Heart, Lung and Circulation (2018) **27,** 1327–1334
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.05.102

REVIEW

Periodontal Disease, Systemic Inflammation and the Risk of Cardiovascular Disease

Edgar Francisco Carrizales-Sepúlveda, MD [a*], Alejandro Ordaz-Farías, MD [b], Raymundo Vera-Pineda, MD [a], Ramiro Flores-Ramírez, MD [a,b]

[a]Internal Medicine Department, Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México
[b]Echocardiography Laboratory, Cardiology Service, Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México

Received 14 April 2018; accepted 11 May 2018; online published-ahead-of-print 2 June 2018

Periodontal and cardiovascular disease are both major health issues. Poor oral health has long been associated with the development of systemic diseases, with the typical example being the risk of endocarditis posterior to dental procedures. Through the years, the association of periodontal disease with other non-infectious systemic diseases has been brought to attention. One of the most interesting associations is the one that exists with the development of cardiovascular disease. Many studies, including systematic reviews and meta-analyses, suggest an important association between periodontal disease and ischaemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation and peripheral artery disease. Among the proposed mechanisms of this relationship, systemic inflammation appears to play a major role. Evidence suggests that periodontal inflammation triggers a systemic inflammatory state that, added to the damage mediated by antibodies that cross react between periodontal pathogens and components of the intimal wall, and the direct lesion of the intima by bacteria entering the circulation, promotes atheroma plaque development and progression. There are other studies that show a clear relationship between periodontal disease severity, elevations of inflammatory markers, and the presence of atherosclerosis. Here, we give a review of the available evidence supporting this association, and the possible mechanisms involved.

Keywords Periodontal disease • Systemic inflammation • Cardiovascular disease • Atherosclerosis

Introduction

The oral cavity serves as home for a large number of microorganisms whose species differ as they are found in the teeth, gum, cheek, gingival sulcus or palate, and interact with their human host, both in health and disease [1]. In total, an adult can have nearly one billion bacteria in the oral cavity. It is well known that, in patients with some degree of periodontal disease (PD), episodes of bacteraemia can occur after daily procedures such as teeth brushing or use of chewing gum, and that this can occur in multiple occasions throughout the day [2]. The mouth has been long recognised as a source of systemic infections, from where the passage of bacteria into the bloodstream is allowed from interruptions of tissue integrity secondary to inflammation in conditions such as periodontitis [3]. The clearest relationship exists between dental procedures and bacterial endocarditis, from whence the still valid recommendations of antimicrobial prophylaxis for patients with risk factors prior to undergoing a dental procedure arise [4,5]. From these observations, a lot of evidence has been generated about the relationship between PD and the occurrence of non-infectious systemic diseases like rheumatoid arthritis (RA) [6], and atherosclerotic cardiovascular diseases (ASCVD) such as ischaemic heart disease (IHD) [7], cerebrovascular disease (CBVD) [8], peripheral artery disease (PAD) [9,10], heart failure (HF) [11] and atrial fibrillation [12].

*Corresponding author at: Internal Medicine Resident, Internal Medicine Department, Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México, Madero and Gonzalitos Av. N/N Col. Mitras Centro Monterrey, N.L., 64460, México. Tel.: +52 81 83333664, Fax: +52 477 724 5231., Email: edgar.carri_89@hotmail.com

Epidemiology of Cardiovascular and Periodontal Disease

Cardiovascular Disease

According to the World Health Organization (WHO), ASCVD remains the leading cause of death worldwide. In 2012 it accounted for about 17.5 million deaths, representing nearly 31% of the total of deaths globally [13]. Ischaemic heart disease is the most frequent form of ASCVD. In its 2017 report, the American Heart Association (AHA) estimates that every 40 seconds a person will suffer an acute myocardial infarction (AMI), also, that nearly 695,000 persons will suffer a new acute coronary event and about 325,000 will have a recurrent event, with 21% of these events being silent myocardial infarctions [14]. In Mexico in 2011, IHD accounted for 71,072 deaths, nearly 11% of the total of deaths in the country [15,16]. Cerebrovascular disease is another frequent form of ASCVD, which represents one of the leading causes of death worldwide. According to the AHA, every year, 795,000 people suffer a new cerebrovascular event (CVE) with 610,000 being first events and 185,000 recurrent events [14]. In Mexico, the accumulated incidence is 232.2 cases per 100,000 persons, with a prevalence of 18.2 cases per 1000 persons in those aged 60 years or older [17]. Peripheral artery disease affects almost 8.5 million people aged 40 years or older. Prevalence rises with ageing, being 22.7% in people of 80 years or more and 1.6% in those of 40 to 49 years [14].

