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Oral health as a modifiable risk factor for cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality worldwide with a high socioeconomic burden. Increasing evidence supports a convincing connection with increased cardiovascular risk of periodontal diseases (PD), a group of widespread, debilitating, and costly dysbiotic relapsing-remitting inflammatory diseases of the tissues supporting the teeth. Herein, we ensembled the best available evidence on the connection between CVDs and PD to review the recently emerging concept of the latter as a non-traditional risk factor for CVDs. We focused on oral dysbiosis, inflammation-associated molecular and cellular mechanisms, and epigenetic changes as potential causative links between PD and CVDs. The available evidence on the effects of periodontal treatment on cardiovascular risk factors and diseases was also described.

Introduction

As strongly supported by increasing experimental and clinical studies, oral health plays a crucial role in general wellness. Although the pathophysiological mechanisms have not been fully explained, an increasing body of evidence accumulated over the last two decades indicate a close relationship between oral and cardiovascular diseases (CVDs) [1–4].

CVDs are a group of disorders of the heart and blood vessels representing the most common non-communicable diseases and the leading cause of death and disability worldwide, with dramatic socioeconomic impact [5]. Although genetic factors are pivotal for CVDs, behavioral risk factors also substantially shape their development and progression. The most important modifiable risk factors include unhealthy diet, physical inactivity, smoking, and alcohol use [6]. To date, it has been clarified that these conditions promote systemic inflammation that has a crucial role in CVDs development [7].

Periodontal disease (PD) is a chronic, progressive inflammatory disease of the structures supporting the teeth that ultimately leads to their loss. It is considered a multifactorial disease [8] where dysbiosis of the oral microbiome plays a key role [9]. In predisposed individuals, PD develops because of plaque accumulation that initially induces gingivitis, a reversible inflammation of the gums and soft tissues around the tooth. If left untreated, gingivitis progresses to periodontitis, an irreversible disruption of bone, cementum, and periodontal ligament, ultimately leading to the final stage of disease, characterized by tooth loss. As early as during disease onset, inflammatory mediators such as interleukin-1β, interleukin-6, tumor necrosis factor-α, and C-reactive protein become detectable in the bloodstream [10] (Fig. 1). PD carries a high socioeconomic burden, representing the first cause of masticatory inability due to teeth loss and, with more that 50% of people affected worldwide, the second most prevalent oral disease globally. Recently, evidence accumulated in support of an epidemiological association of this inflammatory disease of the mouth with a plenty of systemic health conditions, including CVDs [1]. In addition to sharing common denominators including advanced age, smoking habits, male sex, low physical activity, overweight/obesity, low socioeconomic status, and poor education [11,12], new evidence also indicates an independent association between PD and CVDs [13]. Direct and indirect mechanistic links have been proposed as the biological basis for the association between periodontal inflammation and CVDs. Direct pathways include the translocation of proinflammatory

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Abbreviations: AF, atrial fibrillation; CVD, cardiovascular disease; HF, heart failure; NSPT, non-surgical periodontal therapy; PD, periodontal disease; SPT, surgical periodontal therapy.

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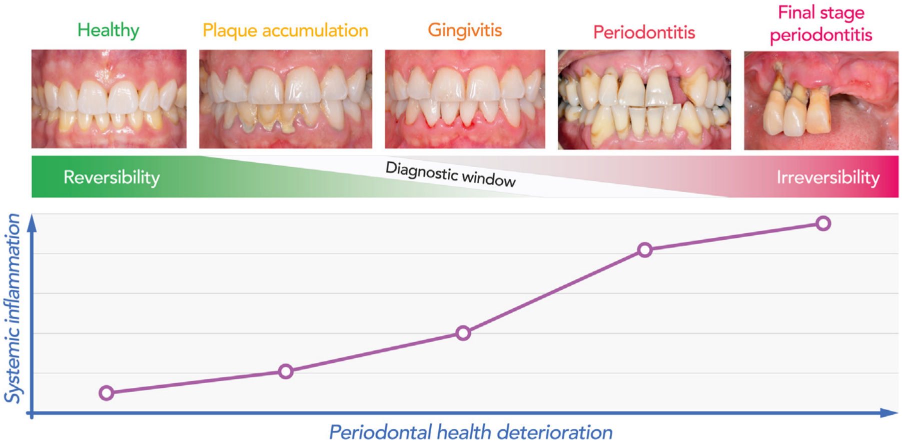

Fig. 1. Natural progression of periodontitis in predisposed individuals. Biofilm accumulation causes periodontal deterioration at various extent depending on both personal and professional oral care habits. Gingivitis is a reversible inflammation of the gums where alveolar bone, periodontal ligament, and alveolar cement are not damaged. Its progression causes periodontal pockets and the irreversible destruction of the periodontal structures, finally leading to tooth mobility and loss. Mechanistically, systemic inflammatory markers (i.e., CRP, IL-1β, IL-6, TNF-α) increase progressively with periodontal health deterioration, with impact on cardiovascular and general health.

bacteria from the oral cavity into the bloodstream and invasion of the cardiovascular system; indirect mechanisms involve the activation of systemic immune pathways causing and maintaining a chronic state of inflammation with possible nonspecific effects. As such, PD has been proposed as an emerging non-traditional modifiable risk factor for CVDs [10,12-15].

