

REVIEW

Current knowledge on the association between cardiovascular and periodontal disease: an umbrella review

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ABSTRACT

INTRODUCTION: Periodontal disease (PD) and cardiovascular diseases (CVD) are among the most common pathologies in the world and their relationship has long been studied. Both conditions lead to a chronic inflammatory process with degenerative characteristics and their biunivocal correlation is now well established. The aim of this umbrella review on cardiovascular and periodontal disease was to evaluate the real degree of association between these two pathological conditions.

EVIDENCE ACQUISITION: We conducted a comprehensive literature search on PubMed/Medline and in the Cochrane Library for systematic reviews focused on clinical evidence regarding the relationship between PD and CVD. The internal validity of systematic reviews and meta-analyses was formally analyzed using the Overview Quality Assessment Questionnaire (OQAQ) Tool. The umbrella review was planned in accordance with current international recommendations and was described as specified by the PRISMA Guidelines.

EVIDENCE SYNTHESIS: Thirty-one systematic reviews, including 8 meta-analyses for a total of 507 clinical studies and over 3,549,966 patients were included. PD resulted to be associated with a higher risk of developing CVD (acute coronary syndrome, acute myocardial infarction) and cerebrovascular diseases (ischemic stroke); however, if the treatment of periodontitis reduces the risk of CVD events related is yet to be investigated.

CONCLUSIONS: To date, the relationship between CVD and PD provides heterogeneous data. There is an association between PD and CVD, but a causal relationship cannot be established. Further research with properly designed long-term follow-up studies are needed in order to examine various physiopathological aspects of their association.

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KEY WORDS: Periodontal disease; Cardiovascular diseases; Atherosclerosis; Inflammation.

Introduction

Periodontal disease (PD) is an infectious-inflammatory disease that arises from the loss of balance between the commensal oral microbi-

ome and the host response, which promotes tissue damage and prevents an effective bacterial clearance.¹

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Periodontitis is associated with a predominantly gram-negative infection. However, there is evidence that the destruction of periodontal tissue is mediated by the host response. Despite the many clinical presentations of PD, the diagnosis of periodontitis is graded upon severity and rate of progression of disease rather than pathogenesis.²

The global prevalence of PD is difficult to evaluate due to the studies heterogeneity, even though a relative higher pooled prevalence of aggressive PD was found in Africa and South America rather than Europe.³ Ikeda *et al.* demonstrated that healthy individuals and periodontitis patients showed not only a different microbial composition, but also different genes expression and metabolic pathways.⁴ It is known that the relationship between bacteria and host is bidirectional, indeed bacteria induces inflammation, while inflammation modifies the growth environment causing shifts in the microbiome composition.¹ This exchange of consequences is not limited to the oral cavity. Recently, it has been evidenced that the oral cavity is the second largest microbiota in the human body, with about 500 different bacterial species identified to date that play a fundamental role in the human health regulation and pathologies determination.⁵ Oral dysbiosis is not only involved in periodontal disorders, but also in metabolic ones, including cardiovascular disease (CVD).⁶ At the same time, today CVD mortality and morbidity represent a huge disease and economic burden on the society,⁷ with ischaemic heart disease, stroke, hypertension (leading to heart failure), being the major cause of CVD related deaths.⁸ Therefore, PD and CVD are among the most common diseases in the world that cause chronic inflammation with degenerative characteristics.⁹ Chronic inflammation is characterized by an increase in the inflammatory cytokines' level, which causes a weakening of the immune system function, thus increasing the risk of atherosclerosis and insulin resistance, which are the main triggers for developing CVD.¹⁰ In literature, the association between PD and diabetes is well-documented in an umbrella review by Seitz *et al.*,¹¹ whereas the association between PD and CVD is currently less investigated. Since diabetes is also an important CVD

risk factor, it can be considered as a *trait d'union* between PD and CVD.

Therefore, the aim of this umbrella review was to exclusively evaluate the association between PD and CVD. This correlation is demonstrated by multiple systematic reviews and meta-analysis, but more studies are needed to further deepen the results. It is important to specify that the word "association" does not necessarily mean a causal relationship, but it refers to a still not well-known link between the two diseases.

