implications. The present review aimed to summarize the mechanisms linking periodontitis and HF, analyze their shared pathophysiological basis, and discuss the potential role of periodontal treatment in improving outcomes for patients with HF. Clinically, periodontal assessment may be considered in patients with heart failure as part of multidisciplinary care, but current evidence remains insufficient to support definitive recommendations that such evaluation or treatment improves HF outcomes.

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1. Introduction

Heart failure (HF) poses a significant global health burden, marked by progressive deterioration of cardiac function that results in considerable morbidity, mortality, and impaired quality of life for millions of individuals worldwide (1,2). As a complex clinical syndrome, HF represents the common end-stage manifestation of various cardiovascular diseases, underpinned by a range of etiological factors such as ischemic heart disease, hypertension, and diabetes mellitus (3). Beyond these established risk factors, accumulating evidence highlights the role of chronic inflammatory conditions as important, although often overlooked, contributors to the pathogenesis and progression of HF (4-6).

Among these conditions, periodontitis, a highly prevalent chronic inflammatory disease of the supporting structures of the teeth, driven by dysbiotic microbial communities and a dysregulated host inflammatory response, has emerged as a potentially modifiable risk factor for systemic diseases, including cardiovascular disorders (7). Once considered a localized oral infection, periodontitis is now increasingly recognized for its systemic implications. The persistent, low-grade inflammation and transient bacteremia associated with periodontal disease are considered to initiate or amplify pathological processes in distant organs (8,9).

Recent epidemiological evidence has suggested an association between periodontitis and HF. Notably, this evidence comes from several types of human studies, including population-based cross-sectional analyses, prospective cohort studies and serological or biomarker-based investigations. Collectively, these studies indicate that more severe periodontitis is associated with a higher prevalence of HF, an increased risk of incident HF and less favorable clinical profiles among patients with established HF (10-12). However, these observational findings primarily support an association rather than a confirmed causal relationship, and the possibility of residual confounding by shared risk factors, such as age, smoking, diabetes and socioeconomic status, should be acknowledged.

These observations suggest the existence of an 'oral-cardiac axis', mediated by multifactorial and interconnected biological pathways. Among them, systemic inflammatory spillover from

periodontal lesions is supported by both human and experimental evidence. By contrast, other mechanisms, including direct bacterial translocation to cardiac tissues, autoimmune responses triggered by molecular mimicry and maladaptive trained immunity and oral-gut axis disruption, are supported mainly by animal studies, *in vitro* experiments, or indirect human observations; therefore, these findings should be interpreted as putative rather than definitively established mechanisms (13-15).

Despite the growing body of evidence, a definitive causal link between periodontitis and HF remains to be established. The present review, aimed to underscore the importance of incorporating oral health into comprehensive cardiovascular risk assessment and management, which may ultimately inform novel preventive and therapeutic approaches for patients at risk of or living with HF. Specifically, first the epidemiological studies evaluating the association between periodontitis and HF were reviewed, then the multifactorial pathophysiology underlying the periodontal-cardiac axis was discussed, and finally the potential clinical implications and limitations of periodontal intervention in the context of HF management were considered.

2. Epidemiological association between periodontitis and heart failure

Epidemiological evidence consistently establishes periodontitis, a chronic inflammatory disease of the supporting tissues of the teeth, as a significant factor associated with an elevated risk of HF, potentially mediated by systemic inflammation and shared risk factors such as hypertension and diabetes. Substantial evidence from large-scale cross-sectional and prospective cohort studies supports this association. For instance, data from the US Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that the incidence of HF was 5.72 times higher in individuals with moderate or severe periodontitis compared with those with no or mild periodontitis. This association remained significant after adjusting for traditional cardiovascular risk factors, with a persistently elevated risk of 3.03-fold, and a dose-response relationship was observed whereby greater periodontitis severity was associated with increased HF risk (16). Long-term follow-up studies further corroborate that periodontitis independently predicts future HF events. An analysis of 2,876 individuals with a history of periodontitis revealed a 30-50% increased risk of HF hospitalization (11,17), with a particularly prominent association noted with HF with preserved ejection fraction (HFpEF). Furthermore, elevated serum IgG antibody titers against key periodontal pathogens, such as *Porphyromonas gingivalis*, were shown to be linked to higher HF prevalence, suggesting a dose-response relationship driven by the level of bacterial exposure (18). Among patients with established chronic HF, the burden of periodontitis is substantial, with moderate to severe forms affecting over two-thirds of cases and associated with heightened levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a prognostic biomarker of cardiac stress, particularly in younger subgroups (11). In summary, a substantial body of epidemiological evidence supports a consistent association between periodontitis and HF, with several studies suggesting a dose-response relationship between periodontitis severity and HF risk. However, these findings should be interpreted cautiously because residual confounding and reverse causation cannot be fully excluded. To visually consolidate these key findings, the evidence from the aforementioned major studies is summarized in Table I.

3. Core mechanistic pathways of the 'periodontal-cardiac axis'

The robust epidemiological evidence independently linking periodontitis with HF strongly suggests a complex pathophysiological relationship that extends beyond mere coincidence or shared risk factors. To elucidate the biological underpinnings of this 'oral-cardiac axis', recent research (19) has increasingly focused on how periodontitis, as a localized inflammatory condition, can exert remote effects to systemically impact cardiac structure and function. The current scientific consensus points toward three primary, interconnected pathways as the core of this mechanism: i) Systemic spillover of inflammation; ii) direct dissemination of periodontal microbes and their virulence factors; and iii) immune cross-reactivity mediated by molecular mimicry (Fig. 1). This section will systematically elaborate on these three core mechanistic pathways, providing an in-depth analysis of how periodontitis evolves from a local infection into a significant risk factor for heart failure.

Systemic inflammation as a key driver of cardiac injury. As a chronic infection, the primary remote pathogenic mechanism of periodontitis is the induction and maintenance of a low-grade systemic inflammatory state. When inflammatory mediators and bacterial products from the periodontal lesion 'spill over' into the circulation, they initiate a complex cascade of events that directly and indirectly inflict damage upon the heart. This process is centered on the amplification of inflammatory signals and the dual targeting of both the heart and the immune system, with the detailed cellular and molecular pathways illustrated in Fig. 2.

Systemic spillover of pro-inflammatory mediators. Periodontitis constitutes a significant source of systemic inflammation that contributes to the pathogenesis of HF through well-defined mechanistic pathways. The primary initiating mechanism involves the systemic dissemination of *Porphyromonas gingivalis*-derived lipopolysaccharide (LPS), which engages Toll-like receptor 4 (TLR4) on innate immune cells, thereby activating nuclear factor-κB (NF-κB) signaling and driving the production of key pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (14). These mediators establish a persistent low-grade inflammatory milieu that directly impacts cardiac structure and function through multiple pathways: IL-6 and TNF-α activate downstream signaling cascades such as NF-κB and mitogen-activated protein kinase pathways, promoting cardiomyocyte apoptosis, extracellular matrix remodeling, and ventricular dysfunction (20). Clinical evidence substantiates this relationship, with elevated IL-6 levels demonstrating a strong, independent association with incident HF; each increasing tertile of IL-6 concentration corresponds to a 68% higher 5-year risk (20-23).

Table I. Summary of Key epidemiological evidence on the association between periodontitis and heart failure.

Study/Data source	Study type	Key findings	(Refs.)
National Health and Nutrition Examination Survey (NHANES III)	Cross-sectional study	-The prevalence of heart failure was significantly higher in individuals with periodontitis compared to those without (4.88% vs. 2.90%). -Moderate-to-severe periodontitis was strongly associated with heart failure risk (Adjusted OR=3.03).	(16)
Swedish cohort study	Prospective cohort study	-A history of periodontitis was an independent risk factor for hospitalization due to heart failure, with a 30-50% increased risk. -The association was particularly prominent for heart failure with preserved ejection fraction.	(11,17)
Atherosclerosis Risk in Communities (ARIC) study	Prospective cohort study	-A dose-response relationship was observed between the severity of periodontitis and the risk of incident heart failure. -Edentulism (complete tooth loss) was also significantly associated with heart failure risk.	(11,18)
Cross-sectional and case-control studies	Cross-sectional/case-control	-In patients with chronic heart failure, the severity of periodontitis was positively associated with levels of N-terminal pro-B-type natriuretic peptide, a biomarker of cardiac stress. -The presence of periodontitis in heart failure patients was linked to higher levels of systemic inflammation (for example, C-reactive protein).	(19,20)
Serological studies	Cross-sectional study	-Serum antibody titers against key periodontal pathogens, such as *Porphyromonas gingivalis* were positively associated with the prevalence of heart failure.	(23)

The systemic inflammatory burden in patients with periodontitis is further evidenced by significantly elevated circulating levels of C-reactive protein and IL-1β, which are associated with early degenerative cardiac changes and increased inflammatory mediator turnover in patients with HF (24,25). Additionally, periodontitis-associated cardiac oxidative stress results primarily from enhanced reactive oxygen species generation rather than impaired antioxidant capacity (26). This pro-inflammatory state also promotes endothelial dysfunction through upregulation of adhesion molecules and induces hematopoietic reprogramming toward trained immunity, sustaining leukocyte hyperreactivity and exacerbating microvascular complications that aggravate ventricular dysfunction (8,27,28). Collectively, these mechanisms establish periodontitis as a clinically significant contributor to inflammatory-driven HF progression, highlighting the potential therapeutic value of periodontal interventions in comprehensive cardiovascular risk management.