Through the present narrative review, we ensemble the literature evidence on the mechanisms leading to increased cardiovascular risk in patients with PD and raise the question of whether PD can be a modifiable risk factor for CVDs. Evidence is reported on the involvement of oral dysbiosis, molecular and cellular mechanisms associated with inflammation, and epigenetic changes as potential causal links between PD and CVDs. Finally, the currently available data on the effects of PD treatment on cardiovascular risk factors and diseases are also discussed.

Search methodology

We conducted a literature search for peer-reviewed published articles in the English language in the time range of January 2000 to January 2023 in Pubmed, Science Direct, and Web of Science databases. Gray literature (unpublished/noncommercial publications) was excluded. The medical evidence subject heading (MeSH) related to periodontal diseases or periodontitis was first combined with the operator 'AND' with the text words "cardiovascular diseases". In addition, numerous other keywords have been crossed, one at a time, with both "periodontal diseases" or "periodontitis" and "cardiovascular diseases", including oral microbiota; oral dysbiosis; inflammation; inflammatory biomarkers. Subsequently, a specific literature search was carried out for each paragraph developed in the review, combining appropriate keywords. A standard three-step search and selection strategy was applied. We searched through the identified databases using combinations of our search approaches. The first level of study selection involved screening the title and abstracts of potentially interesting articles. After removing duplicates, the second screening level involved a full-text evaluation of papers. Thirdly, the reference lists of included studies were also screened for additional manuscripts.

Association between PD and CVDs

Evidence has been reported regarding the relationship between PD and specific CVDs - i.e., heart failure (HF), with its different phenotypes, atrial fibrillation (AF), and atrial fibrosis. In particular, a recent study has investigated the relationship between periodontitis and HF using the Third National Health and Nutrition Examination Survey [16]. The results indicated that patients with moderate/severe periodontitis are at increased risk of HF. Indeed, the incidence in the group with moderate or severe periodontitis was 3-fold higher than the group with no or mild disease. In the Atherosclerosis Risk in Communities Study (ARIC), including 6707 participants with a median follow-up time of 13 years, periodontal status was associated with unfavorable changes in biomarkers of inflammation C-reactive protein and N-terminal brain natriuretic peptide as well as increased risk for both HF with preserved ejection fraction and HF with reduced ejection fraction [17]. On the other hand, a recent study has evaluated the association of periodontitis with different HF phenotypes: HF with preserved ejection fraction, HF with mildly reduced ejection fraction, and HF with reduced ejection fraction. The findings indicated that severe periodontitis was significantly associated with HF with mildly reduced ejection fraction, although no relevant associations were found with HF with preserved ejection fraction [18]. To explain their findings, the authors propose that by inducing systemic inflammation and vascular permeability, PD leads to endothelial dysfunction, which, in turn, can result in myocardial ischemia with direct myocardial injury, potentially accounting for the association of severe PD and HF with mildly reduced ejection fraction. A significant association between plaque accumulation and prevalent AF that was independent of age, sex, high-sensitivity CRP, body mass index, smoking, diabetes, and educational status was also reported, thus supporting the hypothesis that dental plaque and the associated acute inflammatory response may have an impact on the development of AF [19]. In addition, all the parameters of PD, including oral examination, the remaining number of teeth, bleeding on probing, periodontal probing depth, and periodontal inflamed surface area, were positively associated and correlated with atrial fibrosis histologically analyzed in resected left atrial appendages [20]. These findings strongly supported that periodontitis represents a modifiable risk factor for structural heart diseases.

