Current Problems in Cardiology 49 (2024) 102699

Contents lists available at ScienceDirect

Current Problems in Cardiology

journal homepage: www.elsevier.com/locate/cpcardiol

Invited Review Article

Could the periodontal therapy improve the cardiologic patient health? A narrative review

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ARTICLE INFO

Keywords:
Periodontitis
Cardiovascular disease
Inflammation
Peripheral artery disease
Coronary artery disease
Endocarditis
Hypertension: Atrial fibrillation
Therapy
Prevention

ABSTRACT

Background: Cardiovascular diseases (CVD) is the major cause of mortality globally, with increasing evidence suggesting a link between periodontitis, and CVD. This study aims to explore the association between periodontitis and CVD, and the impact of periodontal therapy on cardiovascular health.
Methods: This review synthesized findings from preclinical and clinical studies, without publication year restrictions, examining periodontitis and CVD through various lenses. Scientific databases were inspected with keywords related to periodontitis and CVD.
Results: The review identifies a substantial association between periodontitis and an increased risk of several CVD, supported by both epidemiological and interventional studies. Results suggest the complexity of the relationship, influenced by factors like the severity of periodontitis and the presence of other systemic conditions. Clinical data indicates that periodontal therapy, particularly non-surgical periodontal therapy, may reduce systemic inflammatory markers and thus may play a role in the primary and secondary prevention of CVD events, highlighting the potential of periodontal therapy to not only maintain oral health but also to modulate cardiovascular risk factors.
Conclusions: Current evidence supports a significant association between periodontitis and increased cardiovascular risk, promoting integrated healthcare approaches that consider oral health as a key-component of cardiovascular care and wellbeing.

Introduction

The evaluation of the patient's medical history represents a fundamental step of the health treatment. A compromised healthy state quite often conditions the dental treatment plan and, conversely, the dental treatment plan taking into account the systemic medical status could result in an advantage both from a dental point and systemic point of view.[1–4]

Cardiovascular disease (CVD) leads the ranking of causes of death[5] CVDs have caused 17.9 million deaths worldwide (one-third-of global mortality) and overall 45 % of mortality induced by non-communicable diseases (NCD).[6,7] CVD are responsible of over 33.9

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https://doi.org/10.1016/j.cpcardiol.2024.102699

Available online 7 June 2024

million deaths in Europe, the 45 % of the total. By comparison cancer accounts for just 2 millions of deaths in Europe (European Cardiovascular Disease Statistics 2017). The global death rate for CVD between 1990 and 2013 increased by 41 % despite the decrease in age specific death. This mortality increase seemed to be due by a share of 55 % increase to the aging of population and just by a share of 25 % increase to population growth.[8]

As healthcare improves and life expectancy increases, medicine doctors and dentists will encounter more and more elderly and systemically compromised patients.

Therefore, dentists will increasingly have to treating cardiovascular patients, planning their therapies considering CVDs as prevention of CVD events, also improving the patients' prognosis.

Cardiovascular disease (CVD) covers a wide array of disorders (including diseases of the cardiac muscle and the vascular system supplying the heart, brain and other vital organs), such as sub-clinical CVD, coronary artery disease, cerebrovascular disease and risk of stroke, atrial fibrillation, heart failure (HF) peripheral artery disease (PAD), and other CVDs or conditions.[9–11]

In the past two decades, several studies have showed that periodontitis could increase the risk of CVD. However, various reports denied this association[12,13] but probably it was due to the lack of evidence, we need to study more about this link. Thus, the purpose of this study is to investigate the association between periodontitis and CVD and the effects of the treatment of periodontitis on cardiovascular health.

Methods

This narrative review is based on preclinical and clinical studies in English without restrictions regarding year of publication. The review focused on the following questions:

(i) What is the burden of periodontitis and CVD?
(ii) What could be the common role of inflammation in periodontitis and CVD pathogenesis?
(iii) What is the relationship between periodontitis and CVD?
(iv) What is the therapeutic effect of periodontal therapy (non-surgical periodontal therapy, in particular) in primary and secondary CVD prevention?

The electronic databases Medline (via PubMed), Scopus, and Web of Science were searched for eligible studies in the field of periodontology, cardiology, and immunology. The main search terms were 'periodontal therapy, ' 'periodontitis, ' 'CVD (divided by topics), ' 'primary" and "secondary prevention' and 'inflammation.'

Subsequently, the title and abstract of obtained articles were manually screened for relevance to the research criteria. The inclusion criteria consisted of the following: (i) full text original studies; (ii) full text original studies concerning all at once or, at least, a couple of

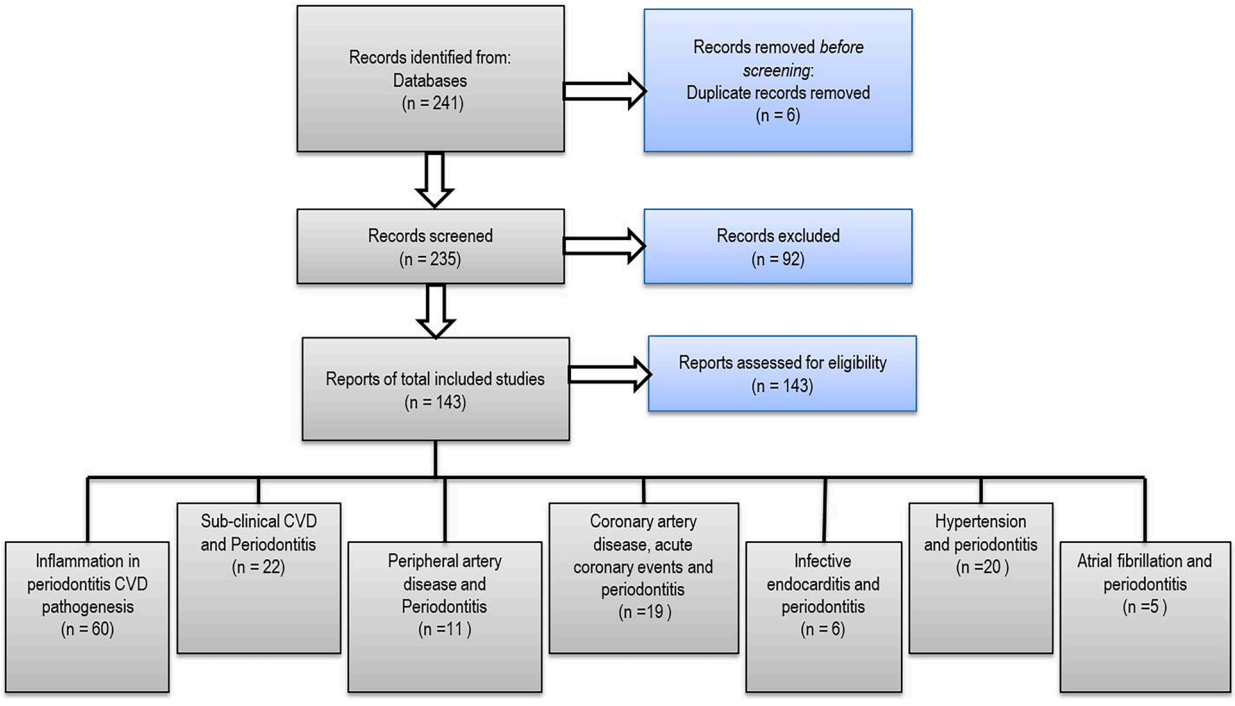

Fig. 1. Flow-diagram of research strategy.

the main search terms research; (iii) articles demonstrating the clinical effect(s) of periodontal therapy on CVD (preferably studies with an extended time follow-up, a large sample size). Fig. 1 shows the literature selection, and bibliography used in correlation to the several CVD.

The references contained in original articles and review articles were also searched for possible inclusion. No further inclusion criteria were applied.

Results and discussion

The burden of periodontitis

Periodontitis is a chronic inflammatory disease that is triggered by bacterial microorganisms and involves a severe chronic inflammation that causes the destruction of the tooth-supporting apparatus and can lead to tooth loss (Fig. 2). It can also lead to systemic health problems (Fig. 3) (EFP,[14–18]).

Periodontitis causes periodontal defects that are not spontaneously reversible and, causes tooth loss, if untreated. Furthermore, periodontitis is associated with several systemic diseases such as CVD, nutritional and metabolic diseases, immune system diseases, skin and connective system diseases, urogenital diseases and pregnancy complications.[15,19–23]

Periodontitis, reumathoid arthritis (RA), diabetes, CVD and the other chronical diseases most likely recognize a substantive pathophysiologic role in the alteration of inflammatory, immune control and in the oxidative stress management, and in the transition from an acute inflammatory response to a chronic inflammatory disease (Figs. 3 & 4).[20–25]

Anyway, pro-inflammatory mediators could lead to bone resorption, periodontal attachment loss, bone ridge resorption, and hinder bone and soft tissue regeneration that are characteristic feature of periodontitis (Fig. 5).[26–29]

Kassebaum et al.[30] reported that severe periodontitis was the sixth most prevalent pathologic condition in the world. The age-standardized incidence of severe periodontitis in 2010 was 701 cases per 100, 000 person-years, and periodontitis affected 10.8 % of the world population, corresponding to 743 million people worldwide.