Periodontal Disease

Through the years, estimating the incidence and prevalence of PD has represented one of the main challenges of the study of this disease. The existence of diverse diagnostic criteria and evaluation methods and the lack of consensus with regard to definition and disease severity has generated imprecise estimates of the real global impact of this condition [18,19]. In 1982, the WHO developed the ''Community periodontal index of treatment needs" (CPITN), which they later modified. This assessment tool aimed to standardise the evaluation of patients with suspected disease and with this, to obtain more reliable and reproducible data [20,21]. Recent data compilations for North and South America show that the average prevalence of severe forms of PD for adults in ages between 35 and 44 years is 20%, and 40% for less severe forms of the disease. In North America, the prevalence of severe disease seems to be low, suggesting that severe forms are more prevalent in South America [22]. Gingival bleeding and dental calculus are the most frequent forms of affection in every group of age. In Mexico, periodontal calculus are present in 31.9 to 35.7% of people between 35 and 44 years and 31.5 to 39% in those between 65 to 74 years [23]. An epidemiological survey showed that up to 56.8% of the population had some degree of PD. Twenty-one per cent had gingivitis, 3.9% shallow periodontal pockets and 0.8% deep periodontal pockets [23]. A consistent fact between epidemiological studies is that prevalence and severity of PD rise with ageing [19,23,24].

Periodontal Disease: Physiopathology and Risk Factors

In the oral cavity, teeth are supported by the periodontal ligament. The space between the higher point of the gingival margin and the point where the gingiva meets the dental surface is called the gingival sulcus, which is colonised with bacteria that form a biofilm or dental plaque. In PD, bacteria trigger an inflammatory process that deepens the gingival sulcus and eventually forms a periodontal pocket; moreover, there is apical displacement of the gingival union to the root surface and of the biofilm, loss of support tissue and alveolar bone, and gingival recession. Over 500 microbial species recovered from the dental plaque have been described [25]. The clean teeth are covered with a plaque of glycoproteins called ''pellicle" that binds to the hydroxyapatite on the tooth surface. Microorganisms inhabit this pellicle above and below the gingival margin as supra and subgingival plaque. The composition of microbial plaque above and below the gingival margin differs [24]. Supragingival space is colonised by *Streptococcus sanguis, Streptococcus oralis, Streptococcus mutans, Actinomyces naeslundii* and *Actinomyces odontolyticus*. In the absence of PD, subgingival space is colonised by *A. naeslundii, S. sanguis, S. oralis, Vellionella parvula, A. odontolyticus*, and *Fusobacterium nucleatum* [26]. Gingival inflammation represents an intermediate state between health and periodontitis, inflammation shifts the composition of bacteria to microaerophilic gram negative bacilli and anaerobes [27,28]. In periodontitis, subgingival microflora turns from being predominantly gram positive, to gram negative and obligated anaerobes like, *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Selenomonas noxia, Campylobacter rectus, Aggregatibacter actinomycetemcomitans, Prevotella intermedia*, and spirochaetes [25–28].

Risk factors for PD are divided between those that can be modified or at least controlled, like, smoking, diabetes mellitus (DM), obesity, alcoholism, osteoporosis and stress; and those that can't be modified, such as gender, ethnicity, age and genetic factors. Males seem to be more affected by PD. The ''National Health and Nutrition Examination Survey" (NHANES), showed that risk of PD is 50% higher in males than in females [29]. Smokers have four to five times greater odds of having PD than non-smokers [30]; and there's a relationship between intensity of smoking and the severity of PD [31]. The relationship between PD and DM has long been known, and it seems to be bidirectional. Most studies come from Pima Indians, where DM prevalence is of 40 to 50%, and these show that PD prevalence and severity is higher in diabetics [32]. Other studies have suggested that glucose intolerance is also related to PD [33]. Some systematic reviews and meta-analyses have shown an association between obesity and frequency and severity of PD [34].