Myeloid cell activation and trained immunity: Systemic reprogramming of innate immunity. Periodontitis contributes to the pathogenesis of HF through two interconnected immunological mechanisms: Molecular mimicry and sustained innate immune reprogramming. The molecular mimicry hypothesis suggests that structural homology between components of periodontal pathogens, particularly, *Porphyromonas gingivalis*, and host myocardial proteins may induce cross-reactive autoimmunity, leading to mistaken immune targeting of cardiac tissues and subsequent myocardial injury (18,29). Concurrently, periodontitis establishes a state of systemic inflammation and trained innate immunity, a persistent functional reprogramming of myeloid cells that amplifies inflammatory responses and sustains cardiac vulnerability. This process is initiated when bacterial products such as LPSs enter the systemic circulation and prime hematopoietic stem and progenitor cells in the bone marrow via IL-1-mediated signaling. The resulting epigenetic reconfiguration promotes myeloid-biased differentiation, yielding monocytes and neutrophils with heightened responsiveness to subsequent inflammatory stimuli (30). This maladaptive trained immunity is characterized by lasting chromatin modifications at proinflammatory gene loci, which facilitate exaggerated releases of cytokines such as IL-6 and TNF-α upon rechallenge. These responses perpetuate a feed-forward cycle of vascular inflammation that drives cardiac fibrosis, ventricular hypertrophy and contractile dysfunction (15). The durability of this immune reprogramming is evidenced by its transmissibility through bone marrow transplantation, where recipient myeloid cells maintain a

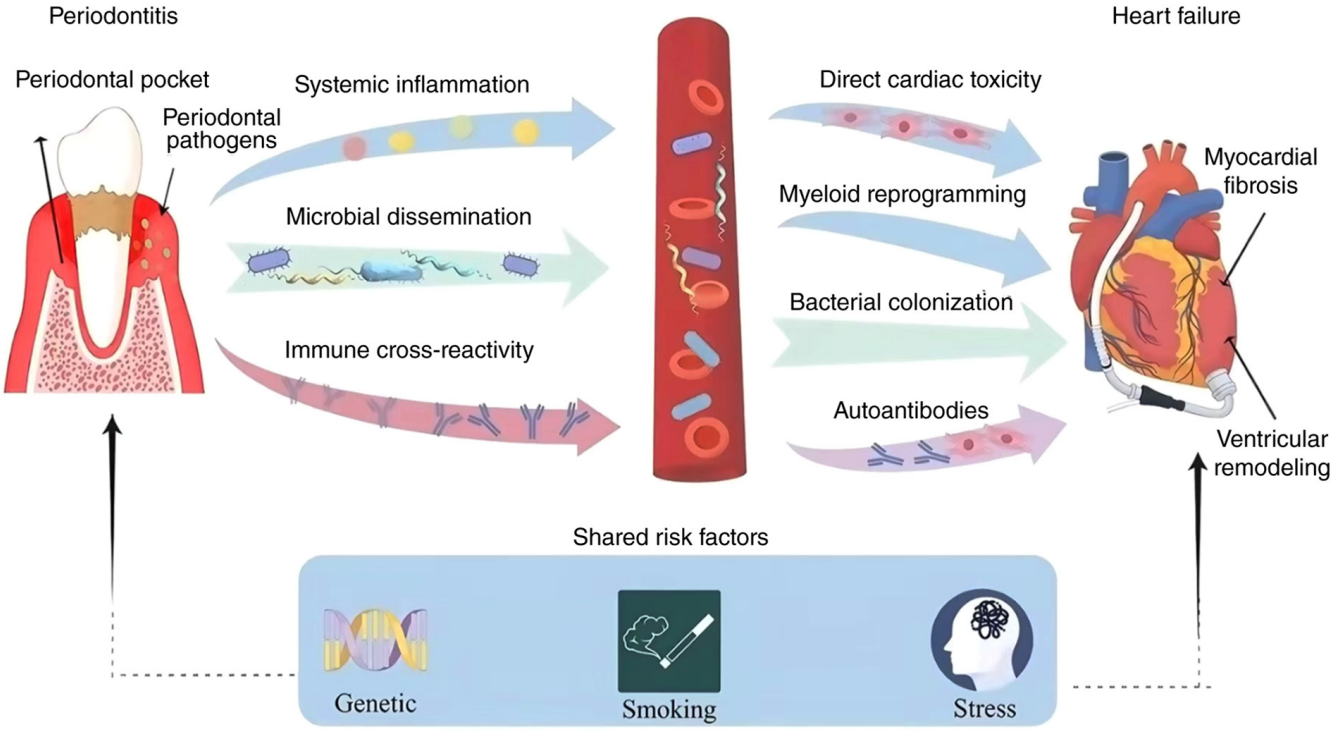

Figure 1. Schematic overview of the core mechanisms linking periodontitis to the pathogenesis of heart failure ('the periodontal-cardiac axis'). Periodontitis, a chronic localized infection, can systemically impact cardiac function and contribute to the development or exacerbation of heart failure through three primary pathways: i) Systemic inflammation: Pathogen-associated molecular patterns, such as lipopolysaccharide released from periodontal pathogens (for example, *Porphyromonas gingivalis*), enter the systemic circulation. This triggers a widespread inflammatory response characterized by elevated levels of pro-inflammatory cytokines (such as IL-6, TNF-α, and IL-1β). These mediators can directly target cardiomyocytes and cardiac fibroblasts, inducing apoptosis and myocardial fibrosis, which leads to adverse ventricular remodeling and cardiac dysfunction. Concurrently, they can act on hematopoietic stem and progenitor cells in the bone marrow, inducing epigenetic reprogramming and a state of 'trained immunity,' which generates hyper-responsive myeloid cells that perpetuate systemic inflammation. ii) Microbial dissemination: Periodontal pathogens can directly invade the bloodstream via transient bacteremia. These bacteria and their virulence factors (such as gingipains) may colonize cardiac tissues or the vasculature, or exert direct cardiotoxic effects, impairing cardiomyocyte function and endothelial integrity. iii) Immune cross-reactivity: Due to molecular mimicry between certain antigens from periodontal pathogens and host cardiac proteins (such as cardiac myosin), antibodies generated against the pathogens may cross-react with self-antigens in the heart, leading to autoimmune-mediated cardiac injury. Furthermore, shared risk factors, such as genetic susceptibility and metabolic syndrome, can predispose individuals to both periodontitis and heart failure, contributing to the complex pathogenic network of the 'periodontal-cardiac axis.'

hyperreactive phenotype associated with accelerated atherosclerosis and ischemic injury, exacerbating HF progression independent of ongoing oral pathogen exposure (28). While some research indicates that periodontitis-induced systemic inflammation may contribute to cardiac injury independently of autoimmunity (31), the collective evidence underscores the synergistic roles of cross-reactive autoimmunity and innate immune reprogramming in periodontitis-related HF pathogenesis.

Targeted cardiac effects of inflammation: Promoting myocardial fibrosis, apoptosis, and ventricular remodeling. Periodontitis significantly exacerbates HF pathophysiology by instigating a systemic inflammatory response that selectively targets cardiac tissues, thereby promoting myocardial fibrosis, cardiomyocyte apoptosis and left ventricular remodeling through the dissemination of pro-inflammatory cytokines and subsequent activation of fibrogenic pathways. In chronic periodontal infection, bacterial toxins translocate into the systemic circulation, inducing a cytokine surge, predominantly IL-1β, IL-6 and TNF-α, that infiltrates the myocardium. This inflammatory milieu upregulates transforming growth factor-β signaling in cardiac fibroblasts, driving excessive extracellular matrix deposition that culminates in interstitial fibrosis and impaired ventricular compliance, thereby predisposing to diastolic dysfunction in HFpEF (14). Furthermore, this pro-inflammatory environment activates intrinsic apoptotic cascades in cardiomyocytes via caspase-3 activation and Bcl-2/Bax dysregulation, mechanisms driven primarily by oxidative stress and mitochondrial dysfunction. Preclinical models demonstrate that periodontitis accelerates myocyte loss and contractile impairment independent of ischemic injury (8). Concomitantly, sustained cytokine exposure orchestrates maladaptive left ventricular remodeling, characterized by eccentric hypertrophy and chamber dilation through matrix metalloproteinase-mediated degradation of structural proteins and enhanced perivascular inflammation. These structural alterations were shown to be associated with HF with reduced ejection fraction (HFrEF) and increased hospitalization risk in clinical cohorts with comorbid periodontitis and HF (32). Collectively, these targeted inflammatory effects establish periodontitis as a modifiable amplifier of cardiac structural pathology, underscoring the need for clinical trials to evaluate whether periodontal interventions can attenuate fibrosis-mediated HF progression.