The national health and nutrition examination survey (NHANES) showed that in 2009 through 2010, the total prevalence of periodontitis in adults aged 30 years and older was 47.2 % (representing about 64.7 million US adults), and 64 % of adults aged 64 years old and older.[28] Besides, in the update study, 2009 through 2012, 8.9 % of US adults 30 years and older had severe periodontitis.[31] The economic burden of dental diseases was $442B, of that $298B was the amount attributable too direct treatment expense, and $144B to indirect expense in terms of productivity losses. About the 37.5 % of the indirect costs ($53, 986.91B) was attributable to periodontitis.[32] Considering data from the Global Burden of Disease Study 1990-2010, information on disability-adjusted life years (DALYs) by country highlighted that oral conditions remained highly prevalent in 2010 and collectively affected 3.9 billion people worldwide. In particular, the prevalence and burden measured by DALYs associated with severe periodontitis showed an increasing significant trend.[30] Considering the increase in the average age, and continue growing of the world population, it is likely that these numbers continue increasing. However, aging alone do not lead to pathological loss of periodontal attachment in healthy elderly people.[33]

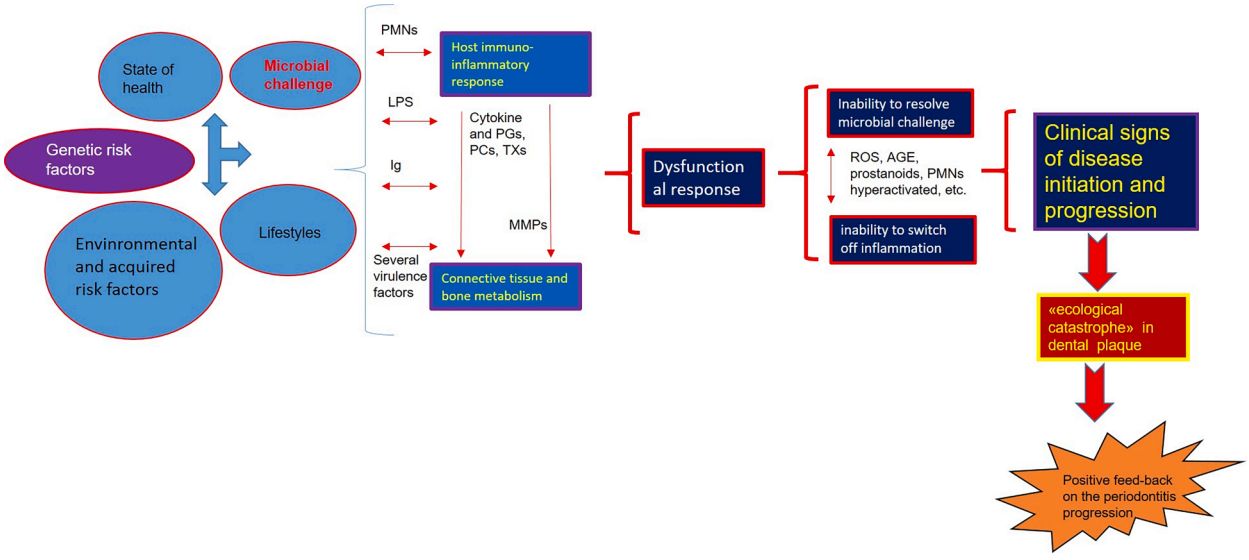

Fig. 2. Pathogenesis of periodontitis.
Legend: ROS=reactive oxygen species; PGs = Prostaglandins; PCs=prostacyclins; TXs=thromboxanes; MMPs=Matrix metalloproteinases; LPS=lipopolysaccharides; Ig=immunoglobulins; AGE=advanced glycation end-product; PMNs=polymorphonuclear neutrophils.

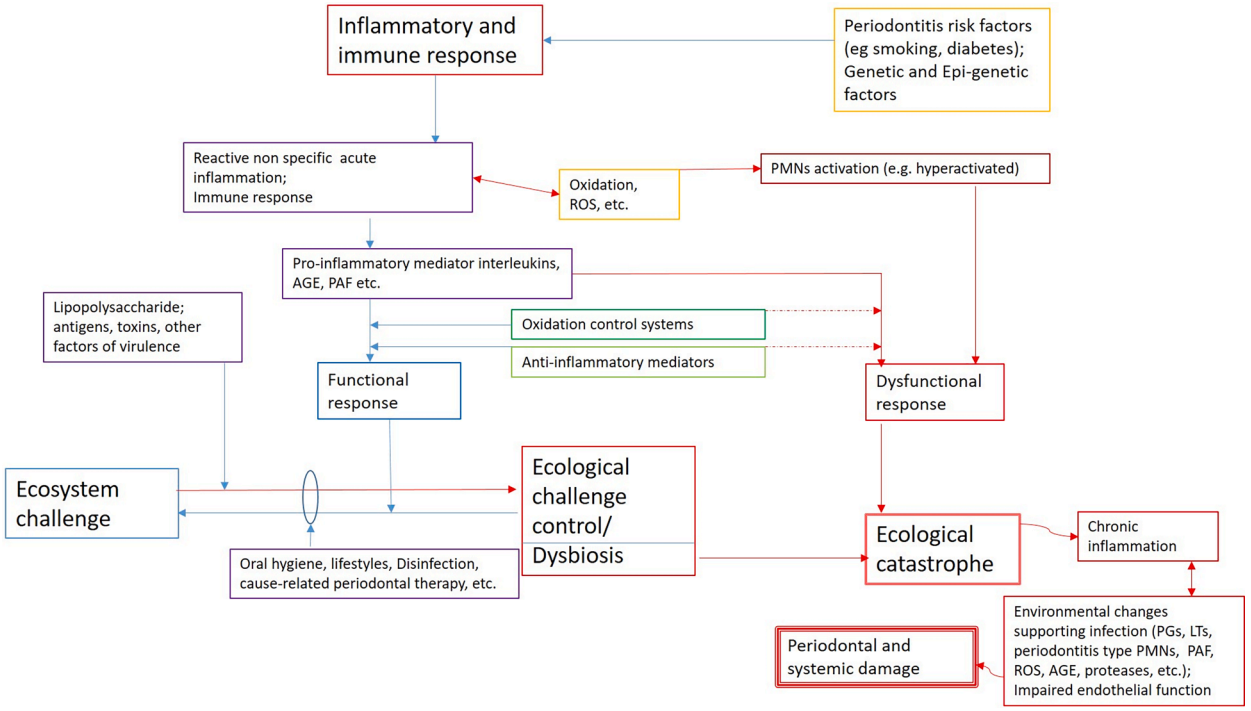

Fig. 3. Pathogenesis of periodontitis and oral and systemic damages.
Legend: ROS=reactive oxygen species; PG = Prostaglandins; PAF = Platelet activating factor; AGE = advanced glycation end-product; LTs = Leukotrienes; PMNs = polymorphonuclear neutrophils.

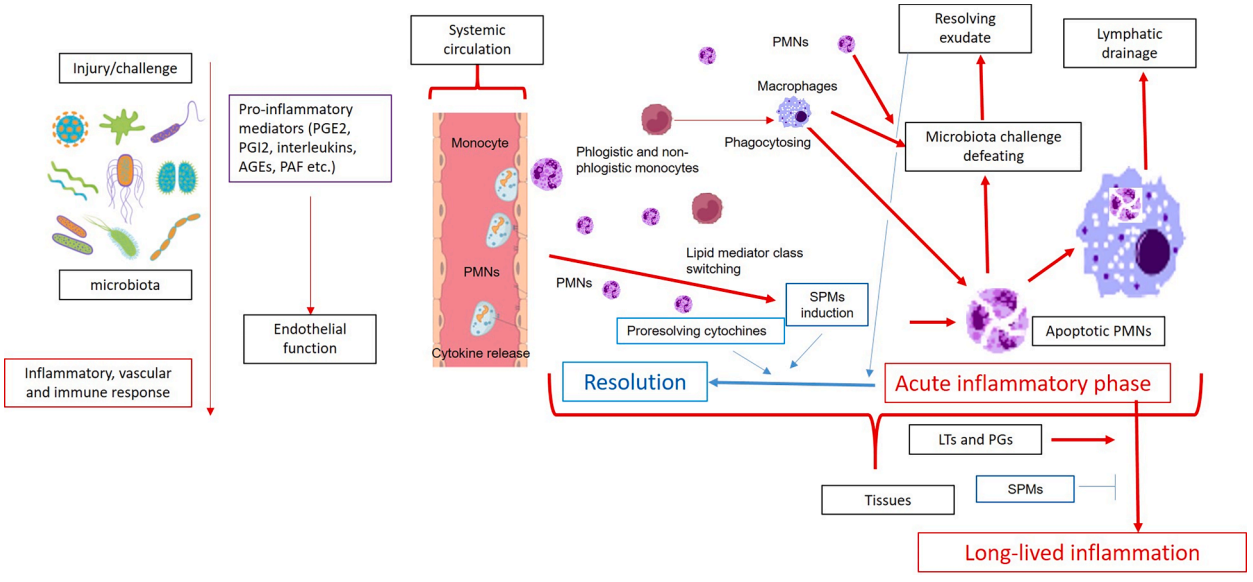

Fig. 4. The acute inflammatory pathway and its possible resolution.
Legend: SPMs = Specialized Proresolving Mediators; PG = Prostaglandins; PAF = Platelet activating factor; AGEs = advanced glycation end-product; LTs = Leukotrienes; PMNs = polymorphonuclear neutrophils.