Relationship Between Periodontal Disease and Cardiovascular Disease

Although periodontal inflammation has been associated for more than 20 years with a greater incidence of cardiovascular events [35], some issues have been raised about the validity of

the evidence suggesting such association. Both PD and ASCVD share an important number of risk factors. Also, both diseases are multifactorial in nature. The presence of multiple shared risk factors has been one of the main limitations of the studies suggesting this association, which have been in the majority, observational. Despite this, through the years, evidence continues to accumulate, with an important part of it suggesting an association [24]. Multiple mechanisms have been suggested as possible links between PD and ASCVD; systemic inflammation, molecular mimicry and direct vascular injury mediated by pathogens are the most important [24]. Figure 1 shows a proposed model for the relationship between PD and CVD.

Inflammation, Cardiovascular Disease and Periodontal Disease

Systemic inflammation is a well-known cardiovascular risk factor. Evidence suggests that patients with higher levels of circulating C reactive protein (CRP) have a greater risk of suffering an AMI or CVE; also, it has been demonstrated that treatment with aspirin diminishes the risk of AMI by almost 55% in patients with high levels of CRP compared with only a 13% reduction in those with low or normal levels of CRP, suggesting that aspirin's protecting effects are mediated partially by its anti-inflammatory properties [36]. Inflammation plays a major role in the genesis and progression of atherosclerosis [37]. Destabilisation of atheromatous plaques in the vascular intima is followed, on many occasions, by plaque rupture exposing the highly thrombogenic components of the endothelium to the blood, leading to the development of AMI or CVE. The main determinants of atheroma plaque vulnerability are the composition of its atheromatous nuclei, the presence of inflammation, and thinning of the fibrous cape that covers the nuclei [24]. It has been demonstrated that the presence of inflammation at the level of the atheromatous plaque interferes with the formation of the fibrous cape, and produces apoptosis and degradation of the extracellular matrix by activation of metalloproteinases augmenting the risk of plaque rupture and consequent development of cardiovascular events [24,38].

There is evidence that supports the association between systemic inflammatory states and cardiovascular disease (CVD). It has been observed that, in patients with chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, inflammatory myopathies and inflammatory bowel disease the incidence of cardiovascular events is increased [39]. It has been proposed that PD also generates a chronic systemic inflammatory state. Studies have demonstrated that patients with PD present higher circulating levels of CRP [40]. Also, other studies have shown that patients with PD have higher levels of other inflammatory markers such as, tumour necrosis factor and Interleukin-1, 6 and 8 [41].

Evidence Supporting the Association Between Periodontal Disease and Cardiovascular Disease

Even though there are classic risk factors for CVD like age, gender, familial history of ASCVD, smoking, DM, hypertension and hypercholesterolaemia; an important number of events remain not fully explained by these risk factors. First, evidence suggesting a link between PD and ASCVD emerged from observational studies that showed that patients admitted to the emergency rooms for acute coronary syndromes had worse dental hygiene that healthy controls.[35] Since then, more evidence has been generated trying to demonstrate that poor oral hygiene with the consequent development of PD can play a role as a risk factor for CVD.[24]

Periodontal Disease and Ischaemic Heart Disease

At least nine systematic reviews and meta-analyses suggesting an association between PD and IHD have been published [7,42–49]. Although most of the studies have shown a positive association between these diseases, concerns have been raised about the validity of these results, mainly because of methodological aspects of the studies. Humphrey et al. [48] demonstrated that different degrees of PD confer an increase in the risk of coronary heart disease (CHD) of about 24 to 35%. Their study showed a greater risk of CHD associated with periodontitis and tooth loss, with a relative risk (RR) of 1.24 (1.01–1.51, 95% CI) and 1.34 (1.10–1.63, 95% CI) respectively, and only a discrete and non-statistical significant increase in the risk for the presence of gingivitis, 1.35 (0.79–2.30, 95% CI) [48]. Bahekar et al. [46] demonstrated a greater incidence of CHD in patients with PD, RR of 1.14 (1.074–1.213, 95% CI) as well as a greater prevalence, with an odds ratio (OR) of 1.59 (1.329–1.907, 95% CI). Other authors have suggested that PD on clinical examination and CVD have a weak relationship, and that systemic bacterial exposure from periodontitis may be a more reliable risk factor. Mustapha and colleagues [47] demonstrated that periodontal disease with elevated markers of systemic bacterial exposure (periodontal bacterial burden, periodontitis specific serology and CRP) had a greater risk of developing CHD compared with subjects without PD.