Oral microbiome dysbiosis in PD and risk factors for CVDs

The oral microbiome is a complex community of microorganisms comprising bacteria, fungi, viruses, archaea and protozoa living in the oral cavity and dynamically interacting with the host [21]. Dysbiosis of the oral microbiota is a feature of PDs' initiation and progression [22,23]. In parallel, oral dysbiosis has increasingly been linked to CVDs [1,23-26]. Patients with periodontitis are exposed to bacteria and their products, which have access to the circulation directly through inflamed oral tissues and indirectly through the gastrointestinal tract, resulting in systemic immuno-inflammatory responses. Periodontitis is associated with persistent endotoxemia, which has been identified as a notable cardiometabolic risk factor [23]. Bacterial biomarkers of oral dysbiosis have been associated with an increased risk of subclinical atherosclerosis, prevalent and future coronary artery disease, and incident and recurrent stroke. The immunological response to periodontal bacterial was also found to be associated with blood pressure profile [25]. In addition, such response might also include the production of persistent, cross-reactive, proatherogenic antibodies against host-derived antigens [23,27].

The oralome, defined as the ensemble of the interactions between the host and local microbes [28], is second only to the gut microbiome in its abundance and diversity harboring over 700 species of bacteria [29]. Disruption of the healthy oral microbiome can cause oral diseases like periodontitis and dental caries. PD originates in response to a specific group of periodopathogens [30]; predominantly, Gram-negative anaerobes, such as *P. gingivalis, F. nucleatum, A. actinomycetemcomitans, T. forsythia, T. denticola* and *T. spirochetes* increase in the subgingival biofilm during the disease. Bacteria infiltrate tissues and create periodontal pockets that represent a microenvironment where the balance between microbes and immune response is disrupted through direct and indirect mechanisms [31]. The related inflammatory response is characterized by the local production of various pro-inflammatory mediators, including C-reactive protein, interleukin-1β, interleukin −6, tumor necrosis factor-α, matrix metalloproteinases, and interferon-gamma [10]. As a result of the increase in such mediators, the degree of destruction of periodontal tissues is accelerated. Periodontal pathogens contain numerous pathogen-associated molecular patterns, such as lipopolysaccharides, cytosine-phosphate-guanine dinucleotide, and peptidoglycan D, which initiate the inflammatory response of innate immunity depending on the recognition of pattern recognition receptors of host cells [32]. The immuno-inflammatory response and destruction of periodontal tissues will produce many damage-associated molecular patterns, which may further affect the progression of atherosclerotic CVD [33]. A recent review summarized the evidence of some representative pathogen-associated molecular patterns and damage-associated molecular patterns as a crucial molecular pathological mechanism bridging periodontitis and atherosclerosis [34]. These molecules and virulence factors of periodontal pathogens stimulate the corresponding Toll-Like Receptors, activate excessive innate immunity, and destroy periodontal tissue. The molecular patterns transfer chronic inflammatory signals from the oral cavity to cardiovascular tissues by releasing them into the blood or by means of ectopic bacterial colonization, thereby driving the activation of innate immunity in the vascular microenvironment and participating in the progression of atherosclerosis. Lipopolysaccharides induce foam cell formation and macrophages to modify native low-density lipoproteins, promotes monocyte chemotaxis and adhesion to vascular endothelial cells through Protein Kinase B and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, and can also induce the expression of angiotensin II and interleukin-6 in vascular endothelial cells, thus favoring endothelial dysfunction [35]. Thus, several pathogen-associated molecular patterns and damage-associated molecular patterns related to PD and the consequent activation of innate immunity could represent a possible bridge between PD and atherosclerosis [34]. Of note, PD-related pathogen-associated molecular patterns and damage-associated molecular patterns may also become new targets for treating patients with CVDs aggravated by PD.

During oral dysbiosis, the alteration of the entero-salivary nitrate-nitrite-nitric oxide pathway is another interesting mechanism behind the correlation between chronic periodontitis and CVDs [36]. Metabolic and cardiovascular homeostasis is supported by nitrite oxidase, a multifunctional signaling molecule representing a potent endogenous vasodilator that prevents the formation of vascular lesions in atherosclerosis. In addition to being synthesized by nitric oxide synthase, nitrite oxidase can also result from the bioconversion of dietary nitrate into nitrite by oral bacteria, through a process known as the NO_3^--NO_2^--NO reduction pathway. By reducing NO_3^--NO_2^-, some commensal oral bacteria can provide bioactive nitrite oxidase, essential for endothelial cell function and the regulation of arterial blood pressure [36,37]. Consequently, in conditions of oral dysbiosis, a reduction of bacteria capable of reducing oral nitrate and an increase in pathogenic bacteria could represent another possible link between periodontitis and CVDs.