Evidence acquisition

Protocol

This umbrella review was performed according to current international recommendations¹²⁻¹⁴ and PRISMA Guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).¹⁵

Bibliographic search and study selection

We conducted a comprehensive literature search in PubMed/Medline and in the Cochrane Library directed to identify systematic reviews focused on clinical evidence regarding the relationship between cardiovascular and periodontal disease. In particular, we used the following search string in PubMed/Medline: ("periodontitis" OR "periodontal disease" OR "periodontal diseases" OR "periodontal" OR "periodontology" OR "periodontal therapy" OR "periodontal treatment" OR "periodontics") AND ("cardiovascular disease" OR "cardiovascular diseases" OR "cardiovascular" OR "cardiovascular problems" OR "myocardial infarction" OR "stroke" OR "atherosclerosis" OR "heart" OR "heart disease") AND ("association"). This research was updated from November 2007 to December 2021. The keywords were combined to get the most results. We included in this umbrella review all the systematic reviews and meta-analyses focused on various aspects of cardiovascular and periodontal diseases (epidemiology, risk factors, pathophysiology, diagnosis, prognosis, therapies, etc.). All the resulting studies were initially considered suitable, with the exception of those in non-English language.

Data extraction and qualitative evaluation

Salient data regarding the study methodology, the pathologies analyzed, the results reported, and their interpretation were extracted for each systematic review (Supplementary Digital Material 1: Supplementary Table I, Supplementary Table II). The internal validity of systematic reviews and meta-analyses was formally analyzed using the OQAQ (Overview Quality Assessment Questionnaire) Tool¹⁶ (Supplementary Digital Material 2: Supplementary Table III, Supplementary Table IV). We extracted salient features of the reviews included and the results have been summarized in a tabular form.

Results

Revision

PubMed search allowed the selection of 3067 results with the keywords entered and combined. A further systematic review¹⁷ included by Seitz *et al.*¹¹ was added from a literature search. Selecting the type of studies, 111 publications including systematic reviews and meta-analyses were reviewed. Of these, 76 were excluded by title, abstract, year of publication, lack of full text and duplicates. The full text of the 35 remaining articles was appraised and 5 more articles were excluded since they were narrative reviews, not related to the topic or non-English articles. Finally, 31 articles were included, as showed in Figure 1 (PRISMA diagram).

Main results in included reviews

Among the 31 selected articles, 11 are systematic reviews, 8 are meta-analyses, and 12 are both systematic reviews and meta-analyses, for a total of 507 studies and over 3,549,966 patients included (Supplementary Table I-IV). The search results pointed out the association between PD and cardiovascular diseases (Figure 2). In this regard, PD may be a CVD risk factor^{18, 19} and, at the same time, the worse cases of PD and tooth loss are more frequent in patients affected by atherosclerosis¹⁷ hypertension²⁰ and peripheral arterial disease than in controls. The evidence shows links between various issues of periodontal dis-

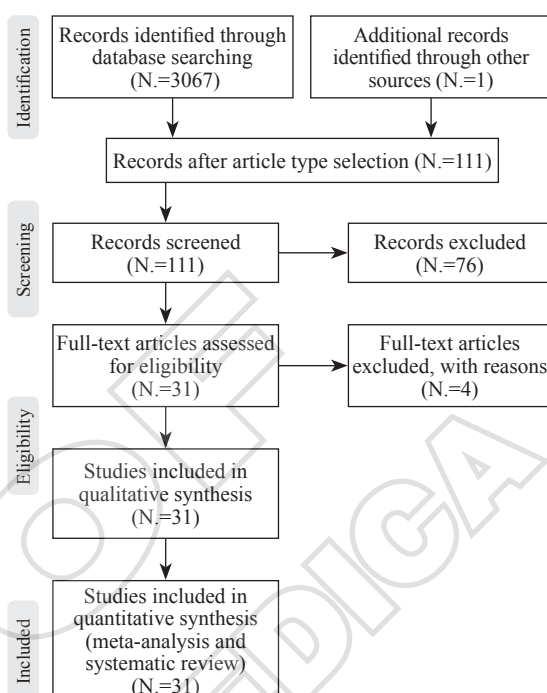


Figure 1.—PRISMA flowchart with the selection of the systematic reviews and meta-analysis included in the umbrella review.