The association between periodontitis and CVDs

In a recent systematic mapping of registered trial, Monsarrat et al.[21] found 56 systemic conditions which were hypothesized to be linked with periodontal diseases (nearly 2 % of the diseases indexed in MeSH vocabulary). Oral health seems to play a role on

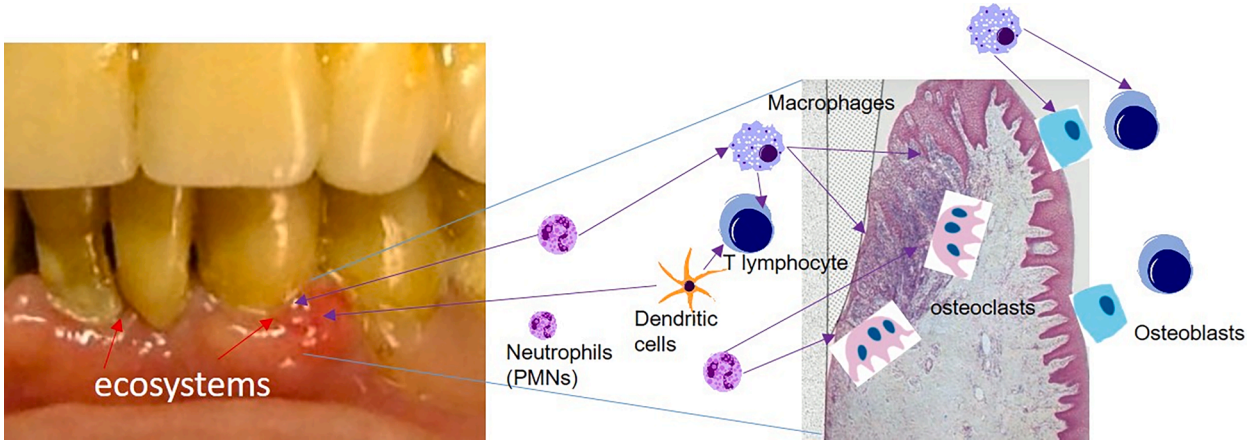

Fig. 5. Host immune microenvironmental cell regulation in periodontitis. The periodontal soft and hard tissues are remodeling with the involvement of immune cells, including a large number of neutrophils, macrophages, dendritic cells, T cells and host stem cells.

atherosclerosis and subsequent CVDs.[19]

Periodontitis cases show higher tendency for coronary heart disease, cerebrovascular disease and cardiovascular mortality,[34] besides, subjects diagnosed with periodontitis show higher tendency for coronary heart disease, cerebrovascular disease and cardiovascular mortality independent of known confounders.[35]

A large number of these studies were carried out on periodontal intervention to improve (or prevent) systemic conditions or on better understanding the links between oral and overall health. Accordingly, observational studies were performed to investigate a pathogenic link between periodontal disease and systemic health (Fig. 1). The idea that periodontal treatment could extend beyond merely preserving natural teeth to also preventing adverse effects on overall health quickly gained significant relevance within both professional and academic communities.

Several pathological pathways were considered to explain relationships between systemic conditions and oral diseases[36–38] and, in particular, some reasons could serve as rationale for the association of periodontitis and CVD: first, the pathophysiological way of both CVD and periodontitis is largely represented by systemic and local inflammation.[14,15,39–41] The pathogenesis of periodontitis takes place through three essential components, the presence of a pathogenic ecosystem, the host acute inflammatory and immune reaction and the inefficiency of these reactions to resolve the infection, becoming, in turn, a causal part of the self-feeding cycle of tissue damage (Figs. 3 & 4).

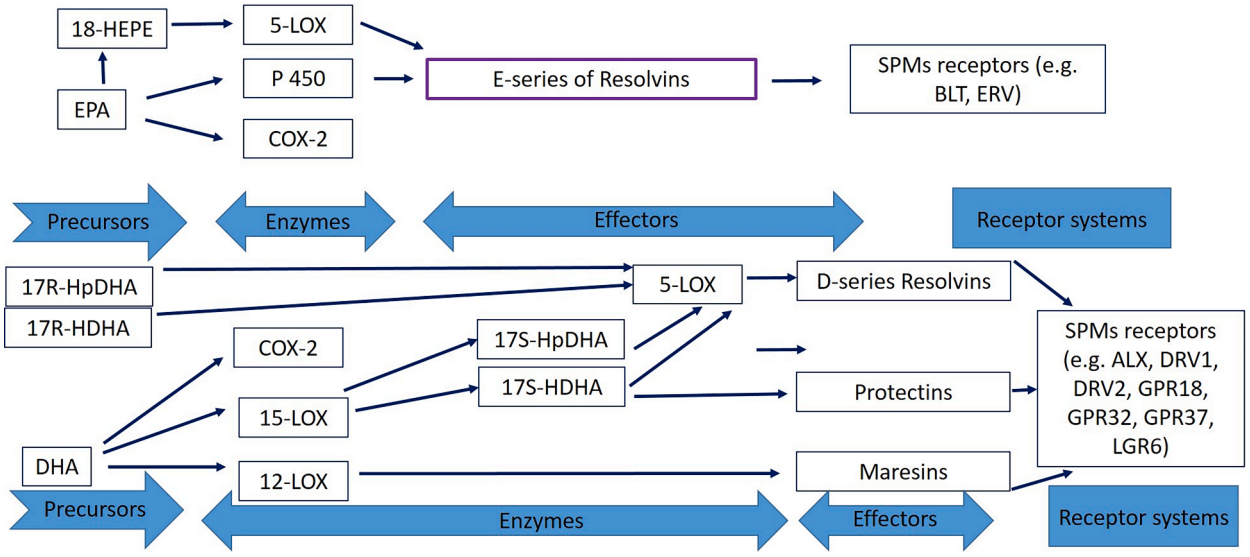

Fig. 6. Specialized proresolving mediators (SPMs).
Legend: 5-LOX = 5- lipoxygenase; P450= cytocrome P 450; 18-HEPE=18-hydroxyeicosapentaenoic acid; COX = cyclooxygenase; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; 17R-HpDHA = 17R-hydroperoxy-docosahexaenoic acid; 17R-HDHA = 17R-hydroxy-docosahexaenoic acid; 17S-HpDHA = 17S-hydroperoxy-docosahexaenoic acid; 17S-HDHA = 17S-hydroxy-docosahexaenoic acid.

Systemic inflammation increases with increasing severity of periodontitis and periodontitis therapy induces a clear reduction of clinical signs and of the levels of systemic mediators of inflammation.[42–44]

The type of inflammation which characterizes periodontitis could be distinguished by the activation of immune components involved during an acute response.[45] Shifting from short-lived to prolonged inflammatory responses can disrupt immune tolerance and result in significant tissue, organ, and cellular alterations, thereby increasing the risk of various non-communicable diseases[45,46] (Figs. 3, 4 & 5). Moreover, systemic chronic inflammation can also hinder and reduce normal immune function, increasing susceptibility to infections, neoplasm or causing a poor response to vaccines.[47,48] Chronic inflammation results essential for the progression of various diseases such as atherosclerosis, obesity, cancer, chronic obstructive pulmonary disease, rheumatoid arthritis (RA), neurodegenerative disease, among others,[49,50] and multiple systemic inflammatory indicators showed strong associations with the onset of CVD.[51,52] The resolution of the inflammatory response was erroneously believed to be a passive process based on the attenuation of pro-inflammatory signaling pathways. However, the resolution of inflammation is not simply a passive restoration of homeostasis; rather, it is an active process controlled by various pro-resolving mediators such as lipoxins, protectins, maresins and resolvins (Figs. 4 & 6).[53,54] Additionally, at the level of the periodontal pocket (i.e. the pathognomonic lesion characterizing periodontitis) tissues exhibit a substantial deficiency in the pro-resolving protein network[16,20] (Figs. 4 & 6). As a consequence, the absence of the multi-protective effects of these proteins (particularly in the presence of acute inflammation) hinders cells in protecting themselves against the cytotoxicity of inflammatory mediators, increases their susceptibility to necrotic cell death and likely compromises an efficient immune response. These pro-resolving protein networks also mitigate the oxidation by scavenging of reactive oxygen species (ROS) exerting an antioxidant action, advanced glycation end-product (AGEs) disposal, preventing chronic inflammation, and, besides, promotes human periodontal ligament preservation (Figs. 4 & 5).

Periodontitis patients demonstrate elevated serum levels of antibodies that cross-react with antigens in cardiovascular tissues, antibodies been shown to activate cytokine production, pro-thrombotic mediators, higher levels of serum IgG against P. gingivalis were associated with periodontitis patients and CVD[55,56]) (Fig. 7). Besides, peripheral blood neutrophils (PMNs) seem to be hyper-responsive in ROS and protease production.[57] The PMNs are involved in periodontal health and defensive system; they result as essential first responder[40,58,59] (Fig. 4).