Reduced bioavailability of nitrite oxidase by dysfunctional endothelium and the consequent impaired vasodilation is responsible for the pathogenesis of several CVDs, including atherosclerosis, hypertension, and coronary heart disease [38]. Thanks to the generation of nitrite oxidase, the entero-salivary nitrate cycle can indeed reduce blood pressure in both young and old subjects [39]. In fact, dietary supplementation of nitrates increases the number of denitrifying species such as *Neisseria flavescens* and *Rothia sp*., while dissimilatory nitrate reduction to ammonium organisms, such as *Veillonella* and *Prevotella,* decrease. These changes are associated with increased plasma levels of nitrites and reduced blood pressure in elderly individuals, as well as a significant improvement in vascular function in patients with hypercholesterolemia [39,40]. Overall, the available evidence suggests that the impact of oral microbiome on the NO_3^--NO_2^--NO pathway and the associated clinical outcomes would largely depend on which nitrate-reducing species and nitrate reduction pathways are predominant under specific conditions.

Inflammatory markers and association between PD and CVDs

Inflammation plays a fundamental role in the genesis, progression, and manifestation of CVDs [41] (Fig. 1). Numerous clinical studies have shown that inflammatory markers, such as the proinflammatory cytokines, reduce the expression of endothelial nitrite oxidase synthase, increase the endothelial synthesis of nicotinamide adenine dinucleotide phosphate oxidase, and promote the expression of endothelial cell adhesion molecules [42,43]. Proinflammatory cytokines are closely associated with CVD risk, and patients with alterations in these inflammatory parameters may be at increased risk even when low-density-lipoprotein levels are controlled [44]. Of note, an inverse association has been reported between the number of teeth and CVD mortality, with lower baseline tooth count being related with reduced CVD survival, and such relation appeared to be mediated by high C-reactive protein levels [45].

The central role of inflammation in the causal pathway of cardiovascular risk is confirmed by the results of the CANTOS study [46,47], in which treatment with a monoclonal antibody, canakinumab, an interleukin-1β antagonist, led to a significant reduction in cardiovascular events without any effect on low-density lipoprotein cholesterol. CANTOS also demonstrated that the extent of clinical benefit observed with canakinumab was proportional to the reduction in circulating C-reactive protein or interleukin-6. In addition to CANTOS, the Colchicine Cardiovascular Outcomes Trial (COLCOT) study evaluated the assumption of low-dose colchicine in patients after myocardial infarction [48]. Current evidence thus indicates that non-selective inhibition of inflammation significantly reduces CVD risk-related events [49,50].

Inflammatory markers that increase in both CVD and PD include white blood cells, C-reactive protein, fibrinogen, intercellular adhesion molecule 1, and pro-inflammatory cytokines. In addition, both diseases share similar risk factors, such as smoking, poor oral hygiene, diabetes mellitus, obesity, stress, and reduced physical activity. Studies based on blood pressure measurement and oral health conditions found an increased risk of hypertension associated with PD [51–53]. In a joint report of the Italian Society of Hypertension and the Italian Society of Periodontology and Implantology, the growing evidence of a positive linear association between the two conditions was reported as being conditioned by periodontitis severity and to strongly influence the systolic component of BP [54].

Further confirmation of the oral-cardiovascular health connection comes from the preliminary results of a recent pilot study, showing that PD patients with higher amounts of some bacterial species, i.e., *A. actynomicetemcomitans, P. intermedia*, and *F. nucleatum*, appeared to be at increased risk of high blood pressure than healthy controls [55]. Analyses of arterial plaques from patients with CVDs have identified bacterial lipids and whole bacteria derived from a dysbiotic oralome, including *P. gingivalis* [56,57].

Compared to healthy controls, patients with severe periodontitis and elevated levels of proinflammatory mediators, such as interleukin-1, interleukin-6, C-reactive protein, and fibrinogen, also had increased neutrophils count in the peripheral blood [58,59]. Neutrophils are attracted to tissues by a variety of chemoattractants, including leukotrienes A4 and B4, which play a role also in atherosclerosis, as symptomatic human atherosclerotic plaques express 5-lipoxygenase, 5-LO-activating protein, and leukotrienes A4 hydrolase [59]. Many diseases associated with oral health disturbances, including CVDs, show alterations in the composition of the blood microbiota and circulating neutrophils phenotypes [59]. In fact, while in the oral cavity, oral microbes and their products can manipulate the activity of neutrophils that can later enter the peripheral bloodstream, thereby exerting an indirect impact on systemic health outcomes. Endotoxin from oral microbes may vary depending on bacterial communities and oral health status, thereby differentially affecting cellular lipopolysaccharides tolerance mechanisms that contribute to the neutrophil phenotype typical of periodontitis [59]. Microorganisms and their products, including lipopolysaccharides, but also proinflammatory cytokines as well as the interaction with activated platelets or endothelial cells can trigger the formation of neutrophil extracellular traps, consisting of a DNA scaffold enriched with antimicrobial peptides that contribute to tissue damage in periodontitis [59]. In parallel, neutrophil extracellular traps were found to contribute to atherosclerosis and thrombosis [59].