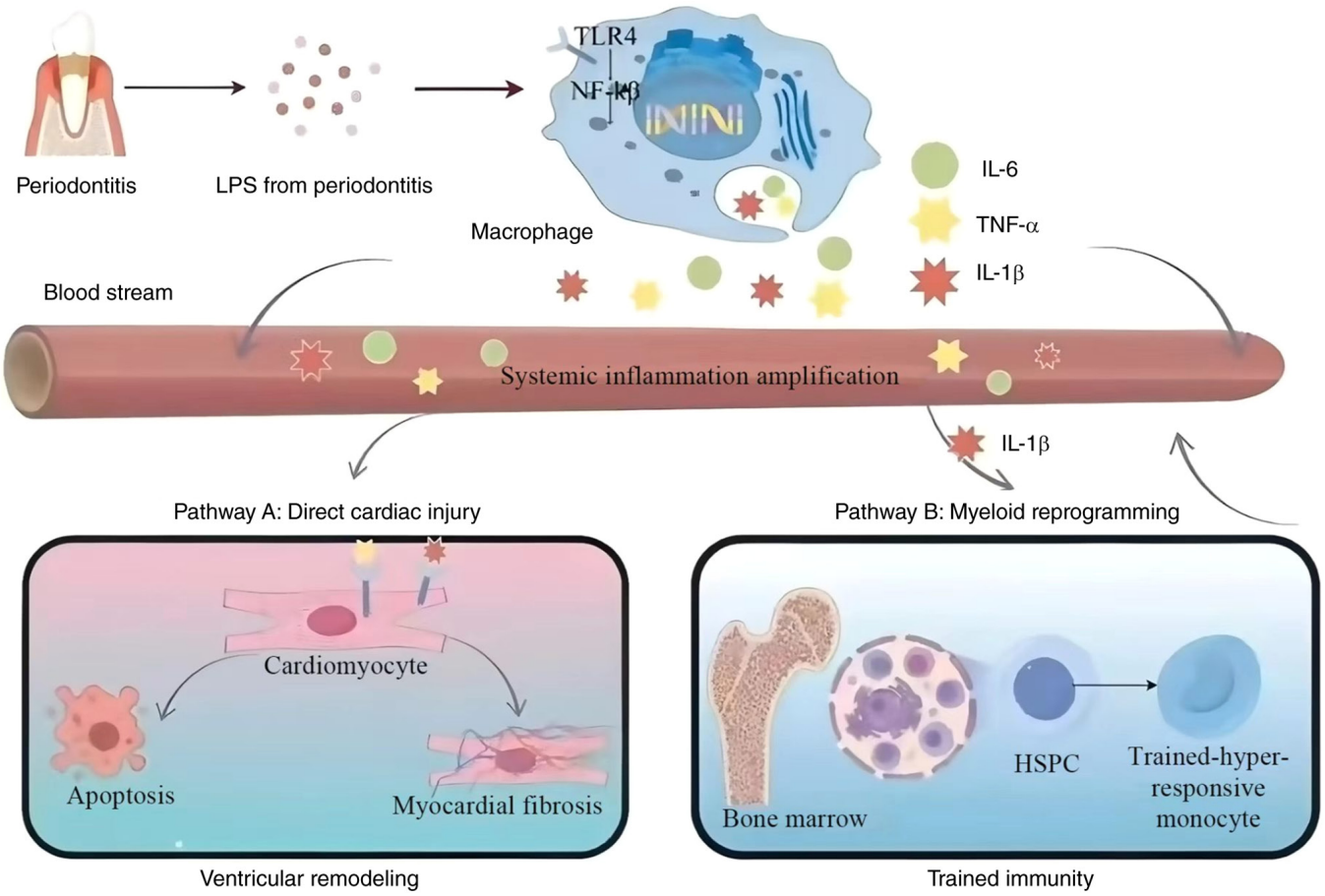

Figure 2. Cellular and molecular pathways of systemic inflammation-driven cardiac injury. Systemic inflammation induced by periodontitis mediates cardiac damage through two synergistic pathways: i) Upstream trigger and signal amplification: LPS released from periodontal lesions enters the circulation and is recognized by TLR4 on the surface of immune cells, such as macrophages. This binding activates key intracellular inflammatory signaling cascades, primarily NF-κB and mitogen-activated protein kinase pathways. Activated immune cells then produce and release large quantities of pro-inflammatory cytokines (such as IL-6, TNF-α, and IL-1β) into the bloodstream, amplifying a local infection into a systemic inflammatory state. ii) Downstream effects: The elevated levels of circulating inflammatory mediators inflict cardiac damage through two principal pathways. Pathway A: Direct cardiac injury: Pro-inflammatory cytokines directly target cardiomyocytes, activating apoptotic programs (for example, via caspase cascades) and leading to cell death. Concurrently, they stimulate cardiac fibroblasts to proliferate and differentiate, promoting excessive extracellular matrix deposition and culminating in myocardial fibrosis. Together, apoptosis and fibrosis drive adverse ventricular remodeling and impair cardiac function. Pathway B: Myeloid reprogramming and trained immunity: Circulating cytokines, particularly IL-1β, can act on HSPCs within the bone marrow. By inducing epigenetic reprogramming (for example, histone modifications), these cytokines skew hematopoiesis toward the myeloid lineage, generating functionally 'trained' and hyper-responsive monocytes/macrophages. These 'trained immunity' cells mount an exaggerated inflammatory response upon secondary stimulation, creating a vicious cycle that perpetuates and amplifies inflammatory damage to the cardiovascular system. LPS, lipopolysaccharide; HSPCs, hematopoietic stem and progenitor cells.

Remote pathogenesis driven by the periodontal microbiome. Beyond exerting indirect effects through systemic inflammation, the periodontal microbiome itself plays a more active role as a direct invader. Periodontal pathogens and their virulence factors can escape the local oral environment and inflict damage on remote cardiac tissues through several direct and indirect routes. These mechanisms include the direct dissemination of bacteria, the remote action of virulence factors and the disruption of the oral-gut microbial axis, as clearly illustrated in Fig. 3.

Bacteremia and bacterial translocation: Direct detection of periodontal pathogens in cardiac tissues. Periodontitis contributes to the pathogenesis and progression of HF through bacteremia-mediated systemic dissemination of oral pathogens and their bioactive metabolites. In patients with active periodontal disease, transient bacteremia induced by mastication or dental procedures has been shown to facilitate the hematogenous spread of keystone pathogens such as *Porphyromonas gingivalis*. These microorganisms subsequently colonize arterial walls, promoting monocyte and macrophage accumulation, impairing vasodilation, increasing arterial stiffness, and accelerating atherosclerotic progression (33). Beyond their local oral effects, these pathogens disseminate systemically to distant organs including cardiac and hepatic tissues, exerting profound extra-oral impacts (34-36). This dissemination is substantiated by the consistent detection of oral bacterial DNA in cardiac tissues, which demonstrates a significant association with increased cardiovascular disease incidence (37).

Complementing direct bacterial translocation, microbial metabolites, including short-chain fatty acids and endotoxins, induce direct cytotoxic effects on cardiomyocytes through the activation of inflammatory signaling pathways and apoptosis, thereby exacerbating HF progression (38). Molecular evidence further confirms the vascular and cardiac colonization of periodontal pathogens: *Porphyromonas gingivalis*