PMNs act through several unique defense mechanisms including the activation of pyroptosis, neutrophil extracellular trapsosis (NETo-sis) and ROS release.[59,60] Periodontitis is associated with a "hyperactivated" PMN phenotype that is qualified by the over-production of proteases and ROS[61].

Recent studies demonstrates that oral PMNs activation states are reduced in gingivitis and suggest that only in periodontitis do PMNs become hyperactivated and tis-sue-damaging.[40] ROS play important biological roles in anti-microbiota defense, gene regulation and cell signaling[62] (A).[40] ROS could be assumed as a "double-edged" blade because they can play a key-role to neutralize invading pathogens, but beyond a certain limit, could become toxic to host tissues and cells, when overactivated (Fig. 5).[20,63–65]

Nibali et al (2007) in a case-control study on 482 patients, showed a possible link between severe periodontitis, systemic inflammation and dysmetabolic state. Severe periodontitis patients showed significantly lower values of high density lipoproteins (HDL) that are considered as " heart protectors"[42].

When inappropriate defensive response is unable to resolve the infectious threat as it normally should, the inflammatory and

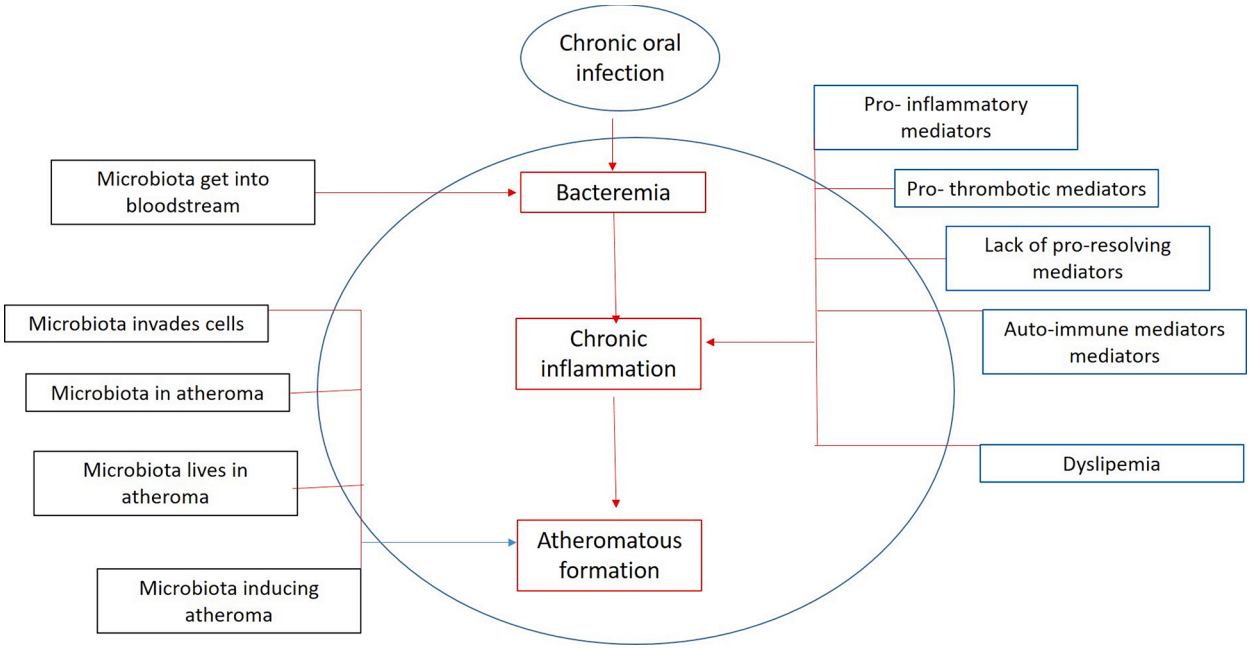

Fig. 7. Genesis of athero-trombotic lesions.

immune response can become chronic, creating a favorable environment for the development of a pathogenic ecosystem. Therefore, local inflammation becomes part of the pathogenic mechanism and, if it was maintained and spread at a systemic level, it causes systemic damage such as at the cardiovascular level. It can therefore be hypothesized that the physiologic inflammation-resolving is ineffective either because the infectious challenge is not resolved or because the physiological mechanisms for resolving inflammation are compromised (Fig. 4). Additionally, chronic systemic inflammation can modify or even impair endothelial function, which also accurately regulates the get through of molecules, such as lipoproteins, and cells through the vascular wall.[66–69] Inflammation promotes atheroma formation within the major arteries, and besides compromises the structural integrity of the arterial plaque creating regions with unstable plaque that lead to predisposition to thromboembolic events[70,71] (Fig. 7).

Growing evidence suggests a connection between inflammation and atherosclerosis.[72] Although inflammation's central role in atherosclerosis pathogenesis and its complications has garnered attention, its integration into clinical practice remains a work in progress.[73,74]

The pathophysiological cascade involves several stages, including the inflammatory activation of endothelial cells, infiltration of monocytes and leukocytes into the atheroma, and secretion of chemokines and chemoattractant proteins to facilitate further inflammatory cell recruitment into the intima.[73] Additionally, phagocytes heighten local inflammatory responses by generating matrix metalloproteinases (MMPs), which degrade extracellular matrix macromolecules, thereby compromising the connective tissue integrity.[74]

Targeting inflammation emerges as a promising avenue to address periodontitis, cardiovascular disease and residual risk.

Furthermore, periodontal bacteria and endotoxin may invade the damaged periodontal tissue, could enter the blood circulation, and further could invade the cardiovascular system, in particular when occurs a chronic and systemic inflammation which is able to modify the endothelial function.[44,56,75,76] Several, periodontal-pathogen bacteria, such as P. gingivalis, B. forsythus, P. intermedia or Aggregatibacter actinomycetemomitans induce aortic and coronary lesions after bacteremia in animal models, and were detected in human carotid atheromas.[77–79] The presence of bacterial DNA from the oral pathogenic micro-organisms in coronary atherosclerotic plaques and the special characteristics of the aortic aneurysms in CVD patients harbouring P. gingivalis is indirectly proven[80–82] (Fig. 7).

The fimbriae of P. gingivalis are important to host cell entry and to promote atherothrombotic lesions in experimental models, and certain bacterial strains expressing P. gingivalis hemagglutinin A have an increased capability to adhere and enter human coronary artery endothelial cells and act as an important virulence factor in atherosclerosis.[83,84] The presence of periodontal pathogens as well as oral bacteria in the atheromas, could cause platelet activation and aggregation and produce cell-specific innate immune inflammatory responses and maintain chronic state of inflammation at sites distant to the oral environment.[44,85] The activated and aggregated platelets, the elevation of thrombotic factors could play a significant role in atheromatous formation, thrombosis, and leading to cardiovascular events.[86–89] Therefore, the CVD in periodontitis really could occur through the conjunction of the different ways taken in account.[36,44] Therefore, we know that the microbiota described in the arteriosus wall could expresses certain pathologic activities (we have described), which were studied on bacteria harvested from the periodontal pockets, but we do not yet know whether the bacteria found in the artery walls could really be the same ones (exactly the same strain of bacteria) spotted in the periodontium and which, in some way, could have reached the wall vascular. This direct evidence is not yet available. It would also remain to explain how bacteria that apparently are confined to a district of the digestive tract, at an oral level, can reach the arterial wall. However, bacteremia was found in 10 % of cases after scaling in healthy subjects, in 20 % in gingivitis subjects after scaling, and in 75 % after scaling, 20 % after chewing and 10 % after brushing in periodontitis patients.[90]

Some common genetic risk factors between periodontitis and CVDs could be shared as an aberrant inflammatory reactivity, determined by genetic variants in the loci CDKN2B-AS1 (ANRIL), PLG, CAMTA1/VAMP3 and VAMP8, elevate levels of C-reactive protein (CRP) linked to CDKN2B-AS1 gene and a subgingival overgrowth of periodontal pathogens linked to CAMTA1/VAMP3 genes.[91–93]

Sub-clinical CVD and periodontitis

Severe periodontitis is associated with subclinical atherosclerosis in young, systemically healthy subjects[94,95] The critical index of increased cardiovascular risk is considered 0.82 mm as carotid intima-media thickness (IMT).[94,96] Periodontitis patients overcome this threshold in comparison with healthy subjects.[94] In a meta-analytic study considering a total of 5452 patients, including cases and controls, Orlandi et al.[97] showed an overall greater IMT (0.08 mm as a mean increase) in perio-patients compared to controls. The relative risk (RR) of future myocardial infarction increases of 1.15 times per every 0.1 mm difference in IMT and for stroke increases of 1.18 times.[98]

The association between subclinical cerebral and carotid atherosclerosis could be even be partially independent of some common risk indices normally considered (such as the pulsatility or the resistance index for the cerebral arteries or the IMT itself) in certain pathological situations such as hypertension.[95] Subjects suffering from periodontitis showed an increased risk of a first coronary and cerebrovascular events, greater in subjects with more severe periodontitis compared to subjects with less severe periodontitis, more than double the risk of cardioembolic and thrombotic stroke, and higher cardiovascular mortality.[99–101] However, the link between periodontal disease and the onset of coronary heart disease was notably significant among younger adults, with no observed evidence of such a connection among individuals over 65 years old.[99] Furthermore, cumulative CVD mortality increased with the severity of the periodontal disease in adults younger than 64 years, whereas no significant difference was found among those older than 65 years.[102] Hence, the correlation between sub-clinical CVD and periodontitis therefore appears to be more pronounced in young adults or during adulthood, and less of elderly in systemically healthy patients.[94] However, the pathological connection between adulthood relatively

to periodontitis and CVD may encounter significant exceptions in individuals who are not systemically healthy.[95]