The PD-associated events leading to systemic endothelial dysfunction

The role of periodontal inflammation in vascular pathology has been consistently highlighted, even if the underlying biomolecular mechanisms have not been fully elucidated so far [60]. Vascular endothelial cells, which play a crucial role in the maintenance of vascular wall integrity and whose functional impairment is critical for CVDs, can secrete various factors able to regulate cell migration and adhesion, vascular thrombosis, smooth muscle cell proliferation and migration, and vessel wall inflammation [61]. When responding to adverse stimuli, the phenotype of Vascular endothelial cells changes to an activated one, i.e., endothelial dysfunction [61]. Endothelial dysfunction promotes the occurrence and progression of vascular and metabolic diseases, such as atherosclerosis, hypercholesterolemia, diabetes, and hypertension. Vascular inflammation involves signaling cascades triggered by endothelial mediators and leading to increased production of cytokines, chemokines, and cell adhesion molecules that direct the recruitment of inflammatory cells [61]. The pathological state of dysfunctional endothelium as an early change occurring before morphologic alterations in the blood vessel wall become detectable is thought to be an independent predictor of the risk and prognosis of CVDs [61].

Many epidemiological studies and clinical evidence have confirmed the correlation between periodontitis and endothelial dysfunction [62]. In a large longitudinal population-based study, periodontitis has been significantly associated with impaired flow-mediated dilation [63]. Moreover, in an updated pilot study, increased tooth mobility has been correlated with endothelial dysfunction, assessed by reactive hyperemia-peripheral arterial tonometry, independent on age and glycosylated hemoglobin [64]. A decrease in functional capillary density, capillary diameters, red blood cell velocity at rest, endothelium-independent vasodilatation, and post-ischemic peak flow was described in patients with periodontitis [62]. As an example, periodontal infection by *P. gingivalis* can modulate the production of inflammatory cytokines, myeloperoxidase, matrix metalloproteinase-2/tissue inhibitor of metalloproteinases 2 complex, and chemokines, such as monocyte chemotactic protein-1, interleukin-8, and CX3C chemokine ligand 1 in vascular endothelial cells [62]. Consequently, the release of inflammatory factors amplifies the migration and adhesion of leukocytes and monocytes to the intimal layer of blood vessels. These immune cells can also transport periodontal bacteria into the vessel wall and secrete more inflammatory factors at the same time, ultimately exacerbating endothelial inflammation [62]. Periodontitis was also associated with higher plasma fibrinogen levels, which can further stimulate the production of monocyte chemotactic protein-1, interleukin-6, interleukin-8, tumor necrosis factor-α, matrix metalloproteinase-1, and matrix metalloproteinase-9, thereby aggravating endothelial inflammation [65].

In addition to the above, an increased endothelial synthesis of reactive oxidative stress and reduced nitric oxide bioavailability were found to occur during periodontitis [66]. Reactive oxidative stress is an essential factor in causing endothelial dysfunction. Excessive reactive oxidative stress accumulation interferes with the nitric oxide signaling pathway, thereby reducing nitric oxide bioavailability, leading to endothelial dysfunction through reducing endothelium-dependent relaxation [66]. Increased mitochondrial reactive oxidative stress production has been observed in endothelial cells infected with *P. gingivalis* [67]. Thus, salivary nitric oxide levels are confirmed as crucial linkage between periodontitis and endothelial dysfunction [68].

Epigenetics in the relationship between PD and cardiovascular risk

The significant role of epigenetics in the relationship between PD and cardiovascular risk constitutes emerging evidence [69]. Oral epithelial cells are the first-line defense against pathogens, and the presence of bacteria and their products can induce alterations in their epigenome that in turn affects inflammatory cells dynamic and functioning by inducing changes in signaling pathways and gene expression. Epigenetic mechanisms and modifications involve environmental factors that modify gene expression without any change in the underlying DNA sequence. As a result, the changes are not encoded in DNA molecules. Still, through subsequent chemical alterations, epigenetics determines a complete remodeling of chromatin, resulting in gene expression activation or suppression. Environmental factors, including lifestyle, exposure to heavy metals and radiation, smoking, and infectious agents, are key drivers of epigenetic dynamics. Crucial epigenetic mechanisms concern DNA methylation, post-transcriptional modifications of histones, which also affect chromatin structure, and gene expression modulation by non-coding RNA (e.g., by means of micro-RNA,). To make things more complex, single nucleotide polymorphisms can interact with epigenetic mechanisms in orienting genes ex-

Table 1
Evidence in favor and against the benefit of periodontal therapy on cardiovascular risk markers.