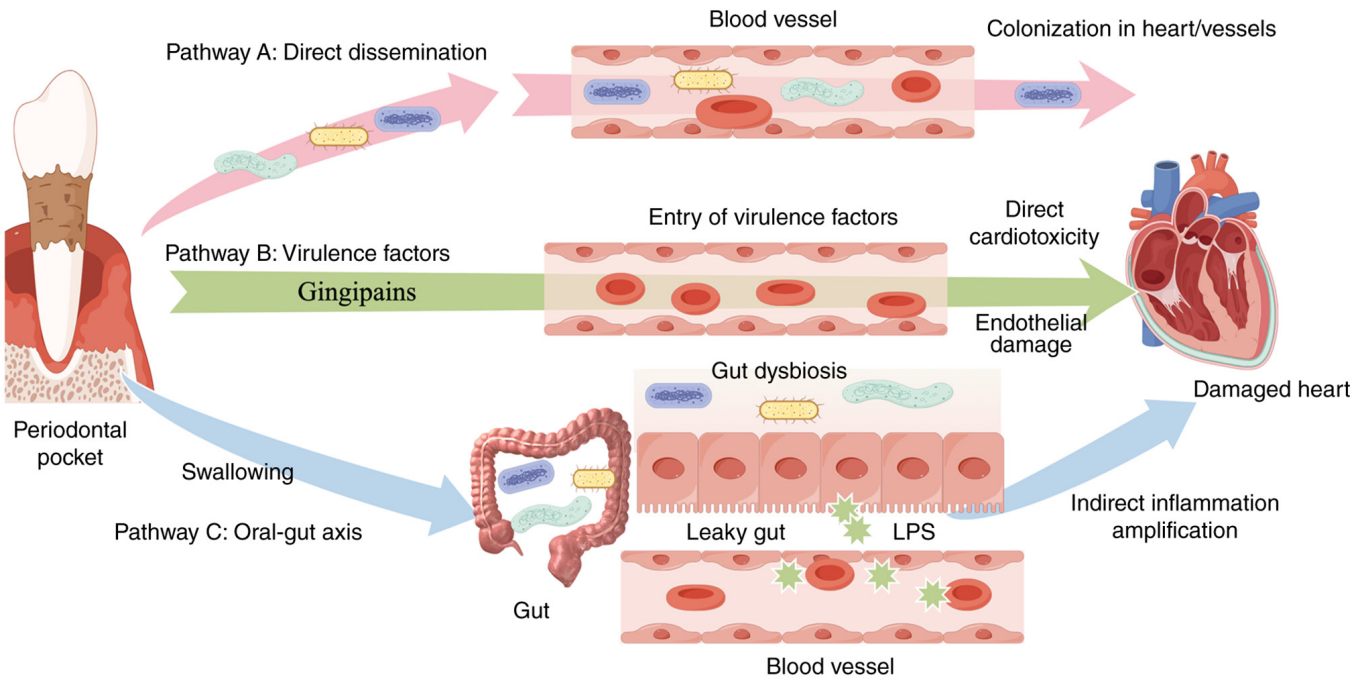

Figure 3. Primary three mechanisms of remote cardiac injury driven by the periodontal microbiota. In addition to indirectly affecting the heart via inflammatory mediators, the periodontal microbiota and its products can actively participate in cardiac pathology through three distinct pathways. i) Direct dissemination: During daily activities (for example, chewing or toothbrushing) or dental procedures, pathogens within the periodontal pocket (notably *Porphyromonas gingivalis*) can breach the compromised periodontal tissue barrier, leading to transient bacteremia. These circulating bacteria can survive in the bloodstream and subsequently colonize distant sites such as heart valves, myocardial tissue, or coronary atherosclerotic plaques, where they can directly induce local inflammation and tissue damage. ii) Remote effects of virulence factors: Even if the bacteria themselves do not survive in circulation, their potent secreted virulence factors can enter the bloodstream and exert remote biological effects. For example, gingipains, a class of proteases produced by *Porphyromonas gingivalis*, can degrade intercellular junction proteins (for example, VE-cadherin) in the vascular endothelium, compromising vascular barrier integrity. Furthermore, they can directly target cardiomyocytes, interfering with critical cellular functions such as autophagy and exerting direct cardiotoxicity. iii) Disruption of the oral-gut axis: Patients with periodontitis continuously swallow saliva containing a high load of periodontal pathogens. These microbes can survive the gastric acid barrier and reach the intestines, altering the composition and function of the intestinal microbiota and causing gut dysbiosis. This dysbiosis can impair the integrity of the intestinal mucosal barrier, leading to increased intestinal permeability ('leaky gut'). This allows a greater translocation of bacterial products (for example, LPS) from the gut lumen into the circulation, thereby indirectly amplifying the systemic inflammatory burden and contributing to cardiac damage.

and *Aggregatibacter actinomycetemcomitans* are frequently identified in coronary atheromas, with a meta-analysis indicating a higher prevalence of *Porphyromonas gingivalis* (39). Additionally, oral bacterial strains, including *Streptococcus mutans* and *Fusobacterium nucleatum*, have been detected in atrial and ventricular biopsies, where their presence was shown to be associated with elevated inflammatory markers and enhanced LPS-binding protein expression, particularly in patients with moderate-to-severe periodontitis (37).

The integration of viable periodontal pathogens into carotid and coronary plaques promotes foam cell formation and extracellular matrix degradation, thereby increasing plaque vulnerability and ischemic risk (40). Furthermore, comparative analyses reveal significantly reduced bacterial detection in cardiac valves and myocardial tissues of edentulous individuals vs. those with active periodontitis, underscoring the crucial role of chronic oral infection in sustaining bacterial dissemination that exacerbates myocardial fibrosis and ventricular remodeling (41). Collectively, these findings established periodontitis as a persistent source of bacterial translocation and metabolite-mediated cardiac injury, highlighting the importance of integrated oral-systemic approaches in HF prevention and management strategies.

Direct cardiotoxicity of bacterial virulence factors. The severity of periodontitis is significantly associated with increased all-cause and cardiovascular mortality in patients with HF, with research reporting substantially elevated all-cause mortality rates among patients with periodontitis compared with those without periodontal disease (42). Mechanistically, this relationship is driven by bacterial virulence factors, particularly gingipains, cysteine proteinases including arginine-specific and lysine-specific variants produced by *Porphyromonas gingivalis*. Following hematogenous dissemination, these proteases disrupt vascular integrity through cleavage of critical adherens junction proteins such as vascular endothelial-cadherin, resulting in increased endothelial permeability, enhanced monocyte infiltration, and accelerated atherosclerotic progression, collectively elevating myocardial workload and ischemic susceptibility in HF-prone individuals (43). Beyond these vascular effects, gingipains exert direct cardiotoxic actions by impairing autophagic flux in cardiomyocytes via proteolytic degradation of essential autophagosomal proteins, vesicle-associated membrane protein 8 and syntaxin-17, leading to accumulated mitochondrial damage and potentiated apoptotic signaling. Experimental models of myocardial infarction demonstrate that *Porphyromonas gingivalis* infection significantly

exacerbates infarct size and ventricular dysfunction through these mechanisms (44-47). Furthermore, gingipain-mediated pathogenesis involves dysregulation of NF-κB signaling in endothelial cells (48), amplifying oxidative stress and pro-apoptotic cascades (49), that drive microvascular rarefaction (48) and fibrotic remodeling (50), thereby perpetuating systolic impairment and HF progression (50,51), through pathways independent of classical inflammatory mediators (51-53). These findings collectively elucidated the dual clinical significance of periodontitis in HF, affecting both mortality outcomes and underlying disease mechanisms, while highlighting the potential therapeutic value of targeting specific virulence factors to mitigate periodontitis-associated cardiac injury.

Oral-gut axis disruption: Indirect amplification of systemic inflammation. Periodontitis significantly exacerbates the progression of HF in patients with comorbidities such as diabetes and chronic kidney disease, leading to elevated rates of hospitalization and mortality (54). In patients with chronic kidney disease, oral health status was revealed to be closely associated with HF outcomes, where effective oral hygiene management was shown to substantially improve prognostic trajectories (55). Mechanistically, periodontitis disrupts systemic immune homeostasis through oral microbiome dysbiosis, which extends to distant sites, including the gut, thereby amplifying systemic inflammation and accelerating HF progression via metabolic and immunomodulatory pathways. Dysbiotic shifts in the oral ecosystem, characterized by the overgrowth of pathobionts such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, facilitate the translocation of microbes or their metabolites to the gastrointestinal tract through salivary ingestion. This disruption of the oral-gut axis induces gut microbiota alterations marked by reduced α diversity and enrichment of pro-inflammatory taxa, which compromises intestinal barrier integrity and promotes systemic translocation of bacterial LPS (56). The subsequent endotoxin-driven activation of hepatic Kupffer cells and TLR signaling pathways enhances the production of systemic cytokines, including IL-6 and TNF-α, sustaining a chronic inflammatory state that induces endothelial dysfunction and myocardial stress. This cascade potentiates fibrotic processes and ventricular remodeling in HF phenotypes (57-59). Furthermore, ectopic colonization of oral-derived bacteria in the gut modulates short-chain fatty acid profiles, reducing anti-inflammatory metabolites such as butyrate while promoting the synthesis of pro-atherogenic trimethylamine N-oxide (60,61). These changes collectively impair cardiac energetics and exacerbate insulin resistance, a common comorbidity in HF, through disrupted enterohepatic signaling (56,62). Notably, in comorbid conditions, this microbiome-mediated immune reprogramming fosters trained immunity in peripheral leukocytes, sustaining a hyperresponsive phenotype and worsened clinical outcomes, independent of direct oral pathogen dissemination (62). These integrated mechanisms establish periodontitis as a modifiable determinant of HF trajectory, underscoring the potential of microbiome-targeted interventions to restore oral-gut equilibrium and mitigate inflammation-driven cardiac deterioration.

Immune-mediated cross-reactivity and autoimmunity

Molecular mimicry between periodontal pathogens and myocardial proteins. Periodontitis modulates the progression of HF through molecular mimicry mechanisms, in which heat shock proteins (HSPs) derived from periodontal pathogens display structural homology with human myocardial proteins. This similarity triggers cross-reactive immune responses that promote autoimmune-mediated cardiac injury and remodeling. For instance, antigenic mimicry between bacterial HSPs such as GroEL from *Porphyromonas gingivalis* and human HSP60 expressed in cardiac myocytes can activate autoreactive T cells. This elicits a Th1-polarized response that facilitates myocardial infiltration and interstitial inflammation, contributing to cardiomyocyte dysfunction and fibrosis, a process often observed in HFrEF (34). Such cross-reactivity also involves B-cell epitopes, leading to the production of autoantibodies targeting endothelial and myocardial HSP60. These autoantibodies exacerbate vascular hyperpermeability and oxidative stress, ultimately promoting maladaptive ventricular hypertrophy and contractile impairment. Preclinical research demonstrated that immunization with *Porphyromonas gingivalis* accelerates autoimmune myocarditis-like pathology, supporting this pathogenic link (63). Furthermore, conserved peptide motifs shared between microbial HSPs and cardiac proteins such as actin or myosin enhance complement activation and antibody-dependent cellular cytotoxicity. These immune mechanisms are associated with elevated serum troponin levels and poorer prognostic indicators in patients with coexisting periodontitis and HF, independent of conventional hemodynamic risk factors (64). Collectively, these findings illustrate how molecular mimicry underpins a state of persistent myocardial autoimmunity initiated by periodontitis. They also highlight the potential of epitope-specific immunomodulatory strategies to disrupt this pathogenic cycle and mitigate the burden of HF in susceptible populations (65).