Despite a large amount of studies and the functionality of the pathogenic association of periodontitis and CVD with chronic systemic inflammation, the association between periodontitis and sub-clinical CVD is still not completely defined. Bailey et al.[103] investigated the association between periodontal disease severity and subclinical markers of CVD in diabetic (type 1 diabetes) and non-diabetic patients. The study concluded that, compared to healthy subjects, diabetic patients had higher mean probing depth, higher mean attachment loss, lower brachial artery distensibility (brachD), higher carotid intima-media thickness (c-IMT), and higher pulse wave velocity (PWV), but, no significant associations between periodontitis and CVD metrics were found, after adjusting for age, gender, race/ethnicity, lipid measures, blood pressure, smoking, and medication use. Another cross- sectional study investigated the systemic impact of periodontitis in patients with metabolic syndrome (MetS), by assessing measures of sub-clinical atherosclerosis. Patients suffering from severe periodontitis had increased average ventricular relative wall thickness (RWT) (e.g. a predictive index of cardiovascular events related to concentric left ventricular remodeling), whereas no associations between periodontitis and c-IMT, PWV, and left ventricular mass index (LVM) were detected after adjusted analyses.[104] Moreover, in a cross-sectional study carried out in patients affected by Type 2 diabetes, Franek et al.[105] observed that the group of patients also suffering from peridontitis showed higher pressure than the other groups, periodontitis and gingivitis groups had higher IMT values than the group with diabetic patients without periodontitis or gingivitis. Periodontitis group had C-reactive protein (CRP) higher than gingivitis group resulted higher in the respectively compared to the diabetic patients group, while lipid parameters and PWV were comparable in all the three groups. Therefore, periodontal inflammation in these patients seems to be associated with increased IMT and BP, but not with greater arterial stiffness.

A large amount of studies highlights the relationships between metabolic syndrome (MetS) and diabetes mellitus and periodontitis, and probably MetS or diabetes are capable of inducing subclinical CVD or worsening those connected to periodontitis[106–109].

Until recently, no studies have directly compared measures of "subclinical" CVD each other stratifying the risk profile for clinical CVD, and it is to consider whether some indices usually considered as indices of subclinical risk were physiologically linked to increasing age, pathologically to other diseases and do not represent a real increase in risk once the subject has been stratified by age or pathologic group.[106]

Some indices seem to appear more effective (e.g. c-IMT and PWV) in predicting CVD events than others[110] as LVM (commonly used for evaluating the target organ damage in arterial hypertension) or ankle-brachial index (ABI) which seems to be more correlated as risk factor with known CVD or diabetic patients.[111] However, a majority of the population with markers of subclinical CVD detectable without needing for particularly in-depth tests and consequently classifiable as having a low or intermediate risk score, actually upon a more in-depth analysis should be reclassified as high risk[111,112]. So, overall, subclinical markers should not be underestimated in terms of risk assessment.

Despite previous findings regarding the complete or partial absence of association between periodontitis and subclinical CVD probably due to limitations of the trial (such as the study design), the limited number of participants with periodontitis, the age of the included subjects[113] or limitation of existing literature on effectiveness of subclinical CVD indices[106,110,111] several systematic reviews and a large number of studies reported that periodontal disease is associated with arterial dysfunction.[75,94,95,97,99,101,102,114–116] Besides, the European Federation of Periodontology (EFP) and the World Heart Federation (WHF) reported that there is evidence from epidemiological studies that periodontitis patients have a higher prevalence of subclinical CVD, exhibiting significant endothelial dysfunction.[34] Finally, given the morbidity of the two pathologies, and the serious risks for systemic health connected above all to CVD, we cannot neglect to consider the association between them even if larger methodologically robust clinical trials with longer follow-ups are needed in order to draw stronger conclusions.

Peripheral artery disease and periodontitis

Peripheral artery disease (PAD), which is usually associated with atherosclerosis, results in a significant reduction of the lumen of peripheral arteries that primarily affects the lower extremities, involves ischemia, and its most common symptom is intermittent claudication.[52] PAD is widely regarded as an important risk factor for all causes of death, especially cardiovascular death.[117] It is estimated that there are 500, 000 to 800, 000 patients with PAD in Japan.[118] In 2010, there were approximately 220 million people with the disease worldwide; notably, this number had increased by nearly 25 % during the previous decade.[118,119]

PAD and CVD are both chronic inflammatory conditions, and they share similar inflammatory factors with periodontitis.[52,84,120]

Mendez et al.[120] in a normative aging study combined with dental longitudinal study at first reported that subjects with clinically significant periodontitis at baseline had more than 2-fold possibility of developing PAD (OR = 2.27, 95 % CI = 1.32–3.9). Soto-Barreras et al.[121] in a case–control study reported as a clinical attachment loss (CAL) $\geq$4 mm in at least 30 % of the six measured sites, was closely correlated with PAD risk (OR = 8.18, 95 % CI = 1.21–35.23). Similar findings were found in another cross-sectional study on Korean adults with an OR of 2.03 (95 % CI: 1.05–3.93) for the association between severe PD and PAD,[122] and Aoyama et al.[123] observed that PAD patients had more missing teeth, a higher rate of edentulism, and higher serum inflammatory factor levels than non-PAD patients. PAD patients had decreased tooth number and worsened oral (mean decayed missing filled teeth -DMFT), alveolar bone loss, and periodontal condition with enhanced systemic inflammation.[121,123,124]

Similar findings have proliferated in recent years. A strong association between periodontitis patients for having PAD (OR: 5.45, 95 % CI: 1.57–18.89) was reported by Chen et al.[125] in a case-control study (after adjusting for age, gender, diabetes, and smoking), and by Calapkorur et al.[126] with an OR of 5.8 after adjusting for confounders (age, gender, diabetes, hypertension, and body mass index - BMI).

In a retrospective cohort study Yeh et al.[127] observed a risk of occlusive PAD greater for periodontitis patients than for the

non-periodontitis group, after adjusting for all variables. However, undergoing at least one dental scaling procedure reduced the risk of PAD increasing attention to oral hygiene, as dental scaling has a trend towards a lower risk of PAD.[127]

Specialized systematic review and meta-analysis has quantitatively assessed the strength of the association between PAD and periodontitis.[52,128]

Yang et al.[52] found a significant difference in the risk for having periodontitis between PAD patients and non-PAD participants (RR = 1.70, 95 % CI = 1.25–2.29, P = 0.01). In addition, a significant difference in number of missing teeth between PAD patients (having more missing teeth) and non-PAD participants were observed. Kaschwich et al.[128] observed an association between periodontitis with an odds ratios of developing PAD ranging from 1.3 to 3.9 (after adjusting for established cardiovascular risk factors).

The presented evidence supports a bijective mapping link between PAD and periodontitis with tooth loss, worsened oral conditions, alveolar bone loss, and enhanced systemic inflammation. The chronic systemic inflammation plays a key role for the pathogenesis of both the diseases and its control represents a pivotal moment in the therapy of both diseases. However, the results examined cannot confirm a causal role of periodontitis in the development of PAD and vice versa. Further studies which address the temporality of PD and PAD are needed.

Coronary artery disease, acute coronary events and periodontitis

Since the 1980s, evidence has emerged of an association between poor dental health and coronary heart disease (CHD), acute myocardial infarction (AMI) and atherosclerosis independently of risk factors as age, total cholesterol, high-density lipoprotein (HDL), triglycerides, C peptide, hypertension, diabetes, and smoking.[19,129,130]

DeStefano et al.[131] demonstrated an increased risk of coronary heart disease in patients suffering from periodontitis, and, in particular, in men younger than 50 years of age, periodontal disease had an effect on coronary heart disease incidence, with a relative risk of 1.72.

However, the studies carried out in those years almost always presented some methodological problems such as the small sample size, or biases in the study design.[130] These matters detracted from the credibility of periodontitis as a risk factor and as specificity of association related to causality. Therefore, considering the evidence pointing toward periodontitis as a causal factor for CVD, Beck et al.[130] determined that there was not sufficient evidence to conclude a specificity of association between periodontitis and CVD, and a relation of causality between the diseases. Given their data, the Authors believed that the evidence of the associations between oral conditions and atherosclerosis/CHD could be met in the not-too-distant future. Lockhart et al.[132] concluded that observational studies to date support an association between periodontitis and atherosclerotic vascular disease independent of known confounders, but they do not support a causative relationship.