Year	Aim	Study design and n. patients	Outcome and follow-up	References
2003	Effect of PD therapy on CVD risk-associated inflammatory markers.	RCT (n. 39 patients)	NSPT didn't significantly influence levels of any of the systemic markers (3-month follow-up).	[82]
2005	Effect of PD therapy on CVD risk factors in patients with severe PD.	Clinical trial (n. 30 patients)	NSPT + systemic antibiotic therapy improved flow mediated dilatation and decreased CRP concentrations. No changes in BP measures and endothelium-independent nitro-induced vasodilation (3-month follow-up).	[83]
2006	Effect of PD therapy on endothelial function.	Pilot trial (n. 22 patients)	NSPT resulted in significant improvements in periodontal pocketing, flow mediated dilatation, and serum IL-6, as well as a trend toward reduction in serum CRP. No significant changes in nitroglycerin-mediated dilation or in cholesterol levels (1-month follow-up).	[84]
2006	Effect of PD therapy on CVD-associated inflammatory markers, lipid profiles and BP.	RCT (n. 40 patients)	NSPT+ local antibiotic therapy reduced systemic inflammatory markers (i.e., IL-6 and CRP) and systolic BP, and improved lipid profiles with subsequent changes in cardiovascular risk (6-month follow-up).	[85]
2007	Effect of PD therapy on endothelial function.	RCT (n. 120 patients)	NSPT+ local antibiotic therapy treatment was associated with improvement in endothelial function (6-month follow-up).	[86]
2008	Effect of PD therapy on CVD-risk.	Periodontitis and Vascular Events (PAVE) pilot study (n. 600 patients)	NSPT to individuals with heart disease resulted in a similar pattern of adverse events as seen in the community care group, which also received some treatment (18-month follow-up)	[87]
2008	Effect on PD therapy on endothelial function and inflammatory markers.	RCT (n.64 patients)	NSPT + systemic antibiotic therapy improved ED and significantly decreased serum concentrations of IL-6 and CRP (24-week follow-up)	[88]
2009	Effect of PD therapy on CHD risk markers.	RCT (n. 101 patients)	NSPT reduced inflammatory markers (IL-6, CRP), and improved flow mediated dilatation in patients with chronic kidney disease and PD, although reported not-statistically significant effects on BP (24-week follow-up).	[89]
2009	Effect of PD therapy on systemic levels of hs-CRP.	RCT (n. 303 patients)	NSPT did not influence CRP levels (6-month follow-up)	[90]
2009	Effect of PD therapy on cardiovascular markers.	RCTs (n. 22 patients)	NSPT was effective in reducing the plasma levels of IL-6, CRP, and fibrinogen in hypertensive patients (3-month follow-up).	[91]
2010	Effect of PD therapy on ED and inflammatory markers.	RCT (n. 50 patients)	NSPT did not have significant effects on ED and systemic levels of CRP (3-month follow-up)	[92]
2010	Effect of initial PD therapy on systemic markers of inflammation and cardiovascular risk.	RCT (n. 125 patients)	NSPT reduced the levels of CRP, fibrinogen, PAI-1, platelets, neutrophils, and total white blood cells but only the difference in fibrinogen levels was statistically significant when compared with the control group (3-month follow-up).	[93]
2011	Effect of PD therapy on CVD-risk associated	RCT (n. 165 patients)	NSPT+ systemic antibiotic therapy reduced CRP and fibrinogen levels in patients with periodontal and metabolic diseases (12-month follow-up).	[94]
2012	Effect of PD therapy on CHD risk markers.	RCT (n. 246 patients)	NSPT led to decrease in CPR, fibrinogen, and white blood cell levels (2-month follow-up).	[95]
2013	Effect of PD therapy on cardiovascular markers and CVD-risk associated.	Interventional prospective cohort pilot study (n. 26 patients)	NSPT significantly reduced levels of CRP, IL-6, fibrinogen, BP, left ventricular mass, and arterial stiffness, lowering cardiovascular risk in refractory hypertensive patients (6-month follow-up).	[96]
2013	Effect of PD therapy on inflammatory markers and lipid profile.	RCT (n. 40 patients)	NSPT led to improvement in TNF-α, IL-6, CRP and LDL values in stable chronic kidney disease patients (3-month follow-up)	[97]
2013	Effect of PD therapy on inflammatory markers in children with congenital heart disease.	RCT (n. 33 patients)	NSPT were effective in reducing fibrinogen, and IL-6 (6-month follow-up).	[98]
2014	Effect of PD therapy on CVD risk-associated inflammatory markers and lipid profile.	RCT (n. 66 patients)	NSPT was effective in reducing the levels of systemic inflammation markers (i.e., CRP, ESR) and improved the lipid profile (6-month follow-up).	[99]
2015	Effect of PD therapy on CRP levels.	Cross-sectional study (n. participants 150)	SPT results in significant decrease in CRP levels (3-month follow-up)	[100]
2015	Effect of short-term PD therapy on inflammatory markers.	RCT (n. 38 patients)	NSPT results in significant increase of CRP, IL-6, and TNF-α levels after 24 h.	[101]
2015	Effect of PD therapy on BP and lipid profile.	RCT (n. 55 patients)	NSPT reduced systolic BP and VLDL values in chronic kidney disease patients (6-month follow-up)	[102]
2016	Effect of PD therapy on CVD risk markers.	Pilot intervention study (n. 109 patients)	NSPT + systemic antibiotic therapy induced a significantly reduction in systolic BP (6-month follow-up)	[103]
2016	Effect of PD therapy on BP and lipid profile in patients with metabolic syndrome.	Case-control study (n. 50 patients)	NSPT induced a reduction of some inflammatory markers (i.e., CRP, IL-6). No change of BP and Hb-A1c (6-month follow-up)	[104]
2017	Effect of PD therapy on CVD risk markers.	RCT (n. 44 patients)	NSPT induced a reduction in CRP (2-month follow-up)	[105]