Induction of autoantibodies against cardiac antigens. Periodontitis promotes the generation of autoantibodies targeting cardiac antigens, such as anti-β1-adrenergic receptor antibodies, which arise through molecular mimicry or sustained immune activation. These autoantibodies contribute to myocardial contractile dysfunction and exacerbate HF phenotypes via dysregulated adrenergic signaling and apoptotic pathways (29). Detected at elevated levels in sera from patients with chronic periodontitis, these autoantibodies bind specifically to the second extracellular loop of β1-adrenergic receptors on cardiomyocytes. This binding induces agonist-like effects that disrupt cyclic AMP production and calcium handling, ultimately impairing inotropic responses and promoting maladaptive ventricular remodeling in predisposed individuals (66). Notably, the formation of these autoantibodies occurs independently of classical infectious triggers such as *Trypanosoma cruzi*, as demonstrated by their association with systemic inflammatory markers in non-Chagasic populations (31). Moreover, these antibodies enhance cardiomyocyte apoptosis through caspase activation and upregulation of nitric oxide synthase, recapitulating the cardiotoxic profile of β1-agonists such as xamoterol. This mechanism accelerates the transition from compensated hypertrophy to overt HF, particularly in patients with comorbid

inflammatory conditions (29). In summary, this autoantibody-mediated pathway identifies periodontitis as a potential instigator of immune-mediated cardiac injury, underscoring the therapeutic potential of immunomodulatory strategies aimed at neutralizing receptor-specific autoantibodies to mitigate disease progression.

Shared risk factors and confounding pathways

Shared genetic susceptibility. Periodontitis influences susceptibility to HF through shared genetic predispositions, particularly involving polymorphisms in inflammation-related genes. These genetic variants may amplify chronic inflammatory responses and endothelial dysfunction, thereby promoting myocardial remodeling and accelerating the progression toward cardiac decompensation in genetically susceptible individuals. Genome-wide association studies revealed overlapping risk loci, such as the 9p21.3 region, which contains the antisense noncoding RNA gene ANRIL (CDKN2B-AS1). Variants in this locus, including rs1333048, show recessive associations with both aggressive periodontitis (odds ratio=1.99) and coronary heart disease, a common precursor to HF. This association may reflect dysregulation of cell cycle inhibitors and enhanced inflammatory signaling in vascular and periodontal tissues (67). Similarly, polymorphisms in the plasminogen gene, which plays a role in fibrinolysis and extracellular matrix remodeling, confer joint risk for periodontitis and atherosclerotic cardiovascular disease. The shared variant rs4252120, for example, was linked to plaque instability and fibrotic processes that indirectly impair cardiac function (68). Further evidence implicates cytokine-encoding genes such as IL6. The polymorphism rs1800795 is associated with elevated systemic inflammation and is enriched in individuals with both periodontitis and HF. This genotype fosters a prothrombotic state and exacerbates ventricular hypertrophy and systolic dysfunction, likely through NF-κB-mediated pathways (69). Additionally, variants in inflammasome-related genes such as PYD and CARD domain-containing protein, for example rs8056505 C/T, with the T allele occurring more frequently in affected populations, appear to increase susceptibility by enhancing caspase-1-dependent pyroptosis and cytokine release. This mechanism sustains a low-grade inflammatory state that contributes to HF pathogenesis independently of environmental factors (70). Collectively, these findings highlight a polygenic architecture underlying the comorbidity between periodontitis and HF. They support the integration of genotype-guided risk assessment into clinical practice, which may facilitate personalized anti-inflammatory interventions and help mitigate disease progression.

Metabolic syndrome as a mechanistic bridge. Periodontitis modulates HF risk through its interplay with metabolic syndrome, in which insulin resistance acts as a central amplifier that aggravates systemic metabolic dysregulation and inflammatory burden, thereby predisposing individuals to adverse cardiac structural changes and eventual decompensation. Chronic periodontal infection promotes insulin resistance via sustained release of pro-inflammatory cytokines such as TNF-α and IL-6 from dysbiotic biofilms. These mediators impair insulin receptor signaling in adipocytes and hepatocytes, leading to hyperglycemia and dyslipidemia, core components of metabolic syndrome (71). Within the metabolic syndrome cluster, which includes central obesity and hypertension, the exacerbation of insulin resistance intensifies endothelial dysfunction and oxidative stress, accelerating atherosclerotic changes that promote myocardial ischemia and fibrotic remodeling, key antecedents of HFrEF (72). A cross-sectional study indicated that patients with moderate to severe periodontitis exhibit elevated homeostasis model assessment of insulin resistance values, corresponding to an odds ratio of 1.38-1.99 for metabolic syndrome components. These components, in turn, independently predict adverse cardiac outcomes such as ventricular hypertrophy and elevated peptide levels (73). Bidirectionally, insulin resistance driven by metabolic syndrome alters the oral microbiome by reducing bacterial diversity and facilitating the colonization of periodontal pathobionts. This shift perpetuates periodontal tissue breakdown while indirectly impairing cardiac energetics through disrupted glucose metabolism and enhanced lipid peroxidation (74). Together, these mechanisms establish periodontitis as a modifiable risk factor in the HF continuum via its role in metabolic syndrome amplification. This perspective supports integrated treatment strategies aimed at improving insulin sensitivity to reduce the burden of cardiometabolic comorbidity (75).

4. Clinical and therapeutic implications

The robust epidemiological and mechanistic links between periodontitis and HF have paved the way for critical translational inquiry into whether treating periodontitis can mitigate HF risk. This issue requires explicit and critical evaluation of the available interventional evidence. At present, intervention studies conducted specifically in patients with established HF are extremely limited, and no completed randomized controlled trial has yet demonstrated that periodontal therapy reduces HF hospitalization, cardiovascular mortality, or other hard clinical outcomes in HF populations. The most directly relevant HF-specific study is the ongoing randomized PERIO-HF trial (ClinicalTrials.gov identifier: NCT07036289), which is evaluating the effects of periodontal treatment on NT-proBNP levels at 3 and 6 months in patients with HF. However, even this study is primarily focused on surrogate endpoints rather than definitive clinical HF outcomes such as hospitalization, mortality, or symptom burden. Therefore, although PERIO-HF is expected to provide more direct evidence in an HF population, it will not by itself establish whether periodontal therapy improves hard outcomes in HF.

By contrast, most currently available interventional studies in this field have been conducted in non-HF populations. For example, the randomized controlled trial (RCT) by Wang *et al* (76) in patients with type 2 diabetes and periodontitis demonstrated that intensive non-surgical periodontal therapy, compared with oral hygiene instruction alone, significantly improved diastolic function together with inflammatory and cardiac biomarkers. Similarly, an RCT by Isola *et al* (77) in patients with stage III periodontitis and pre-post studies by Fazal *et al* (78) and Ari *et al* (79) reported improvements in HF-relevant surrogate biomarkers following periodontal treatment in non-HF populations. Collectively, these studies indicated that periodontal therapy may influence

Table II. Summary of available interventional studies evaluating periodontal therapy in relation to HF-relevant surrogate markers and cardiovascular parameters.

First author/s, year	Study design and population	HF-specific population	Main endpoints	Main findings	Key limitation and relevance to HF	(Refs.) or NCT identifier
Wang *et al*, 2020	RCT: Patients with type 2 diabetes and moderate-to-severe periodontitis	No	E/e' ratio, LV mass index, NT-proBNP, CRP, IL-6	Intensive non-surgical periodontal therapy improved E/e' ratio and was associated with favorable trends in LV mass index, NT-proBNP, and inflammatory biomarkers at 6 months.	Conducted in a non-HF population; evaluated surrogate cardiovascular markers rather than HF hospitalization, mortality, or symptom burden.	(76)
Isola *et al*, 2023	RCT: Patients with stage III periodontitis	No	NT-proBNP, hs-CRP, ECM-1, NGAL	Intensive full-mouth scaling and root planing was associated with greater reductions in NT-proBNP and related inflammatory biomarkers than basic oral hygiene measures.	Not conducted in patients with established HF; biomarker improvements do not constitute direct evidence of benefit for clinical HF outcomes.	(77)
Fazal *et al*, 2022	Pre-post study: Systemically healthy patients with chronic periodontitis	No	Gingival crevicular fluid NT-proBNP, serum NT-proBNP	Non-surgical periodontal therapy reduced gingival crevicular fluid NT-proBNP and showed a trend toward lower serum NT-proBNP.	Uncontrolled exploratory study in a non-HF population; no hard cardiovascular or HF-specific endpoints were assessed.	(78)
Ari *et al*, 2023	Pre-post study: Patients with severe chronic periodontitis	No	Salivary NT-proBNP, gingival crevicular fluid NT-proBNP	Periodontal flap surgery was associated with reduced salivary NT-proBNP levels after 6 months.	Non-HF population and surrogate biomarker endpoints only; clinical relevance to HF outcomes remains uncertain.	(79)
PERIO-HF Trial, 2024-ongoing	Ongoing RCT: Patients with established HF	Yes	NT-proBNP and cardiac function metrics	Ongoing trial; no published outcome data are currently available.	Most directly relevant HF-specific randomized study identified to date, but it primarily evaluates surrogate endpoints rather than hard HF outcomes such as hospitalization, mortality, or symptom improvement.	NCT07036289

HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; ECM-1, extracellular matrix protein-1; NGAL, neutrophil gelatinase-associated lipocalin; RCT, randomized controlled trial.

cardiovascular-related biological pathways and HF-relevant surrogate markers (80). Nevertheless, surrogate biomarker improvement should not be conflated with proven reduction in incident HF, slower HF progression or improved prognosis in patients with established HF. Likewise, although observational and cohort studies support an association between periodontitis and prevalent or incident HF, there remains a lack of interventional evidence directly demonstrating that treatment of periodontitis alters the clinical course of HF.