However, several studies and systematic review based on observational epidemiologic studies, suggested pathogenic pathways and found a relationship between periodontitis, CVD and atherosclerotic cardiovascular disease (ACVD).[19,23,36,66–68,70,77–85,90,99,130,133–136] The fimbriae of porphyromonas gingivalis (PG) are important to host cell entry and to promote atherothrombotic lesions in experimental models,[83] and hinder regulatory T cells in modulation of autoimmune response.[84] The periodontitis induces aortic and coronary lesions after bacteremia in animal models,[66] and periodontal bacteria obtained from human atheromas can cause atherosclerosis in animal models of infection.[76] Surrogates (markers, endpoint that substitutes for a clinical endpoint) predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic evidence (Biomarkers Definitions Working Group 2001). Furthermore, since the last lusters, a large number of surrogates of periodontitis seem to confirm a causal relationship between periodontitis and systemic diseases.[34,97,137–141]

In a systematic review by Dietrich et al.,[99] it was found an evidence for an increased risk ACVD in patients with periodontitis compared to patients without. This association was stronger in younger compared with older patients, and more obvious in men than in women. There is limited evidence to suggest an association between chronic periodontitis and the risk of recurrent CVD (secondary events) in patients with atherosclerosis.[99] Xu & Lu[102] obtained substantially similar results on mortality rates. They found that cumulative CVD mortality rate were increased across the severity of periodontitis in men and women aged 30–64 years, more markedly in men. On the contrary, no significant difference was found in men and women aged more than 65 years. In addition, Briggs et al. (2014) corroborated previous findings, the association between ACVD and the progression of periodontal disease in individuals over 40 was indicated. In 2016, Ryden et al.[142] in a multicenter case–control large study showed that the risk of a first AMI was significantly increased in patients with periodontitis even after adjustment for confounding factors in patients <75 years of age. However, Bengtsson et al.[143] carried out the first long-time (17-year) follow-up report on periodontitis and the incidence of CVD and death. Bengtsson (2021) and her team demonstrated that periodontitis was a statistical risk indicator for ischemic heart diseases in older adults. Periodontitis was significantly associated with mortality over the time studied.[144]

One limitation on elderly patients was that the most fragile and medically compromised individuals were not able to participate. The fact that the most fragile individuals did not participate may have affected the results, possibly lowering the associations between periodontitis and CVD. Another limitation proper of studies with long- time follow-up, is that many patients died during the study, and often the cause of death was not known.[143]

These considerations could be particularly important in relation to multifactorial diseases such as periodontitis or even acute events such as AMI, stroke or heart failure (HF).

Missing teeth have also been proposed as a proxy for current or past periodontitis as it is considered to reflect an accumulation of oral inflammation.[145] Missing teeth were also associated with CVD incidents, MI, HF, diabetes and mortality.[145,146] On the contrary, the number of teeth lost was not significantly related to stroke.[145,146]

Periodontitis resulted associated incident stroke risk (particularly cardioembolic and thrombotic stroke subtype), and HF, in

particular considering ejection fraction.[101,144,147–149] Over the last 30 years, three classifications of periodontal disease have been officially used., so it is difficult to standardize the various studies on the relationships between periodontitis and CVD and, even more so, between missing teeth as a consequence of periodontitis and CVD. Besides, periodontitis, cardiovascular diseases or diabetes and other systemic chronic diseases show a very complex pathogenesis, which intersects with each other, with chronic inflammation, heredity and much more. The specific pathogenic pathways which peculiarly characterize each of these inflammatory-based pathologies and how these ways could influence each other are still being studied. However, according to the consensus jointly organized by the European Federation of Periodontology (EFP), the World Heart Federation (WHF)[3] and the World Organization of Family Doctors,[22] we agree on a consistent and strong epidemiological evidence that periodontitis imparts increased risk for future CVD and AMI. The joint workshop also concluded the impact of periodontitis on CVD was biologically plausible, via translocated circulating oral microbiota, which may directly or indirectly induce systemic inflammation acting on a dysfunctional inflammation-initiating and resolving mechanisms leading to an increase in several chronic inflammatory markers. The set of this occurrences impacts upon the development of CVD and atherothrombogenesis (Fig. 7).[3,22,144] So, patients with CVD should be questioned about any signs and symptoms of periodontitis, and, it is recommended that periodontal treatment should seriously be followed in patients with CVD.

Infective endocarditis and periodontitis

Infective endocarditis (IE) is a severe disease that affects one or more of the aortic, mitral, tricuspid valves but seldom the pulmonary valve. Preexisting valve diseases such as mitral valve prolapse, rheumatic fever, mitral stenosis, aortic stenosis and aortic regurgitation, bicuspid aortic valve, coarctation of the aorta, previous endocarditis, prosthetic heart valves, and intravenous drug use are predisposing factors. Periodontitis may result in the transmission of bacteria from the oral cavity to the bloodstream.[19]

The oral cavity is a frequent origin of bacteremia due to the presence of the viridans group streptococci (VGS, as Streptococcus mitis, mutans, and oralis which are the most common VGS found in the oral cavity), the HACEK group (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella), Staphylococcus aureus, and Enterococcus or strict anaerobes, including Tannerella forsythia, Fusobacterium nucleatum, Porphyromonas gingivalis, and Prevotella intermedia.[150–154] As they are part of the dental plaque, they can enter the bloodstream, causing bacteremia through daily habits, such as chewing or tooth brushing, and poor periodontal health appears to increase the risk of cardiovascular and pulmonary diseases, preterm birth, and low birth weight.[155] The circulating oral microbiota, which is apparently quite frequent in periodontitis subjects,[90] is a plausible biological basis of IE and CVD in periodontitis.[90,154,155]

Oral microbiota is considered one of the most significant risk factors for IE[154] Ninomiya et al.[156] study observed a significant increase in the percentage of alveolar bone loss in valvular heart disease patients with IE compared with that of patients without IE. The ratio of Porphyromonas gingivalis in patients with IE was significantly higher than in patients without IE. Nakatani et al.[157] found that decayed teeth and periodontitis were the leading predisposing factors and VGS were isolated in 52 % cases whereas staphylococci were isolated in 32 % cases.

A significant correlation between the occurrence of IE and clinical oral findings (number of remaining teeth and rate of alveolar bone loss) was observed.[156]

However, a direct causal relationship between periodontitis and IE is not easy to prove, although, from a pathogenic point of view, it would seem very likely. The reason for this difficulty derives both from the ubiquitous distribution of the microbiota of IE lesions which can derive from different types of tegumental diseases and also from oral cavity pathologies such as caries, ulcerative lesions, endodontic infections as well as from periodontitis[151,154] Moreover, the causal model for IE predicts that an early bacteremia may target the endothelial surface of the heart over many years and promote valve thickening thereby rendering the valve susceptible to adherence and colonization by a later bacteremia, that could culminate at the utmost over a few weeks into fulminant infection.

Thus, the induction of the pathology should require a long time, results elaborate end involves several steps: in particular a chronic stimulation that allows the overcoming of barriers (such as the surface epithelium, defensins, electrical barrier, antibody-forming cells, and the reticuloendothelial system) to prevent bacterial penetration from dental plaque into the bloodstream and the tissue. The transient bacteremia is usually eliminated by the reticuloendothelial system within minutes and is generally asymptomatic to the host. Besides, the IE induction includes bacterial adherence, platelet activation and fibrin overlaying. Thereby, it seems that more comprehensive studies are needed to investigate the effect of periodontitis on IE. On the other hand, therapy which prevents a chronic infection (such as the periodontal pocket) or treats it effectively seems to have a significance on the genesis and prognosis of IE.

Hypertension and periodontitis

It is currently conjectured that arterial hypertension seems to be correlated to periodontitis.[158–160]

Several studies showed that systolic and diastolic pressure is higher in patients who have suffered from periodontitis, and, besides, a positive relationship between arterial hypertension and periodontitis was found.[159–162] Severe and generalized chronic periodontitis seem to play a role as risk indicators for hypertensive patients and non-surgical periodontal therapy (NSPT), the cause-related therapy was effective in improving periodontal clinical data and in reducing the plasma levels of surrogates of inflammation.[160,163,164]

Könnecke et al.[165] in cross-sectional analysis of data from a large population-based health survey showed an independent association between periodontitis and arterial hypertension. However, patients with normal blood pressure showed an inverse relationship between prevalence and periodontitis severity. In contrast, the prevalence increased considerably from no/mild, moderate to severe periodontitis in the untreated patients with hypertension, whereas patients with controlled hypertension showed a much more leveled increase. The under-treatment of hypertension (untreated and poorly controlled hypertension) was quite common both in periodontitis

and without periodontitis patients.[165]

Taskos et al.[162] analyzed data from the third National Health and Nutrition Examination Survey (NHANES). The study showed that patients with periodontitis had a higher probability of arterial hypertension in both sexes, but a clear linear trend was observed only in men.

Tooth loss is related to high blood pressure levels.[166] As we know, periodontitis is the main reason for tooth loss in adults[20] (B).[166]

Machtei et al.,[167] in patients with little or no periodontitis, showed that patients with high blood pressure lost twice as many teeth as did normotensives, but without statistical significance. Taguchi et al.,[168] in a study on non-smoking healthy women, found a significant association between the incidence of hypertension and the number of teeth lost. Tooth loss seems to be related to high blood pressure.[166,169]

Sometimes, the greater number of teeth lost may also be explained by the dentist, considering the likelihood of treating subjects with complex systemic conditions, preferring extraction over an elaborate treatment plan that might have to preserve these teeth.[20] Moreover, a significant percentage of patients affected by periodontitis are made up of patients with multimorbidity.[144]

However, Bertoldi et al.[20] in a cross-sectional study found an independent direct correlation between the number of teeth lost and systolic blood pressure, and a direct correlation of both systolic and diastolic blood pressure with the periodontal screening and recording index (PSR) that is a index of need for periodontal treatment.