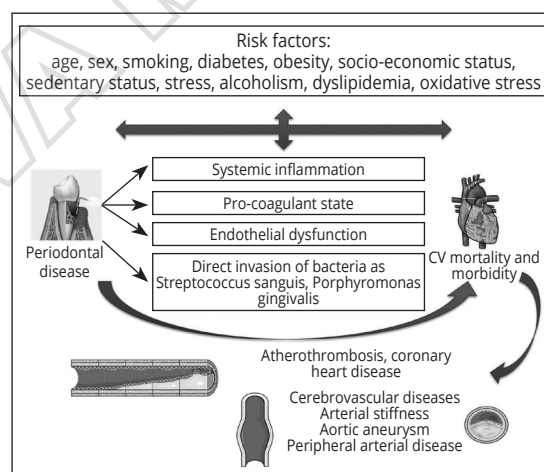


Figure 2.—Correlation between periodontitis and atherosclerotic cardiovascular disease.

ease (clinical,^{17, 21, 22} microbiological,^{17, 23, 24} immunological,^{17, 18, 25-27} pathophysiological,²⁸⁻³⁹ risk of onset²² and treatment^{19, 40, 41}) and different manifestations of cardiovascular diseases (coronary heart disease,^{9, 18, 25, 42, 43} atherosclerosis,^{17, 27, 41} atherothrombosis²¹ stroke,^{28, 29, 31, 32, 35}

myocardial infarction,^{23, 38} peripheral arterial occlusive disease,^{22, 30, 37} hypertension,^{20, 40} thickness and flow mediated dilation of the intima-media carotid,^{26, 39} abdominal aortic aneurysm,²⁴ arterial stiffness¹¹ and carotid atherosclerosis³⁹). Despite the evidence showing a strong association between the two pathologies, currently there is no clear causal relationship between the two diseases and further investigations are needed in order to better define the physiopathological aspects of this correlation.

Summary of results

This umbrella review did not reveal a strong, unquestionably cause/effect relationship between PD and CVD. However, it is possible to conclude that periodontitis and CVD are linked by a bidirectional association (Supplementary Digital Material 3: Supplementary Table V). In fact, PD may be a risk factor for the onset of CVD^{18, 19} and worse stages of PD are noted in patients with atherosclerosis,¹⁷ hypertension²⁰ and peripheral arterial disease.⁴⁴

Periodontitis and cardiovascular diseases

Cardiovascular diseases are known to be a major cause of death worldwide and the number of patients with CVD has grown over the years.⁴⁵ CVD are caused by multiple determinants that can be divided into un-modifiable and modifiable risk factors. Among the main modifiable traditional cardiovascular risk factors there are hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking; all possible targets for pharmaceutical intervention in order to lower the global cardiovascular risk. Inflammation is one of the fundamental processes in numerous diseases and key mechanisms underlying the development of CVD. Periodontitis (PD) is a chronic oral inflammatory disease resulting in a deregulated local and systemic inflammatory response. Several studies suggest a relationship between CVD and PD focusing mostly on the role of common inflammatory pathways linking the two pathological conditions, however whether the association is causal is still debated.⁸ Berlin-Broner *et al.* conducted a systematic review to assess the link between apical periodontitis (AP) and CVD confirmed by the presence of one of

the following criteria: diagnosed coronary artery disease, angina pectoris, acute myocardial infarction, stroke or mortality caused by cardiac pathology; although most of the published studies found a positive association between AP and CVD, the quality of the evidence was low, and a causal relationship cannot be established.⁴⁶ Blaizot *et al.* conducted a meta-analysis on epidemiological and observational studies concluding that the risk of developing CVD appeared to be approximately one-third greater in subjects affected by PD compared to healthy individuals. Moreover, the study pointed out that Scandinavian and American populations showed limited correlation between PD and coronary heart diseases respect to Europeans. Although previous trials suggested a causal relationship between PD and CVD, this meta-analysis cannot answer the question of whether treating the PD is able to reduce the risk of CV events.¹⁹ The aim of the systematic review updated in 2017 and re-analyzed in 2019 by Liu *et al.* was to investigate the effects of periodontal therapy in preventing CVD occurrence in patients with chronic periodontitis.⁴⁷ Regarding primary prevention of CVD, the authors identified insufficient evidence to support that PD therapy can prevent long-term CV events recurrence. No rugged data on secondary prevention of CVD was found. Li *et al.* investigate the effects of periodontal therapy in preventing the occurrence of CVD in patients with chronic periodontitis including as eligible randomised controlled trials (RCTs) and quasi-RCTs. The authors found insufficient evidence to support whether periodontal therapy can prevent CVD in the long term in patients with chronic periodontitis.^{47, 48}