Only a few studies have assessed the presence of early markers of coronary disease. Groves et al. [50] found that, in patients with type 1 DM, duration of PD has a significant relationship with the development and progression of coronary artery calcium. Also, other studies have found a relationship between severity of PD and presence of cardiac calcifications (i.e. valvular calcification), which are markers of subclinical atherosclerosis [51].

Periodontal Disease and Cerebrovascular Disease

The Multi-Ethnic Study of Atherosclerosis (MESA) study, evaluated 4476 people aged 60 years or older without known history of CVD with ultrasound measurements of the carotid-artery intima and media thickness (CIMT). After a 6.2 year follow-up, it was demonstrated that increases in the CIMT are directly associated with an increased risk of AMI and CVE [52]. The Atherosclerosis Risk in Communities (ARIC) study was the first to demonstrate that PD is related to an increase in the CIMT. Patients were divided based on the severity of PD

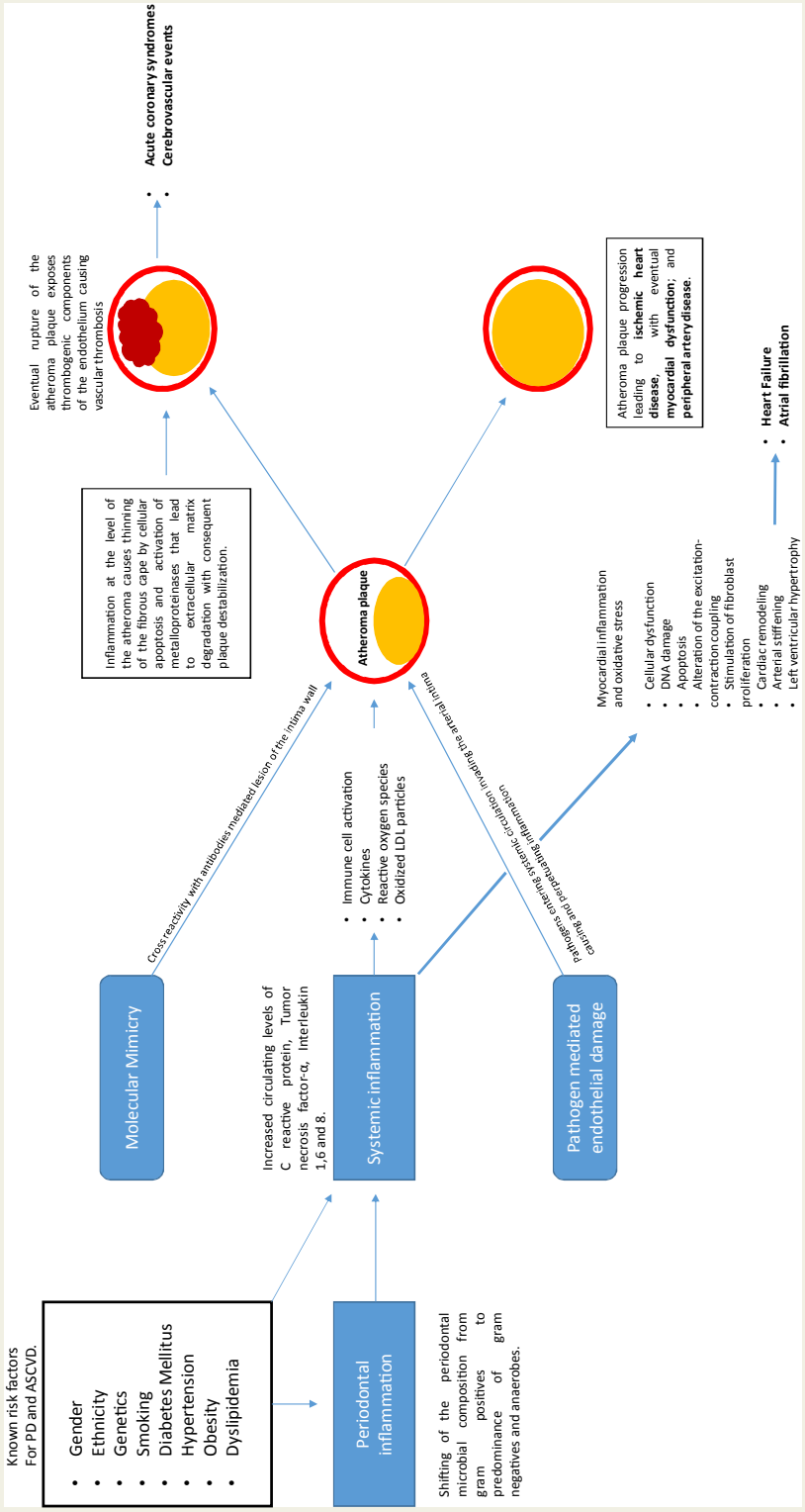

Figure 1 Proposed model for the relationship between periodontal disease and cardiovascular disease.
Periodontitis is associated with a pro-inflammatory systemic state. Activation of both innate and adaptive immune response trough cells and cytokines, generation of oxidative stress and promotion of low density lipoproteins (LDL) oxidation contributes to atheroma plaque development. Antibodies against periodontal pathogens cross react with elements of the intimal wall due to molecular mimicry causing damage and promoting plaque development. Persistent inflammation eventually destabilises the atheroma plaque causing its rupture with the development of acute coronary syndromes and cerebrovascular events. Myocardial inflammation and oxidative stress also cause DNA damage with apoptosis and fibrosis that lead to structural changes and ventricular dysfunction, eventually causing heart failure and atrial fibrillation.