Although these findings should not yet be interpreted as definitive evidence that periodontal treatment reduces incident HF or improves hard HF outcomes (81), they nevertheless support greater clinical attention to oral and periodontal health in patients with HF, particularly within a multidisciplinary care framework (82). Population-based (16) and cohort studies (12,32) showed that periodontitis is associated with prevalent HF, incident HF, and adverse cardiac structural or functional alterations, suggesting that periodontal status may help identify patients with a higher systemic inflammatory and cardiovascular burden rather than serving as an isolated therapeutic target at the current stage of evidence. In elderly (83) or hospitalized patients with acute HF, poor oral health was also linked to reduced physical function, decline in activities of daily living, dysphagia, and impaired recovery of nutritional status, all of which may complicate rehabilitation, discharge readiness, and overall care complexity (84,85). Accordingly, oral and periodontal assessment may reasonably be incorporated into multidisciplinary HF care, particularly in elderly, frail or repeatedly hospitalized patients, primarily as a component of holistic risk assessment, supportive management, and timely referral for dental or periodontal care, rather than as a stand-alone intervention with proven efficacy for reducing HF hospitalization or mortality.

However, the current body of evidence is constrained by limited sample sizes and short follow-up durations, heterogeneous study populations, and a predominant reliance on surrogate endpoints. There is a clear need for large-scale, multicenter RCTs powered for hard clinical endpoints, such as HF-related hospitalization and cardiovascular mortality. To facilitate critical appraisal of the currently available interventional evidence, the designs, populations, endpoints, and principal findings of the relevant studies are summarized in Table II.

Most currently available studies are observational and therefore mainly support an association rather than a confirmed causal relationship between periodontitis and HF. Residual confounding by shared risk factors, such as age, smoking, diabetes, obesity, chronic kidney disease, socioeconomic status, and access to dental care, cannot be fully excluded, and reverse causation is also possible in patients with advanced HF (12,86,87). In addition, heterogeneity in study design and the reliance of intervention studies on surrogate rather than hard clinical endpoints limit interpretation. Future studies should focus on standardized definitions, clearly phenotyped HF populations and RCTs with clinically meaningful outcomes.

5. Conclusion and future perspectives

In conclusion, the present review summarized the current evidence linking periodontitis and HF, analyzed the potential mechanisms underlying their association and shared pathophysiological basis and discussed the possible role of periodontal treatment in improving outcomes for patients with HF. The 'periodontal-cardiac axis' is now understood as a multifaceted pathogenic framework for understanding these complex and interwoven interactions. From a clinical perspective, periodontal assessment may be considered in patients with HF as part of multidisciplinary care; however, current evidence remains insufficient to support definitive recommendations that such evaluation or treatment improves HF outcomes.

Looking ahead, several critical avenues of research are essential to translate these mechanistic insights into tangible clinical benefits. First, large-scale, prospective, RCTs are urgently needed. These trials should move beyond surrogate endpoints and evaluate 'hard' clinical outcomes, such as HF hospitalization rates, cardiovascular mortality and improvements in cardiac function, (such as ejection fraction and NT-proBNP levels), following standardized periodontal treatment in diverse HF populations (including both HFpEF and HFrEF). Such studies are paramount to definitively establish causality and quantify the therapeutic impact. Second, future research should focus on elucidating the specific molecular pathways with greater precision. Advanced multi-omics approaches (genomics, proteomics, and metabolomics) can help identify specific bacterial strains, virulence factors, or host genetic polymorphisms (such as in the ANRIL or IL6 loci) that confer the highest risk. This will pave the way for personalized risk stratification and the development of targeted therapies, such as specific virulence factor inhibitors (such as gingipain inhibitors) or immunomodulatory agents that can disrupt maladaptive trained immunity. Third, the diagnostic and prognostic utility of periodontal status in HF management warrants investigation. Studies should explore whether integrating periodontal screening into routine cardiovascular risk assessment can improve the prediction of adverse outcomes. Developing composite biomarkers that combine periodontal and cardiac inflammatory markers could offer a more holistic view of a the risk profile of a patient. Finally, interdisciplinary collaboration between cardiologists and dental professionals is crucial. Developing integrated care models that incorporate routine oral health screening and treatment into standard HF management protocols could represent a novel, cost-effective strategy to reduce the systemic inflammatory burden and potentially improve long-term patient outcomes.

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XZ performed structured literature searches, critically synthesized and interpreted findings, and wrote major sections of

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC and Coats AJS: Global burden of heart failure: A comprehensive and updated review of epidemiology. Cardiovasc Res 118: 3272-3287, 2023.
2. Shahim B, Kapelios CJ, Savarese G and Lund LH: Global public health burden of heart failure: An updated review. Card Fail Rev 9: e11, 2023.
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, *et al*: 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American college of Cardiology/American heart association joint committee on clinical practice guidelines. Circulation 145: e895-e1032, 2022.
4. Dick SA and Epelman S: Chronic heart failure and inflammation: What do we really know? Circ Res 119: 159-176, 2016.
5. Roman-Pepine D, Serban AM, Capras RD, Cismaru CM and Filip AG: A comprehensive review: Unraveling the role of inflammation in the etiology of heart failure. Heart Fail Rev 30: 931-954, 2025.
6. Shirazi LF, Bissett J, Romeo F and Mehta JL: Role of inflammation in heart failure. Curr Atheroscler Rep 19: 27, 2017.
7. Hajishengallis G: Periodontitis: From microbial immune subversion to systemic inflammation. Nat Rev Immunol 15: 30-44, 2015.
8. Martínez-García M and Hernández-Lemus E: Periodontal inflammation and systemic diseases: An overview. Front Physiol 12: 709438, 2021.
9. Hajishengallis G and Chavakis T: Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol 21: 426-440, 2021.
10. Chen Y, Rao R, Wu X, Qin Z, Chen Y, Li Q and Li W: Periodontitis and the risk of heart failure: A Meta-analysis and mendelian randomisation study. Oral Health Prev Dent 23: 149-164, 2025.
11. Sharma S, Mathur D, Goswami S, Gupta MK, Bhardwaj P, Kumar P and Deora S: Prevalence of periodontitis in chronic heart failure patients and its relationship with NT-ProBNP: A cross-sectional study. Indian Heart J 77: 110-113, 2025.
12. Walther C, Wenzel JP, Schnabel RB, Heydecke G, Seedorf U, Beikler T, Borof K, Nikorowitsch J, Schrage B, Blankenberg S, *et al*: Association between periodontitis and heart failure in the general population. ESC Heart Fail 9: 4189-4197, 2022.
13. Miyauchi S, Kawada-Matsuo M, Furusho H, Nishi H, Nakajima A, Phat PT, Shiba F, Kitagawa M, Ouhara K, Oda N, *et al*: Atrial translocation of *Porphyromonas gingivalis* exacerbates atrial fibrosis and atrial fibrillation. Circulation 151: 1527-1540, 2025.
14. Ferrara E, D'Albenzio A, Bassignani J, Di Tanna I, Murmura G and Balice G: The Periodontal-cardiovascular disease association: Molecular mechanisms and clinical implications. Int J Mol Sci 26: 7710, 2025.
15. Mitroulis I, Hajishengallis G and Chavakis T: Bone marrow inflammatory memory in cardiometabolic disease and inflammatory comorbidities. Cardiovasc Res 119: 2801-2812, 2024.
16. Yan Y, Mao M, Li YQ, Chen YJ, Yu HD, Xie WZ, Huang Q, Leng WD and Xiong J: Periodontitis is associated with heart failure: A Population-based study (NHANES III). Front Physiol 13: 854606, 2022.
17. Schmalz G, Hennecke A, Haak R, Kottmann T, Garbade J, Binner C and Ziebolz D: Secondary analysis of potential associations between oral health and infection-related parameters in patients with severe heart failure-results of a German cohort. BMC Cardiovasc Disord 23: 573, 2023.
18. Aoyama N, Kure K, Minabe M and Izumi Y: Increased heart failure prevalence in patients with a high antibody level against periodontal pathogen. Int Heart J 60: 1142-1146, 2019.
19. Foroughi M, Torabinejad M, Angelov N, Ojcius DM, Parang K, Ravnan M and Lam J: Bridging oral and systemic health: Exploring pathogenesis, biomarkers, and diagnostic innovations in periodontal disease. Infection 53: 2277-2302, 2025.
20. Cainzos-Achirica M, Enjuanes C, Greenland P, McEvoy JW, Cushman M, Dardari Z, Nasir K, Budoff MJ, Al-Mallah MH, Yeboah J, *et al*: The prognostic value of interleukin 6 in multiple chronic diseases and all-cause death: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 278: 217-225, 2018.
21. Jug B, Salobir BG, Vene N, Sebestjen M, Sabovic M and Keber I: Interleukin-6 is a stronger prognostic predictor than high-sensitive C-reactive protein in patients with chronic stable heart failure. Heart Vessels 24: 271-276, 2009.
22. Duprez DA, Gross MD, Kizer JR, Ix JH, Hundley WG and Jacobs DR Jr: Predictive value of collagen biomarkers for heart failure with and without preserved ejection fraction: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Heart Assoc 7: e007885, 2018.
23. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, Levy D, Wilson PW and D'Agostino RB; Framingham Heart Study: Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: The Framingham Heart Study. Circulation 107: 1486-1491, 2003.
24. Schulze-Späte U, Mizani I, Salaverry KR, Chang J, Wu C, Jones M, Kennel PJ, Brunjes DL, Choo TH, Kato TS, *et al*: Periodontitis and bone metabolism in patients with advanced heart failure and after heart transplantation. ESC Heart Fail 4: 169-177, 2017.
25. Köse O, Arabacı T, Gedikli S, Eminoglu DÖ, Kermen E, Kızıldağ A, Kara A, Ozkanlar S and Yemenoglu H: Biochemical and histopathologic analysis of the effects of periodontitis on left ventricular heart tissues of rats. J Periodontal Res 52: 176-185, 2017.
26. Köse O, Arabacı T, Yemenoglu H, Ozkanlar S, Kurt N, Gumussoy I, Gedikli S and Kara A: Influence of experimental periodontitis on cardiac oxidative stress in rats: A biochemical and histomorphometric study. J Periodontal Res 52: 603-608, 2017.
27. Suh JS, Kim S, Boström KI, Wang CY, Kim RH and Park NH: Periodontitis-induced systemic inflammation exacerbates atherosclerosis partly via endothelial-mesenchymal transition in mice. Int J Oral Sci 11: 21, 2019.
28. Schulze-Späte U, Wurschi L, van der Vorst EPC, Hölzle F, Craveiro RB, Wolf M and Noels H: Crosstalk between periodontitis and cardiovascular risk. Front Immunol 15: 1469077, 2024.
29. Reina S, Ganzinelli S, Sterin-Borda L and Borda E: Pro-apoptotic effect of anti-β1-adrenergic receptor antibodies in periodontitis patients. Int Immunopharmacol 14: 710-721, 2012.
30. Li X, Wang H, Yu X, Saha G, Kalafati L, Ioannidis C, Mitroulis I, Netea MG, Chavakis T and Hajishengallis G: Maladaptive innate immune training of myelopoiesis links inflammatory comorbidities. Cell 185: 1709-1727.e18, 2022.
31. Scherbaum I, Heidecke H, Bunte K, Peters U, Beikler T and Boege F: Autoantibodies against M5-muscarinic and beta1-adrenergic receptors in periodontitis patients. Aging (Albany NY) 12: 16609-16620, 2020.
32. Molinsky RL, Yuzefpolskaya M, Norby FL, Yu B, Shah AM, Pankow JS, Ndumele CE, Lutsey PL, Papapanou PN, Beck JD, *et al*: Periodontal status, C-reactive protein, NT-proBNP, and incident heart failure: The ARIC study. JACC Heart Fail 10: 731-741, 2022.
33. Bourgeois D, Inquimbert C, Ottolenghi L and Carrouel F: Periodontal pathogens as risk factors of cardiovascular diseases, diabetes, rheumatoid arthritis, cancer, and chronic obstructive pulmonary Disease-Is there cause for consideration? Microorganisms 7: 424, 2019.

34. Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, *et al*: Periodontal disease and atherosclerotic vascular disease: Does the evidence support an independent association?: A scientific statement from the American Heart Association. Circulation 125: 2520-2544, 2012.
35. Tonetti MS and Van Dyke TE: Periodontitis and atherosclerotic cardiovascular disease: Consensus report of the Joint EFP/AAPWorkshop on periodontitis and systemic diseases. J Periodontol 84 (Suppl 4S): S24-S29, 2013.
36. Byun SH, Lee S, Kang SH, Choi HG and Hong SJ: Cross-Sectional analysis of the association between periodontitis and cardiovascular disease using the Korean genome and epidemiology study data. Int J Environ Res Public Health 17: 5237, 2020.
37. Ziebolz D, Jahn C, Pegel J, Semper-Pinnecke E, Mausberg RF, Waldmann-Beushausen R, Schöndube FA and Danner BC: Periodontal bacteria DNA findings in human cardiac tissue-Is there a link of periodontitis to heart valve disease? Int J Cardiol 251: 74-79, 2018.
38. Kurek-Górecka A, Kłósek M, Pietsz G, Balwierz R, Olczyk P and Czuba ZP: Ethanolic Extract of Propolis and CAPE as Cardioprotective Agents against LPS and IFN-α stressed cardiovascular injury. Nutrients 16: 627, 2024.
39. Joshi C, Bapat R, Anderson W, Dawson D, Hijazi K and Cherukara G: Detection of periodontal microorganisms in coronary atheromatous plaque specimens of myocardial infarction patients: A systematic review and meta-analysis. Trends Cardiovasc Med 31: 69-82, 2021.
40. Czerniuk MR, Surma S, Romańczyk M, Nowak JM, Wojtowicz A and Filipiak KJ: Unexpected relationships: Periodontal diseases: Atherosclerosis-plaque destabilization? From the teeth to a coronary event. Biology (Basel) 11: 272, 2022.
41. Pardo A, Signoriello A, Signoretto C, Messina E, Carelli M, Tessari M, De Manna ND, Rossetti C, Albanese M, Lombardo G and Luciani GB: Detection of periodontal pathogens in oral samples and cardiac specimens in patients undergoing aortic valve replacement: A pilot study. J Clin Med 10: 3874, 2021.
42. Sebring D, Buhlin K, Lund H, Norhammar A, Rydén L and Kvist T: Endodontic inflammatory disease and future cardiovascular events and mortality: A report from the PAROKRANK study. J Endod 50: 1073-1081.e73, 2024.
43. Ajoolabady A, Pratico D, Lin L, Mantzoros CS, Bahijri S, Tuomilehto J and Ren J: Inflammation in atherosclerosis: Pathophysiology and mechanisms. Cell Death Dis 15: 817, 2024.
44. Shahab M, Aiman S, Alshammari A, Alasmari AF, Alharbi M, Khan A, Wei DQ and Zheng G: Immunoinformatics-based potential multi-peptide vaccine designing against Jamestown Canyon Virus (JCV) capable of eliciting cellular and humoral immune responses. Int J Biol Macromol 253: 126678, 2023.
45. Ivaldo C, Passalacqua M, Furfaro AL, d'Abramo C, Ruiz S, Chatterjee PK, Metz CN, Nitti M and Marambaud P: Oxidative stress-induced MMP- and γ-secretase-dependent VE-cadherin processing is modulated by the proteasome and BMP9/10. Sci Rep 13: 597, 2023.
46. Harki O, Bouyon S, Sallé M, Arco-Hierves A, Lemarié E, Demory A, Chirica C, Vilgrain I, Pépin JL, Faury G and Briançon-Marjollet A: Inhibition of vascular endothelial cadherin cleavage prevents elastic fiber alterations and atherosclerosis induced by intermittent hypoxia in the mouse aorta. Int J Mol Sci 23: 7012, 2022.
47. Slack MA and Gordon SM: Protease activity in vascular disease. Arterioscler Thromb Vasc Biol 39: e210-e218, 2019.
48. Xie M, Tang Q, Yu S, Sun J, Mei F, Zhao J and Chen L: *Porphyromonas gingivalis* disrupts vascular endothelial homeostasis in a TLR-NF-κB axis dependent manner. Int J Oral Sci 12: 28, 2020.
49. Charoensaensuk V, Chen YC, Lin YH, Ou KL, Yang LY and Lu DY: *Porphyromonas gingivalis* induces proinflammatory cytokine expression leading to apoptotic death through the oxidative Stress/NF-κB pathway in brain endothelial cells. Cells 10: 3033, 2021.
50. Sato H, Suzuki JI, Aoyama N, Watanabe R, Kaneko M, Shiheido Y, Yoshida A, Wakayama K, Kumagai H, Ikeda Y, *et al*: A Periodontal pathogen *Porphyromonas gingivalis* deteriorates Isoproterenol-Induced myocardial remodeling in mice. Hypertens Res 40: 35-40, 2017.
51. Shiheido-Watanabe Y, Maejima Y, Nakagama S, Fan Q, Tamura N and Sasano T: *Porphyromonas gingivalis*, a periodontal pathogen, impairs post-infarcted myocardium by inhibiting autophagosome-lysosome fusion. Int J Oral Sci 15: 42, 2023.
52. Sheets SM, Potempa J, Travis J, Fletcher HM and Casiano CA: Gingipains from *Porphyromonas gingivalis* W83 synergistically disrupt endothelial cell adhesion and can induce caspase-independent apoptosis. Infect Immun 74: 5667-5678, 2006.
53. Tada H, Matsuyama T, Nishioka T, Hagiwara M, Kiyoura Y, Shimauchi H and Matsushita K: *Porphyromonas gingivalis* Gingipain-dependently enhances IL-33 production in human gingival epithelial cells. PLoS One 11: e0152794, 2016.
54. Huh Y, Yoo JE, Park SH, Han K, Kim SM, Park HS, Cho KH, Ahn JS, Jun SH and Nam GE: Association of dental diseases and oral hygiene care with the risk of heart failure in patients with type 2 diabetes: A nationwide cohort study. J Am Heart Assoc 12: e029207, 2023.
55. Thorstensson H, Kuylenstierna J and Hugoson A: Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontol 23: 194-202, 1996.
56. Kunath BJ, De Rudder C, Laczny CC, Letellier E and Wilmes P: The oral-gut microbiome axis in health and disease. Nat Rev Microbiol 22: 791-805, 2024.
57. Zeng T, Zhang CL, Xiao M, Yang R and Xie KQ: Critical roles of Kupffer cells in the pathogenesis of alcoholic liver disease: From basic science to clinical trials. Front Immunol 7: 538, 2016.
58. Slevin E, Baiocchi L, Wu N, Ekser B, Sato K, Lin E, Ceci L, Chen L, Lorenzo SR, Xu W, *et al*: Kupffer cells: Inflammation pathways and Cell-cell interactions in Alcohol-associated liver disease. Am J Pathol 190: 2185-2193, 2020.
59. Rivera CA, Adegboyega P, van Rooijen N, Tagalicud A, Allman M and Wallace M: Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. J Hepatol 47: 571-579, 2007.
60. Hernández-Cabanyero C and Vonaesch P: Ectopic colonization by oral bacteria as an emerging theme in health and disease. FEMS Microbiol Rev 48: fuae012, 2024.
61. Su S, Ni X and Lin Y: The oral-gut microbiota axis in cardiovascular diseases: Mechanisms, therapeutic targets, and translational challenges. Front Cell Infect Microbiol 15: 1658502, 2025.
62. Li Y, Zhu M, Liu Y, Luo B, Cui J, Huang L, Chen K and Liu Y: The oral microbiota and cardiometabolic health: A comprehensive review and emerging insights. Front Immunol 13: 1010368, 2022.
63. Ford PJ, Yamazaki K and Seymour GJ: Cardiovascular and oral disease interactions: What is the evidence? Prim Dent Care 14: 59-66, 2007.
64. Sánchez-Caraballo A, García-Solano V, González-Rangel SK, Grattz-Lamadrid V and Munera-Gomez M: Molecular mimic between cardiovascular diseases and microorganism antigens. Rev Alerg Mex 71: 61, 2024 (In Spanish).
65. Seymour GJ, Ford PJ, Cullinan MP, Leishman S, West MJ and Yamazaki K: Infection or inflammation: The link between periodontal and cardiovascular diseases. Future Cardiol 5: 5-9, 2009.
66. Segovia M, Ganzinelli S, Reina S, Borda E and Sterin-Borda L: Role of anti-β1 adrenergic antibodies from patients with periodontitis in cardiac dysfunction. J Oral Pathol Med 41: 242-248, 2012.
67. Schaefer AS, Richter GM, Groessner-Schreiber B, Noack B, Nothnagel M, El Mokhtari NE, Loos BG, Jepsen S and Schreiber S: Identification of a shared genetic susceptibility locus for coronary heart disease and periodontitis. PLoS Genet 5: e1000378, 2009.
68. Aarabi G, Zeller T, Seedorf H, Reissmann DR, Heydecke G, Schaefer AS and Seedorf U: Genetic susceptibility contributing to periodontal and cardiovascular disease. J Dent Res 96: 610-617, 2017.
69. Duenas S, McGee Z, Mhatre I, Mayilvahanan K, Patel KK, Abdelhalim H, Jayprakash A, Wasif U, Nwankwo O, Degroat W, *et al*: Computational approaches to investigate the relationship between periodontitis and cardiovascular diseases for precision medicine. Hum Genomics 18: 116, 2024.
70. Daily ZA, Al-Ghurabi BH and Al-Qarakhli AM: PYCARD gene polymorphisms and susceptibility to periodontal and coronary heart diseases. J Med Life 17: 195-200, 2024.
71. Gurav AN: Periodontitis and insulin resistance: Casual or causal relationship? Diabetes Metab J 36: 404-411, 2012.
72. Marchetti E, Monaco A, Procaccini L, Mummolo S, Gatto R, Tetè S, Baldini A, Tecco S and Marzo G: Periodontal disease: The influence of metabolic syndrome. Nutr Metab (Lond) 9: 88, 2012.
73. Benguigui C, Bongard V, Ruidavets JB, Chamontin B, Sixou M, Ferrières J and Amar J: Metabolic syndrome, insulin resistance, and periodontitis: A cross-sectional study in a middle-aged French population. J Clin Periodontol 37: 601-608, 2010.