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Table 1 (*continued*)

Year	Aim	Study design and n. patients	Outcome and follow-up	References
2017	Effect of PD therapy on platelet reactivity and number.	Clinical trial (n. 25 patients)	NSPT reduced the expression of platelet marker activation (P-selectin, CD63 expression, and PAC-1) and platelet count.	[106]
2017	Effect of PD therapy on BP and endothelial function.	RCT (n. 95 patients)	NSPT without any antihypertensive medication therapy is an effective means to lower levels of BP and EMPs in patients with prehypertension (6-month follow-up).	[107]
2018	Effect of PD therapy on vascular health parameters.	RCT (n. 55 patients)	NSPT+ systemic antibiotic therapy led to a reduction of PWV, and an increase of PPao. No change was registered in AIx, and RRsys (12-month follow-up)	[108]
2018	Effect of short-term PD therapy on inflammatory markers.	RCT (n. 31 patients)	NSPT led to an increase of proinflammatory cytokines after 24 h.	[109]
2019	Effect of PD therapy on endothelial function.	RCT (N. 69 patients)	NSPT led to a reduction of sVCAM-1, sICAM-1, and P-selectin (3-month follow-up)	[110]
2019	Effect of PD therapy on inflammatory markers.	RCT (n. 101 patients)	NSPT improved BP, endothelial function, and inflammatory markers (INF-γ, IL-6), previously implicated in hypertension (2-month follow-up).	[111]
2019	Effect of PD therapy on inflammatory markers.	RCT (n. 82 patients)	NSPT lowered levels of CRP, IL-6 and IL-8 in cardiovascular patients with high CRP levels (3-month follow-up).	[112]
2019	Effect of PD therapy on inflammatory markers, and lipid profile.	RCT (n. 30 patients)	NSPT+SPT significantly improved serum lipid profile and reduced CRP levels (3-month follow-up)	[113]

pression. Epigenetic modifications and micro-RNA play a decisive role in the pathogenesis of CVDs, are involved in the progression of atherosclerosis, and are rather impactful in the development and vulnerability of atherosclerotic plaque [70]. A recent review summarized the main pathways through which epigenetic mechanisms occur [71]. The initial pathway concerns the effect of external environmental factors on human cells and can cause changes at the DNA level. Next, the non-coding RNAs, the epigenetic initiator, and the epigenetic maintainer are responsible for inheritance of such changes across generations of cells. During periodontitis, the presence of chronic inflammation, combined with the constant presence of Gram-negative bacteria due to poor oral hygiene, can promote DNA methylation patterns and histone protein modification [72]. In turn, epigenetic mechanisms regulate the effect of cytokines, such as interleukin-1 and interleukin-6, protagonists in the progression of periodontitis. For their role in inducing epigenetic modifications of relevance in disease pathogenesis, environmental factors are crucial and can influence the individual predisposition to develop CVD risk factors [73].

Can CVDs be prevented or controlled through treatment of PD?