(severity was classified according to the extent of attachment loss, ≥3 mm in <10% (mild), 10 to <30% (moderate) and ≥30% (severe) of the dental pieces). Results showed that the probability of having a CIMT ≥ 1 mm was greater for patients with moderate to severe forms of PD, OR 1.40 (1.17–1.67, 95% CI) and 2.09 (1.73–2.53, 95% CI) respectively, compared with those without PD [53]. Other studies have shown that up to 31.3% of patients with PD have unilateral carotid calcifications that are visible on panoramic radiographs, and 7.2% have bilateral calcifications also visible with this method [54]. Also, it has been demonstrated that the presence of carotid calcifications on panoramic radiographs correlates with their presence on Doppler ultrasound with a positive predictive value (PPV) of 79.3% for plaques >10 mm [54]. A relationship between PD, systemic inflammation and atherogenesis in the carotid arteries has also been suggested. Tapashetti and colleagues [55] demonstrated that persons with PD present higher levels of circulating CRP when compared to controls, (19.58 ± 17.03 vs. 5.54 ± 1.63, $p < 0.004$), also, that CIMT is greater in PD patients, ($1.09 \pm .45$ vs. 0.57 ± 0.06, $p < 0.001$), and that elevated CRP correlate with the increase in the CIMT with a correlation coefficient of 0.863. Some meta-analyses that evaluate the relationship between PD and CBVD have been published [8,44,56]. In a meta-analysis of cohort studies, Lafon et al. [56] reported that patients with periodontitis and tooth loss had an increased risk of presenting a CVE, with a RR of 1.63 (1.25–2.00, 95% CI) and 1.39 (1.13–1.65, 95% CI), respectively. Sfyroeras et al. [8] demonstrated, in a meta-analysis of prospective and retrospective studies, that PD increased the risk for CVE with a RR of 1.47 (1.13–1.92, 95% CI) for prospective studies and 2.63 (1.59–4.33, 95% CI) for the retrospective studies.