74. Pirih FQ, Monajemzadeh S, Singh N, Sinacola RS, Shin JM, Chen T, Fenno JC, Kamarajan P, Rickard AH, Travan S, *et al*: Association between metabolic syndrome and periodontitis: The role of lipids, inflammatory cytokines, altered host response, and the microbiome. Periodontol 87: 50-75, 2021.
75. Aizenbud I, Wilensky A and Almoznino G: Periodontal disease and its association with metabolic Syndrome-A comprehensive review. Int J Mol Sci 24: 13011, 2023.
76. Wang Y, Liu HN, Zhen Z, Pelekos G, Wu MZ, Chen Y, Tonetti M, Tse HF, Yiu KH and Jin L: A randomized controlled trial of the effects of non-surgical periodontal therapy on cardiac function assessed by echocardiography in type 2 diabetic patients. J Clin Periodontol 47: 726-736, 2020.
77. Isola G, Tartaglia GM, Santonocito S, Polizzi A, Williams RC and Iorio-Siciliano V: Impact of N-terminal pro-B-type natriuretic peptide and related inflammatory biomarkers on periodontal treatment outcomes in patients with periodontitis: An explorative human randomized-controlled clinical trial. J Periodontol 94: 1414-1424, 2023.
78. Fazal I, Shetty B, Yadalam U, Khan SF and Nambiar M: Effectiveness of periodontal intervention on the levels of N-terminal pro-brain natriuretic peptide in chronic periodontitis patients. J Circ Biomark 11: 48-56, 2022.
79. Ari G, Rajendran S, Mahendra J, Ambalavanan N, Vijayaraj S, Mahendra L, Madapusi Balaji T, Ali Baeshen H, Patil S, Reda R and Testarelli L: Estimation of GCF and salivary levels of NT-proBNP in systemically healthy subjects with severe chronic periodontitis before and after periodontal flap surgery. Int J Gen Med 16: 1809-1816, 2023.
80. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, Butler J, Lam CSP, Ponikowski P, Emdin M, *et al*: N-Terminal Pro-B-Type natriuretic peptide and clinical outcomes: Vericiguat heart failure with reduced ejection fraction study. JACC Heart Fail 8: 931-939, 2020.
81. Tran AH, Zaidi AH, Bolger AF, Del Brutto OH, Hegde R, Patton LL, Rausch J, Zachariah JP; American Heart Association Cardiovascular Disease Prevention Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Clinical Cardiology, *et al*: Periodontal disease and atherosclerotic cardiovascular disease: A scientific statement from the American heart association. Circulation 153: e73-e88, 2026.
82. Leelaviwat N, Kewcharoen J, Trongtorsak A, Thangjui S, Del Rio-Pertuz G, Abdelnabi M and Navaravong L: Association between periodontal disease and heart failure: A systematic review and meta-analysis. Acta Cardiol 79: 405-409, 2024.
83. Uemura Y, Shibata R, Ishikawa S, Takemoto K, Murohara T and Watarai M: The association between oral health status and physical function in elderly patients with acute heart failure. Clin Exp Dent Res 10: e824, 2024.
84. Matsuo H, Yoshimura Y, Fujita S, Maeno Y and Tanaka S: Association of poor oral health with increased incidence of dysphagia and impaired improvement in nutritional status among patients with acute heart failure: A prospective cohort study. Eur Geriatr Med 14: 879-888, 2023.
85. Nakamura M, Yamamoto K, Nozaki S, Saeki T, Omi W, Kato C, Inoue M, Harada T and Sakagami S: Decline in oral function contributes to decreased activities of daily living at discharge in elderly patients with heart failure. PLoS One 20: e0323806, 2025.
86. Fröhlich H, Herrmann K, Franke J, Karimi A, Täger T, Cebola R, Katus HA, Zugck C and Frankenstein L: Periodontitis in chronic heart failure. Texas Heart Inst J 43: 297-304, 2016.
87. Hopkins S, Gajagowni S, Qadeer Y, Wang Z, Virani SS, Meurman JH, Leischik R, Lavie CJ, Strauss M and Krittanawong C: More than just teeth: How oral health can affect the heart. Am Heart J Plus 43: 100407, 2024.