The effects of periodontal treatment on several markers of systemic inflammation, cardiovascular health parameters, and metabolic control are encouraging, strongly supporting the causal association of PD with CVDs [74–76]. A growing number of clinical and translational studies suggest that, by improving oral microbiome composition, mechanical biofilm removal with periodontal treatment leads to a reduced burden of disease-associated bacteria and decreases inflammatory markers [77,78]. The results of a recent nationwide, real-world, opportunistic survey by our group indicate that home oral hygiene habits, specifically tooth brushing frequency and modality, are inversely associated with blood pressure profile, independent of relevant confounders, thus providing the first evidence of an association between oral hygiene practices and blood pressure [79]. Of note, in a nationwide general population based longitudinal study including 161,286 participants, oral hygiene expressed in terms of frequent toothbrushing, and professional dental cleaning was reported to reduce the risk of AF and HF [80]. Similarly, a study of 247,696 healthy adults ($\geq$40 years) without baseline CVDs, undergoing an oral health screening program showed a 9% reduction in the risk of fatal/nonfatal cardiovascular events, including myocardial infarction, stroke, HF, and cardiovascular death, for every unitary increase in daily toothbrushing frequency, and even more so if regular professional oral hygiene was reported [77]. Based on the results of a longitudinal study on 256 patients with a confirmed diagnosis of coronary artery disease (median follow-up of 18.8 years), a higher baseline tooth count was associated with increased CVD survival, and better oral hygiene performance was associated with significant survival benefits against CVD mortality [81].

On the other hand, the evidence of the effect of intensive PD therapy (oral hygiene education, scaling, and root planning) in reducing CVD risk, even if encouraging, is still controversial. To give a broader picture of the available results from the clinical trials, Table 1 shows the evidence in favor and against the efficacy of surgical or non-surgical periodontal treatment (SPT or NSPT, respectively) in terms of cardiovascular protection. First of all, limitations of the available trials include relatively small sample size, which may affect the reproducibility of the results, and the short observational period (follow-up mostly lower than 12 months). In addition, most trials used surrogate outcomes, which could not reflect a real effect on major adverse cardiovascular events. Prospective studies and further trials with larger sample sizes and extended observation periods are required to evaluate the benefits of reducing inflammatory markers to decrease global cardiovascular risk.

Conclusions and future directions

The crucial role of inflammation in CVDs and the growing evidence relating PD with cardiovascular risk-associated biomolecular events has led to identifying PD as an emerging modifiable non-traditional risk factor in the development and progression of CVDs. Thanks to several experimental, clinical, and translational studies, the framework of the mechanisms underlying the causal association between PD and CVDs is being enriched with new elements of great interest as potential protagonists in the main events associated with cardiovascular risk, including oral microbiome dysbiosis, inflammatory pathways, pathogen-associated molecular patterns and damage-associated molecular patterns, pattern recognition receptors, entero-salivary nitrate-nitrite-nitric oxide pathway, endothelial dysfunction, and epigenetic modifications. The resulting picture is highly complex and intricate. From a diagnostic point of view, it may be helpful to define a suitable panel of

PD-associated salivary or blood biomarkers that correlate with the main parameters linked to cardiovascular functions.

As the relationship between PD and CVDs is strongly supported by evidence, it is rational to explore whether periodontal treatment can contribute to the management or prevention of the occurrence or recurrence of CVDs. Even though randomized controlled trials are still too few to draw definitive conclusions, the results of many studies aimed to evaluate the effect of periodontal therapy on cardiovascular conditions are encouraging and sustain the causal association with CVDs. With an estimated extension of the inflamed area during active disease that equals the palm of one's hand, achieving control of gums inflammation might represent a biologically plausible complementary approach to systemic wellbeing. Indeed, recent interventional and mechanistic evidence highlights a potential benefit of periodontal therapy on cardiovascular health that is at least in part mediated by its effects on periodontal microbiome and low-grade systemic inflammation. In this perspective, periodontal medicine, currently recognized as a novel discipline interacting with other health professions in a multidisciplinary/interdisciplinary context, will be able to appropriately address PD-associated systemic diseases by implementing periodontal therapies. Indeed, controlling the overall inflammation status by means of a good periodontal maintenance program could prevent or control the progression of CVDs in PD patients. As recently suggested [3], this model will allow not only the prevention of many oral and systemic diseases of epidemiological importance, but also promote health and healthy lifestyles in the population. So, given the importance of oral health for systemic wellbeing and the high prevalence of oral diseases, in the next future it will be necessary to provide evidence that supports the need to integrate oral health care within health promotion strategies for oral and general wellness.

Ethical statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that all authors are responsible for the content and have read and approved the manuscript; and that the manuscript conforms to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published in Annals in Internal Medicine

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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