Periodontal Disease and Peripheral Artery Disease

The term, peripheral artery disease, PAD, refers to the occlusive disease of the arteries with origin distal to the aortic bifurcation, the most common cause is atherosclerosis, and most common symptom is intermittent claudication [57]. The presence of PAD, defined as an ankle-brachial index (ABI) < 0.9 has been associated with an increased risk of cardiovascular events. Leng and colleagues [58] evaluated a prospective cohort of 1592 men and women aged 55 to 74 years for 5 years. After follow-up, they found that people with an ABI <0.9 had more risk of death from cardiovascular causes, RR 1.85 (1.15–2.97, 95% CI) and death from any cause, RR 1.58 (1.14–2.18, 95% CI). Another analysis of the same cohort, found that patients presenting with symptoms of PAD had a greater risk of developing angina, RR 2.31 (1.04–5.10, 95% CI) [59]. Multiple studies have evaluated the relationship between PD and PAD [9,10,60–62]. Chen and colleagues [10] evaluated 25 patients with aorto-iliac and/or femoro-popliteal disease that had undergone bypass surgery. They analysed specimens from the anastomotic site of distal bypasses with polymerase chain reaction for the detection of periodontopathic bacteria. Almost 52% of specimens had detectable bacteria. Patients with PAD grade III and IV of Fontaine classification had higher detection frequency of *P. gingivalis* compared of those with grades II of Fontaine (57.1% vs. 22%, p = 0.09). After adjusting for age, gender, DM and smoking, it was found that periodontitis increases up to five times the risk of developing PAD [10]. Soto-Barreras and colleagues [9] evaluated a Mexican population and found that the presence of attachment loss ≥ 4 mm in more than 30% of the dental pieces was associated with a six-fold increased risk of PAD.

Periodontal Disease and Heart Failure

Heart failure is a clinical syndrome involving cardiac structural and functional alterations that result in diminished cardiac output and/or increased ventricular filling pressures at rest or during stress, and may feature reduced or preserved left ventricular ejection fraction (LVEF) [63]. Despite differences in demographics, aetiology, pathophysiology, clinical presentation and function, heart failure features a chronic and dysregulated inflammatory state that contributes to the progression of myocardial damage, decline in functional capacity and poor outcomes [64–66]. Recently, oxidative stress has been described as another mechanism that favours the development and progression of HF [67]. Presence of reactive oxygen species (ROS) causes cellular dysfunction, oxidation of proteins and lipids, and damage to the deoxyribonucleic acid (DNA), which translate in cellular death; also, ROS alter the contractile function by modifying proteins that are crucial for the excitation-contraction coupling, and stimulate fibroblast proliferation and metalloproteinases activation favouring cardiac remodelling [67]. Experimental animal studies have suggested an association between PD, oxidative stress and cardiac stress. Köse and colleagues [68] evaluated a group of rats with periodontitis induced by silk suture and found that compared with healthy rats, rats with induced PD had higher levels of oxidative damage markers found in left ventricular tissue.

Only two studies have assessed for the presence of HF in patients with PD [11,69]. Wood and Johnson [69] were the first to suggest an association between these diseases. They evaluated over 17,000 patients from the NHANES III and found that patients with PD had higher rates of self-reported HF; also, they found that monthly tomato consumption had a protective effect on HF, possibly explained by higher levels of lycopene, a carotenoid with anti-oxidant and anti-inflammatory properties present in tomatoes. Another study by Fröhlich et al. [11] evaluated patients with chronic stable HF, and found that, compared with controls, patients with HF had higher prevalence of PD. Also, they found that severity of PD is not associated with the aetiology of heart failure and does not correlate with HF symptom severity.