In a recent systematic review Larvin *et al.* demonstrated an increased risk of CVD in people with PD.⁴² Males and people with severe PD have the highest risk of developing CVD suggesting that population-targeted interventions could be beneficial.⁴³

Periodontitis and arterial stiffness

Endothelial cells play a fundamental role in vascular homeostasis. Inflammations causes increase in vascular permeability and imbalance in the synthesis/secretion of vasodilating substances (nitric

oxide and prostacyclin) and vasoconstrictor (endothelin 1, thromboxane and angiotensin II).⁴⁸ Vascular endothelial dysfunction has been associated to traditional risk factors for atherosclerosis (including age, hypertension, dyslipidaemia, diabetes, smoking, obesity), so as to cardiovascular and cerebrovascular diseases and infectious and inflammatory processes, such as periodontal disease. Several studies demonstrated that PD is related to endothelial dysfunction, atherosclerosis and CVD.⁴⁹ Arterial stiffness is considered a marker of arteriosclerosis and a CVD risk factor.⁵⁰ A number of studies have used pulse wave velocity (PWV) as a measure of arterial stiffness. Schmitt *et al.* conducted a literature systematic review on clinical studies using PWV to assess arterial stiffness in patients with periodontitis, concluding that even if patients with periodontitis appear to have higher values of PWV compared to controls, the effect of periodontal treatment on arterial stiffness still remains unclear.³⁴ Nicolosi *et al.* conducted a study to determine possible differences in arterial stiffness and endothelial function parameters between patients with and without severe PD. The study findings revealed worse parameters of arterial stiffness and endothelial dysfunction in patients affected by PD and a moderate correlation between these results and the clinical features. Arterial distensibility (measured by compliance) was not correlated with endothelial function.⁵¹ In their systematic review and meta-analysis Orlandi *et al.* investigated the association between carotid intima-media thickness (c-IMT), flow-mediated dilatation (FMD) and periodontitis. The authors assessed the effect of periodontal treatment on c-IMT and FMD, concluding that an association exists between increased c-IMT, impaired FMD and PD. Indeed, findings from the analysis of 3 randomized controlled trials supported a protective role of PD treatment on FMD, probably due to the improvement in endothelial function.²⁶ The association between PD and carotid atherosclerosis has also been evaluated in the meta-analysis published by Zeng *et al.*, including fifteen observational studies and 17,330 participants. The patients affected by PD reported significantly higher prevalence of carotid atherosclerosis. Moreover, this association appeared to be directly proportional to the

severity of PD and independent from other confounders such as smoking or diabetes. However, the mechanism linking these conditions is not yet well understood and other studies are needed to define more conclusive results.³⁹

Periodontitis and atherosclerosis

Atherosclerosis is a multifactorial inflammatory process of the cardiovascular system and represents the key mechanism underlying the development of CVD.⁵² Atherosclerosis is now considered a chronic inflammatory disease of blood vessels and is characterized by a maladaptive immune response resulting in the formation of lipid-rich, inflamed plaques.⁵³ Atherosclerotic cardiovascular diseases (ACVDs) include coronary heart disease (angina, myocardial infarction), ischemic cerebrovascular disease (stroke/transient ischemic attack), and peripheral arterial disease.⁵⁴ The causes of ACVDs are complex but several studies suggested that PD could exacerbate atherosclerosis, thus reinforcing the hypothesis of a link between the two pathological conditions. In their systematic review, Almeida *et al.* aimed to assess the association between periodontitis and atherosclerosis in adults concluding that there is a relationship between the two diseases, with increased levels of inflammatory markers, mainly C-reactive protein and interleukin 6 (IL-6).⁵⁵ Navarro *et al.* documented that patients with ACVDs present a worse oral hygiene and fewer teeth concluding that there is an association between ACVDs and chronic apical periodontitis.²¹ In their systematic review and meta-analysis Roca-Millan *et al.* analyzed the effects of periodontal treatment on cardiovascular risk parameters in patients with ACVDs. The clinical trials analyzed suggested that periodontal treatment has a beneficial effect on some of the biochemical parameters considered to represent cardiovascular risk (C reactive protein, TNF-alpha, IL-6, fibrinogen and leukocytes), but the magnitude of this intervention is still unknown.⁴¹ Finally, Teeuw *et al.* demonstrated that periodontal treatment increases endothelial function and reduces biomarkers of atherosclerotic disease, especially in subjects with co-morbidities (CVD and/or diabetes), suggesting that treating PD may improve the patients' atherosclerotic profile.²⁷