Torrungruang et al.[170] in a 5-year longitudinal study on a study population included 901 hypertension-free participants, aged 50–73 years, assessed periodontitis and blood pressure changes. Poor oral hygiene, greater mean periodontal pocket probing depth (PPD) and the number of periodontal pockets were associated with elevated systolic blood pressure and increased hypertension risk. The systemic inflammation could be a mediator of these associations.[170] Conceptually similar results were highlighted by Jung et al.[144] in a nationalwide cross-sectional study on $\geq$19 years adults.

Periodontitis is associated with a higher risk of hypertension especially for severe periodontitis. However, no conclusions could be made regarding the causative involvement of periodontitis mainly due to the reduced number of available prospective studies and remaining questions regarding underlying biological mechanisms.

Several mechanisms were suggested which may explain this relationship include endothelial dysfunction, due to the systemic inflammation caused by periodontitis,[171,172] oxidative stress,[173] inflammatory mediators[170,174] and bacteremia/sepsis.[175,176] On the other hand, it has been observed that high blood pressure can worsen the periodontal disease due to the microcirculation changes and subsequent ischemia in the periodontium, which favors periodontitis.[166]

A causal relationship between periodontitis and arterial hypertension cannot not be considered concluded. However, a recent Mendelian randomization study demonstrated that periodontitis linked single nucleotide polymorphisms (SNPs) were associated with increased periodontitis, suggesting that the relationship between periodontitis and arterial hypertension may in fact be causal.[177]

Atrial fibrillation and periodontitis

Atrial fibrillation (AF) is the most typical cardiac arrhythmia worldwide.[178,179] Inflammation is known to have at least an additive role in AF development.[179,180] About AF and periodontitis, a scanty number of studies were performed to investigate this relationship. Chen et al.[181] conducted a retrospective cohort study from the Taiwanese National Health Insurance Research Database (NHIRD) on 393, 745 patients with periodontitis and 393, 745 non-periodontitis individuals, and concluded that there was a 31 % higher risk of AF or atrial flutter, and an increased risk of HF in the periodontitis group compared with the patients without periodontitis. Sen et al.[182] carried out a Atherosclerosis Risk in Communities Study (ARIC) cohort study on 5, 958 US patients. Participants were classified as regular or episodic dental care users. They concluded that periodontitis was associated with AF. The association could explain the periodontitis-stroke risk.[95,182] Besides, regular users had a lower risk of incident AF compared with episodic users.[182] Chang et al.[183] conducted another retrospective cohort study among 161, 286 subjects from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) which had no medical history of AF, HF, or cardiac valvular diseases. To assess oral hygiene, they evaluated the presence of periodontitis, any dental visit, number of missing teeth, etc. They concluded that oral hygiene care improvement was associated with decreased risk of AF and HF. Moreover, healthier oral hygiene by accurate tooth brushing and professional dental cleaning may reduce risk of AF and HF.

However, a causal relationship between periodontitis and AF needs of further studies.

A recent large prospective study based on in-depth health information, seems to indicate a pathogenic inflammatory pathway. Yang et al.[52] performed their study using UK Biobank (i.e. prospective cohort containing in-depth health information) including 478, 524 patients. Yang and his team obtained the clinical, genetic, and biochemical data of participants through questionnaires, genotyping, sample assays, physical measures, and linked electronic health data. The study highlighted that multiple systemic inflammatory indicators showed strong associations with the onset of AF/ flutter, ventricular arrhythmia, and bradyarrhythmia, of which the latter two have been rarely studied. Active systemic inflammation management might have favorable effects in reducing the arrhythmia.[52]

However, excluding AF/atrial flutter, regard the other types of arrhythmia the literature results lacking in studies that assess a possible relationship with periodontitis, and burden and further randomized controlled studies are needed.

Effectiveness of periodontal therapy in CVD prevention

Epidemiological studies largely support an association between periodontitis and CVD, independently of known confounders. However, significant intervention studies need to have an extended time follow-up, extended at least between onset of subclinical CVD and clinical event, and an extremely large sample size. A limited number of studies follow these needs in the literature. On a sample of

11, 869 men and women (mean age 50.0), who participated in the Scottish Health Survey, which drew a nationally representative sample of the general population living in households in Scotland, de Oliveira et al.[184] carried out a study with a follow up average 8.1 years aimed to analyze the association of oral hygiene with incident CVD and markers of inflammation and coagulation. The study recorded 555 CVD events (170 fatal). Participants who reported poor oral hygiene had an increased risk of a CVD event, and increased concentration of both CRP and fibrinogen. In particular, participants who brushed their teeth less had a 70 % increased risk of CVD compared with participants who brushed their teeth twice a day, and less frequent toothbrushing was associated with increased concentrations of CRP and fibrinogen. The study results confirmed the association between oral hygiene and the risk of CVD due to systemic inflammation. Holmlud et al.[145] considered 5, 297 individuals treated at a specialized clinic for periodontal disease. Periodontal data were compared at baseline and after active periodontal treatment. Poor response to treatment was defined as having >10 % sites with PPD >4 mm and bleeding on probing index (BoP) at ≥20 % of the sites 1 year after active treatment. During a median follow-up of 16.8-year, 870 incident CVD cases were observed. Poor responders (13.8 % of the sample) had a significant increased incidence of CVD (23.6 %) when compared with responders (15.3 %).

The risk for CVD was clearly elevated for poor responders, as the number of remaining teeth increased. On the contrary, in the responder group, few remaining teeth predicted higher risk for CVD. Interestingly the number of remaining teeth would seem to be an advantage if periodontal damage can be treated while it would represent a disadvantage when this does not happen. This disadvantage linked to residual teeth would depend more on the permanence of deeper periodontal pockets, capable of producing all the local and systemic effects of periodontitis as a whole, rather than on the variation of only a local inflammation index (bleeding on probing - BoP index). Therefore, the successful periodontal treatment might effectively influence progression of subclinical CVD.

Another study with a very large sample (720, 343 patients; 511, 630 with periodontitis and 208, 713 without periodontitis) and a long follow-up period (10-year) was performed by Lee et al.[185] using the longitudinal health insurance database of the Taiwanese NHIRD. A total of 10, 046 patients developed CVD events (incidence rate = 0.17 %/year). Among patients with periodontitis, the incidence rate (IR) of CVD events was lowest in the dental prophylaxis patients (0.11 %/year) and highest in the patients without treatment group (0.31 %/year; $P < 0.001$).

The risk of AMI was significantly lower in patients with no periodontitis, in patients with periodontitis underwent to dental prophylaxis and higher in patients suffering from periodontitis without periodontal treatment.

Park et al.[186] analyzed data of 247, 696 healthy adults aged 40 years or older who underwent an oral health-screening program and had no history of major cardiovascular events. Over a median follow-up of 9.5 years, 14893 major cardiovascular events including cardiac death, AMI, stroke, and heart failure occurred equating to a 10-year event rate of 6.84 %. Cardiovascular events were more frequent when a subject had periodontal disease, more dental caries, or a higher number of tooth loss. More careful dental care, regular dental visits (at least once a year) for professional cleaning reduced cardiovascular risk by 14 % (independently of potential confounding factors or oral diseases), and carrying out one more tooth brushing a day was shown to reduce a significant 9 % the risk