Systemic inflammation appears to have an important impact on structure and function of the left ventricle (LV). A study evaluated 1016 people using echocardiography, they measured the relative wall thickness (RWT), left ventricular mass index (LVMI), and E/A index. Also, they did measures for 10 inflammatory markers. They found that persons with LV concentric remodelling and concentric and eccentric LV hypertrophy, had higher levels of high sensitivity CRP and E-

selectin, compared to controls. Also, they found that I-selectin and CRP levels had an inverse relation with the E/A index [70]. One study in patients with dilated cardiomyopathy showed that atorvastatin use is associated with an important reduction in the level of circulating inflammatory markers (IL-6 and TNF) and levels of brain natriuretic peptide (BNP); as well as a reduction in the LV systolic and diastolic diameters and improvement of LVEF, probably associated with atorvastatin anti-inflammatory and anti-oxidant effects [71]. Jockel-Schneider and colleagues demonstrated that, compared to controls, patients with PD had an increased arterial stiffness, measured by pulse wave velocity (PWV), augmentation index (AIx), and pulse pressure amplification (PPA) [72]. It is well known that the increase in arterial stiffness is associated with the presence of LV hypertrophy [73,74]. Only three studies have evaluated the presence of structural alterations in the LV in patients with PD. Angeli and colleagues [75] evaluated 104 patients with prior diagnosis of arterial hypertension without treatment using echocardiography and periodontal evaluation, patients were classified using the WHO CPITN; results showed that increases in PD severity correlated with increases in LV mass, 39 ± 2.7 g/height$^{2.7}$ for CPITN 0 (healthy periodontium), 40.2 ± 6.4 g/height$^{2.7}$ for CPITN 1 (gingival bleeding), 42.7 ± 6.8 g/height$^{2.7}$ for CPITN 2 (calculus), 51.4 ± 11.7 g/height $^{2.7}$ for CPITN 3 (4–5 mm pocket), and 76.7 ± 11.3 g/height$^{2.7}$ for CPITN 4 (> 6 mm pocket). Another study compared patients with PD CPITN 3-4 with CPITN 0-2 and found that LV mass was increased in patients with more severe disease and that this correlated with increases in central venous pressure and pulse pressure [76]. The most recent study analysed diabetic patients without PD, and with gingivitis and periodontitis, and found that, compared to controls, patients with different degrees of PD had higher LV mass [77].

Periodontal Disease and Atrial Fibrillation

Atrial fibrillation (AF) remains the most common sustained arrhythmia in adults worldwide, with a prevalence that is expected to increase up to three-fold in the next three decades [78]. Atrial fibrillation physiopathology consists of atrial remodelling with deposition of connective tissue, fibroblast activation and inflammation that eventually leads to fibrosis and atrial dilatation [79]. Inflammation seems to play a major role in the development and perpetuation of AF, furthermore, it is also associated with platelet and coagulation cascade activations, leading to thrombosis, suggesting that, not only does it promote the development of AF, but it also contributes to AF thrombotic complications [80]. Only one study has assessed the risk of AF in patients with PD [12]. This population based cohort study, used data from the Taiwanese National Health Insurance Research Database and enrolled 393,745 patients with PD and 393,745 without PD. They found that patients with PD had an incidence rate of atrial fibrillation/flutter of 200 cases per 10^5 years vs. 181 cases per 10^5 years in patients without PD. This study had important limitations, which are pointed out by the authors. There was no information about other possible risk factors for AF, there was no clinical data to validate the diagnosis of AF/flutter, there are also concerns about the accuracy of PD diagnosis, and later, authors had no information about severity of PD [12].

Conclusions

Periodontal disease and CVD are both major health issues. Both diseases are multifactorial in nature and share an important number of risk factors. Inflammation plays an important role in the development of cardiovascular disease, and PD is associated with a systemic inflammatory state. Evidence suggests a strong association between both diseases and inflammation appears to be one of the main connections. Most of the available data comes from observational studies, assessing major outcomes like myocardial infarction, heart failure, stroke, or death from cardiovascular causes, but only a few studies have focussed on preclinical markers of cardiovascular disease in patients with PD. Some studies even suggest that healthy patients with evidence of PD have signs of atherosclerosis, so PD could account for a percentage of cardiovascular events that cannot be explained by the presence of common cardiovascular risk factors. Studies should focus on the use of new images techniques such as cardiovascular nuclear magnetic resonance, new modalities of echocardiography, coronary computed tomography, and others, to try to detect early stages of cardiovascular disease or subtle alterations in cardiovascular structure and function related to PD, in order to achieve a deeper understanding of the relationship between both diseases.

Funding

None.

Conflict of Interest

No conflict of interest to disclose.

All authors had full access to data and a role in the preparation of this manuscript.

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