Periodontitis and hypertension

Arterial hypertension represents an important and proven risk factor for numerous cardiovascular conditions, such as ischemic heart disease (angina and myocardial infarction), heart failure, stroke and peripheral arterial disease. Essential or idiopathic hypertension (90-95% of cases), namely the presence of high blood pressure values without an identified cause, is a combination of environmental factors such as obesity, stress, sedentary lifestyle, incorrect diet and genetic predisposition, able to influence its course and prognosis. Arterial hypertension and periodontitis are two highly prevalent worldwide conditions with a significant impact on cardiovascular burden. Poor periodontal health is associated with increased prevalence of hypertension and may have an influence on blood pressure (BP) control. Recent evidence suggests that periodontitis and hypertension are independently related and may be causal in nature.⁵⁶ The main mechanism underlying this association seems to be low-grade systemic inflammation and redox imbalance; however, the nature of this relationship is currently being studied. Moreover, recent findings indicate that common genetic bases could orient the immune profile towards this clinical phenotype with important therapeutic implications thus necessitating targeted strategies of public health interest.

In their meta-analysis Muñoz Aguilera *et al.* critically evaluated the evidence linking hypertension and PD, concluding that there is a positive association between the two pathological conditions. In fact, there is an increased prevalence of periodontitis in patients with hypertension and oral health assessment could improve quality of life and could also be relevant in the management of hypertensive patients, though only few studies demonstrated that periodontitis therapy entails a reduction in BP values.²⁰ Moreover, heterogeneity among populations and common risk factors make the interpretation of the results difficult. Another study aiming to determine the magnitude of the association between PD and hypertension is the meta-analysis of Martin Cabezas *et al.*, who concluded that patients with PD, particularly with severe forms of PD, reported a higher frequency of hyperten-

sion.⁴⁰ However, the limited availability of prospective studies does not allow drawing definitive conclusions on the causative involvement of PD, so questions about the underlying biological mechanisms still remain unanswered.

Periodontitis and coronary heart disease

Atherosclerotic coronary heart disease (CHD), leading to myocardial infarction (MI) and ischemic cardiomyopathy, is the main cause of cardiovascular mortality, morbidity, and health economic burden worldwide.⁵⁷ Epidemiologic data have shown that inflammation is independently and strongly associated with future cardiovascular events in both primary and secondary prevention.

Furthermore, several studies have proven that chronic inflammatory diseases are burdened by a higher spectrum of atherosclerotic CHD.⁵⁸⁻⁶⁰ The association between chronic periodontitis and CHD is still controversial, despite the plethora of research on this topic. Many studies investigated the relationship between these two pathological conditions: Voinescu *et al.* in a recent systematic review observed that prevalence of PD in patients with ischemic cardiac disease was high, although the underlying mechanism was not yet clearly proven.³⁶ The meta-analysis of Bahekar *et al.* showed that both the prevalence and incidence of CHD are significantly higher in patients affected by PD and therefore periodontitis may be a risk factor for CHD.¹⁸ Recent data suggested an important role of chronic inflammation in the development of CHD. In a systematic review and meta-analysis published in 2008 Humphrey *et al.* concluded that PD is a risk factor/marker for CHD, appearing as an additional CV risk factor beside the traditional ones, including socioeconomic status.²⁵ One of the proposed pathways that links periodontitis and myocardial infarction is the microbial translocation from inflamed periodontal pockets into coronary atheroma *via* systemic circulation. In their meta-analysis Joshi *et al.*, observed that a consistent detection of periodontal bacterial DNA in coronary atheroma has been described in literature, suggesting their systemic dissemination from periodontal sites.²³ The quality of published systematic reviews focused on the association between PD and CHD