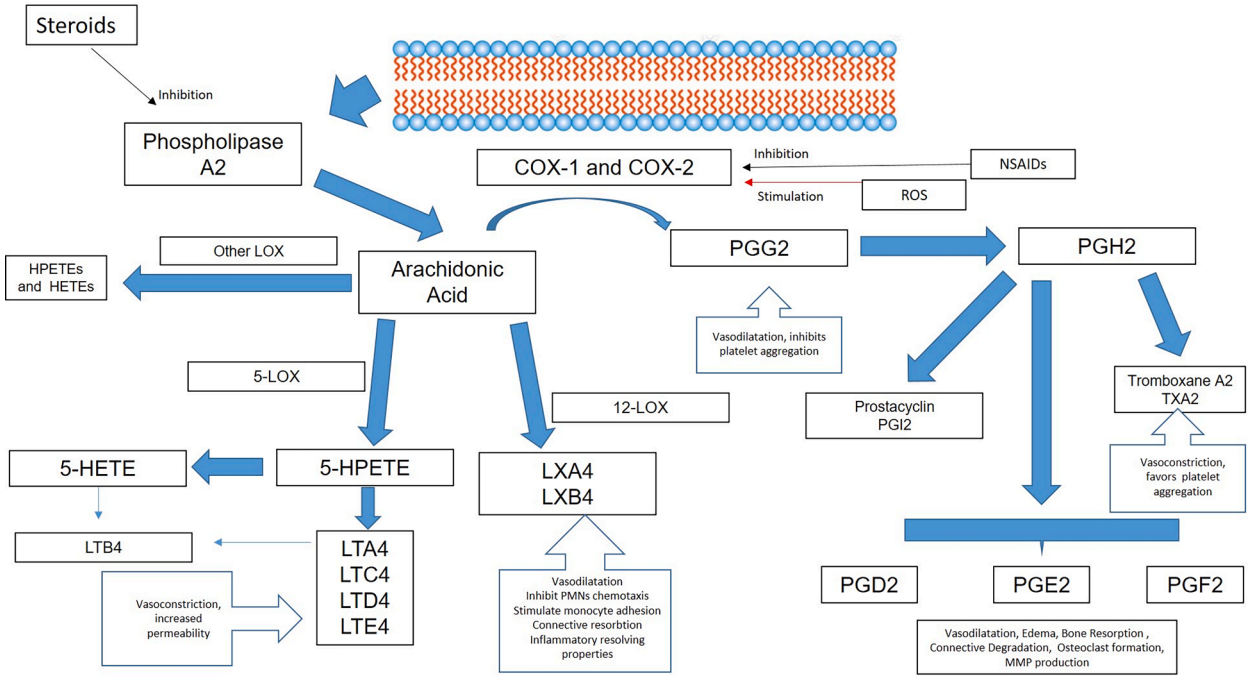

Fig. 8. Arachidonic acid cascade.
Legend: 5-LOX = 5-lipoxygenase; COX = cyclooxygenase; NSAID =nonsteroidal anti-inflammatory drugs; ROS = reactive oxygen species; 5-HPETE = 5-hydroperoxyeicosatetraenoic acid; 5-HETE 5-Hydroxyeicosatetraenoic acid; PG = Prostaglandin; LX = Lipoxin; LT = Leukotriene; PMNs = polymorphonuclear neutrophils; MMP = Matrix metalloproteinase.

associated with cardiovascular events. Daily personal oral hygiene is key to preventing periodontitis. However, it is important to note that toothbrushing alone is insufficient for complete oral care, as it only addresses dental deposits below the gingival margin, professional cleaning by a dentist or dental hygienist (i.e. NSPT) also removes subgingival ecosystems and mineralized plaques[62,187] (A),[187] (B).[186] Overall, regular dental visits, improved self-performed oral hygiene behaviors attenuated the CVD risk originating from periodontal disease, dental caries, and tooth loss modifying the association between oral health and CVD. The results were confirmed even in subjects with poor oral conditions.

The regular dental care was associated with lower adjusted stroke risk, overall mortality, PAD and ischemic heart diseases.[23,127,130,143,185,188] Broadly, oral hygiene (self-performed oral hygiene habits, increased dental visits, etc.), dental prophylaxis, and periodontitis treatment seems to be a method of preventing arterial hypertension and of increasing the effectiveness of anti-hypertensive treatment.[160] However, Rodrigues et al.[189] observed that the NSPT, despite the benefits in periodontal clinical parameters, reduced the plasma level of CRP but not the blood pressure in patients with combined refractory arterial hypertension and periodontitis.

NSPT resulted effective in improving periodontal clinical data and in reducing the plasma levels of surrogates of periodontitis in patients suffering from periodontitis or peri-implantitis.[69,137,140,141,163,188] Orlandi et al.,[97] in the previously mentioned meta-analytic study, considering the endothelial function by measurement of the diameter of the brachial artery during flow (flow-mediated dilatation) found that periodontal therapy determined improvement in FMD of 6.64 % in periodontitis patients. Another systematic review and meta-analysis[139] confirmed that periodontal therapy improves individuals' inflammatory and lipidic profile, especially in those with other comorbidities (i.e. diabetes and CVD). Other systematic review studies including periodontal therapy for diabetic subjects, confirmed the reduction in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) after periodontal therapy[69,138,190].

Given the pivotal role of the lipid profile in the pathogenesis of CVD, many studies have investigated the potential therapeutic role of statins in periodontitis. In addition to their lipid-lowering effect, statins exert pleiotropic effects that depend on their direct activity in a target site. These pleiotropic effects include the downregulation of some pro-inflammatory interleukins, of MMP-1 and MMP-3 (enzymes correlated to periodontitis) released from macrophages and endothelial cells, as well as the reduced levels of inducible nitric oxide synthase (iNOS), receptor activator of nuclear factor κB (RANK), RANK ligand (RANKL). Conversely, statins increase the level of osteoprotegerin (OPG) within periodontal tissues.[191–193] Besides, arachidonic acid cascade (Fig. 8) and polyunsaturated fatty acids n-3 (ω-3 PUFA) are able to produce inflammatory proresolving molecules as resolvins, protectins and maresins (maresins can also derive from ω-6 PUFA) or lipoxins (LX).[191,192] The resolvins and protectins share similar proresolving properties to LX, by acting as agonists of receptors that promote the resolution of inflammation[191] (Figs. 6 &8). Statins and aspirin are able to induce the production of a longer acting epimer of LX.[54]

However, systemic statin intake does not enhance the outcomes of NSPT.[193–195] On the contrary, the local administration of statins as a solely adjuvant of the NSPT showed additional benefits in PPD, clinical attachment level, and intrabony defect, when compared to the groups without statin (simvastatin, in particular). Locally delivered drug is, probably, an approach that presents the advantage of making drug bioavailability high as intrasucular drug concentration directly in the target site with a reduced dosage, better patient compliance, and reduced side effects in comparison to its systemic administration.

Most of the significant studies investigating the efficacy of periodontal therapy in preventing CVD focus on NSPT as the standard reference treatment. This choice stems from the considerable variation in periodontal therapies, with NSPT being the most standardized therapeutic approach. Thus, considering less standardized therapies could introduce a high risk of bias.[138] However, NSPT is strongly associated with inflammatory response.[90,137]

Moreover, the full-mouth non-surgical treatment (FM-SRP) triggers a greater inflammatory acute-phase response of 24 h duration compared to the less intensive pattern of NSPT (i.e. quadrant scaling). So, treatment time seems to be related with the inflammatory response.[137] An increased risk of vascular events could be advocated by the observed post-therapeutic inflammation. Lee et al.[185] observed an hazard ratio of AMI significantly lower in the dental prophylaxis group and higher in periodontitis patients without treatment, and in the intensive treatment group. Minassian et al.[196] analyzed data from 9, 901, 464 subjects in the U.S. Medicaid claims database, who experienced their first hospitalization for ischemic stroke or AMI at least 24 weeks after enrollment. They observed a significant increase in the rate of vascular events during the first 4 weeks after invasive dental treatment, which gradually returned to baseline rate within 6 months. This positive association persisted after exclusion of persons with pre-existing conditions such as diabetes, hypertension, coronary artery disease or persons with prescriptions for antiplatelet or salicylate drugs before treatment. However, Minassian and her team still concluded that the absolute risks are minimal, and the long-term benefits on vascular health will probably outweigh the short-lived adverse effects.

Nordendahl et al.[197] tested the hypothesis that the incidence of a first AMI within 4 weeks after invasive dental treatments is increased. The case patients included 51, 880 individuals with a first fatal or nonfatal AMI from the nationwide health care and population registries in Sweden. There was no association between invasive dental treatments during the 4 wk preceding the AMI.

In patients with established CVD, no association between invasive dental treatments during the 4 weeks preceding the AMI was detected. The established CVD did not increase the incidence of cardiovascular events as a consequence of the periodontal treatment. Delivering periodontal treatment is safe also with regards to cardiovascular risk in patients with established CVD.[130,198]

Conclusions

CVD are directly associated with periodontitis, independently of known confounders. Periodontitis, being an infectious and multifactorial disease, shares common pathogenic pathways with CVD such as chronic inflammation or bacteremia. However, establishing a precise pathogenic relationship remains challenging, mainly due to the complexity of the underlying pathophysiological

systems, which are not yet fully understood.

Periodontitis therapy requires the control of the pathological oral ecosystems, of the pathological niches in order to reduce the inflammatory stress caused by the microbiota that the host's immune-inflammatory system is unable to effectively control.

The analysis of significant intervention studies with extended time follow-up and large sample size indicates that periodontitis therapy yields clinically positive effects in relation to subclinical and clinical CVD. The secondary effects of periodontitis treatment with an increase in inflammatory indices do not seem to constitute a contraindication to the treatment itself from a cardiovascular standpoint even in subjects already diagnosed for CVD. On the contrary, the subsequent beneficial effects outweigh the disadvantage of inflammation immediately after therapy.

Insufficient evidence exists to determinate whether CVD treatment can induce clinically positive effects on periodontitis. However, it is known that certain drugs used in CVD management, such as statins, can also have positive effects on periodontitis, albeit requiring local administration.

Therefore, it is better for physicians who treat patients with CVD to assess their oral health, oral hygiene behavior, and symptoms such as gingival bleeding during the brushing, tooth mobility, tooth lost, bad breath, dental abscess or bad taste of mouth, which relates to oral infection. Any suspected cases of oral tissue inflammation or periodontal disease, should be promptly referred to a periodontist for further evaluation and treatments including oral health instruction, cause-related therapy, and other tailored complementary therapies.

Author Contributions

Carlo Bertoldi: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing, original draft, writing, review & editing. **Roberta Salvatori:** Conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, writing, original draft, writing, review & editing. **Marcello Pinti:** Investigation, resources, writing, original draft, writing. **Anna Vittoria Mattioli:** Data curation, formal analysis, investigation, methodology, resources, validation, writing, original draft, writing.

Ethics approval and consent to participate

Not applicable.

Funding

This research received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We acknowledge Filippo Graziani for his support throughout this project.

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