was evaluated by Kelly *et al.* by using established systematic review assessment checklists. The results showed a significant structural and methodological variability among the published systematic reviews and meta-analyses regarding the connection between periodontitis and CHD with important practical implications for clinicians.⁹ In an updated meta-analysis conducted on prospective cohort studies, Leng *et al.* indicated that PD was significantly and independently associated with an increased risk of CHD.³³ Finally, Xu *et al.* investigated the association between PD and MI in a meta-analysis on observational studies, suggesting that PD is associated with increased risk of future MI. However, the causative relation between PD and MI remains not well established and more studies are warranted.³⁸

Periodontitis and cerebrovascular diseases

Stroke is the second leading cause of death and the third cause of disability worldwide as well as one of most important cause of disability in the elderly population. Multiple risk factors are associated with this condition (age, hypertension, dyslipidaemia) but the role of inflammation in the pathogenesis and progression of the disease is still a debating issue.⁶¹⁻⁶³ Several studies have investigated the possible association between PD and multiple causes of stroke. In a recent meta-analysis Fagundes *et al.* explored the association between stroke and periodontitis, concluding that there is a strong association between both diseases and that periodontitis may represent a risk factor especially for ischemic strokes.²⁹ Cheng *et al.*, performed a dose-response meta-analysis showing a statistically significant correlation between tooth loss and both cardiovascular and stroke risk, suggesting that tooth loss was independently associated with lethal coronary heart disease and stroke risk increase.²⁸ Lafon *et al.*, aimed to determine the relationship between PD and stroke incidence by a meta-analysis including cohort studies that evaluated the incidence of stroke (fatal or non-fatal, ischaemic or haemorrhagic) and baseline periodontal status. The analyses were conducted separately for three outcomes: periodontitis, gingivitis and loss of teeth and the results varied depending on the outcome considered and the type of stroke. The

risk of stroke appeared significantly increased by the presence of periodontitis, while did not vary markedly with the presence of gingivitis. Tooth loss resulted also a risk factor for stroke.³¹ The association between PD and ischemic stroke was investigated in the meta-analysis of Leira *et al.* Case-control, cross-sectional and cohort studies involving patients with PD and ischemic stroke were included in the analysis. The study demonstrated an association between periodontitis and ischemic stroke. Moreover, the risk of cerebral ischemia appeared also higher in subjects with periodontitis, but further, well-designed, prospective studies should be conducted to better elucidate the magnitude of this association.³² Even though there are evidence that PD is associated to CVD and stroke, interpretation of results requires caution because of the studies heterogeneity and the differences in the definition of periodontitis, as highlighted by Sfyroeras *et al.* in a review about this topic.³⁵ For this reason, to date, further studies are necessary to reach a consistent conclusion about the degree of the relationship between PD and cerebrovascular disease.

Periodontitis and peripheral arterial disease

As well as coronary heart disease (CHD), peripheral arterial disease (PAD) is also caused by atherosclerosis but with different characteristics. The association between CHD and periodontitis has already been confirmed by several studies. Nowadays, there is scientific consensus that the development of PAD is partially related to chronic subclinical inflammation.⁶⁴ The oral cavity is an inflammatory focus in humans, and it was proposed that chronic oral inflammation might be able, in concert with other risk factors, to trigger PAD. In a recent nation-wide, population-based cohort study Cho *et al.* highlighted that poor oral hygiene status increases the risk of PAD and that patients with periodontitis have a higher incidence of PAD, prospecting the possibility that the treatment of PD may have a strong impact in the prevention of PAD.⁴⁴ In a recent systematic review Kaschwich *et al.* evaluated the association between PD (all degrees of severity) and PAD (all degrees of severity) concluding that, although a causal role of PD in the development of PAD cannot be confirmed, it is likely

that it plays a contributing role in PAD pathogenesis.³⁰ Yang *et al.* conducted a meta-analysis to critically assess the strength of the association between PAD and periodontitis, which revealed a significant relationship between these two conditions. Moreover, the meta-analysis indicated that PAD patients had more missing teeth than control subjects.²² The systematic review of Wang *et al.* was conducted to evaluate how periodontitis contributes to the pathogenesis and progression of PAD; the results confirmed that PD represents an independent risk factor for PAD, with significant data supporting its correlation with both lower extremity arterial disease and carotid artery disease.³⁷

Periodontitis and abdominal aortic aneurysm

Abdominal aortic aneurysm (AAA) is a chronic vascular degenerative disorder. It is known that genetic and environmental risk factors (older age, male sex, smoking, white ethnicity) can promote the disease. The AAA physiopathology and progression are characterized by the inflammatory destruction of the abdominal aortic wall and the presence of an intraluminal thrombus. The association between periodontitis and systemic diseases such as diabetes or cardiovascular disorders has been well described, however, the prevalence of periodontitis in patients with AAA is not available in the scientific literature. Nevertheless, a systematic review by Salhi *et al.* emphasized that periodontitis seems to play a role in AAA development and progression, suggesting that the presence of periodontal bacteria in the bloodstream or in the vascular lesion represents a risk factor associated with aneurysmal disease progression.²⁴ Even more recently Salhi *et al.*, in a cross-sectional study, explored the relationship between the severity of periodontitis and of AAA comparing patients with stable and unstable AAA based on aortic diameter, growth rate, and eligibility for surgical intervention. The results showed that periodontitis was highly prevalent in both stable and unstable AAA patients and that severe periodontitis (stage IV and grade C) shows the trend to be more frequent in groups of patients with unstable AAA, thus reinforcing the evidence of a potential relationships between these two diseases.⁶⁵ Finally, a

systematic review conducted by Kaschwich *et al.* demonstrated that an association between PD and peripheral arterial occlusive disease is likely, even though the results cannot confirm a causal role between the two conditions.⁶⁶

Discussion

The PD is a multifactorial chronic infectious disease of the teeth supporting structures. It begins as a localized inflammation (gingivitis) caused by a bacterial biofilm, mainly induced by gram-negative germs. This condition is often reversible, since gingivitis is tractable with a good oral hygiene. Sometimes a not well-treated gingivitis may deteriorate in periodontitis, which represents an irreversible chronic inflammatory disease characterized by progressive destruction of teeth insertion apparatus (connective tissue, ligament and bone) with increase in tooth mobility and often in tooth loss. The local inflammation could lead to systemic inflammatory status, which is a known factor for CVD. Periodontitis has previously been correlated to several systemic conditions such as rheumatoid arthritis⁶⁷ and metabolic syndrome⁶⁸ emphasizing the impact of oral health on the systemic homeostasis.

The umbrella review that we performed has gathered systematic reviews and meta-analyses showing that periodontitis is linked to various types of CVD. We found evidence of significant correlation between PD and atherosclerosis, hypertension, PAD (carotid intimal hyperplasia and abdominal aortic aneurysm), coronary heart disease and cerebrovascular disease.⁶⁹ Specifically, patients affected by PD have shown a greater carotid intima-media thickness compared with controls and impaired flow mediated dilatation, which appeared restored by periodontal treatment⁷⁰ as well as more prevalence of abdominal aortic aneurysm⁷¹ or modifications of arterial stiffness. It has also been found that treating periodontitis effectively improved the function of the vascular endothelium and may play a protective role in vascular injury.⁷² Moreover, individuals with PD exhibited 2-fold higher risk of developing PAD and PD represents an independent risk factor for PAD. Furthermore, we found evidence that treating intensively patients affected by PD induced a significant reduction in blood pressure

values if compared to not-intensive PD treatment; this helps identifying PD as an additional, non-traditional risk factor of hypertension, such as lifestyle modifications. Additionally, oral health seems to be correlated with ischemic coronary events⁷³ since PD prevalence is higher in patients affected by coronary heart disease (CHD) than in general population, showing that PD may be considered an independent risk factor/marker for CHD. Finally, even cerebrovascular events and PD appeared to be independently associated. Indeed, the prevalence of different types of strokes, mainly the ischemic ones, is higher (about 2.3 times as much) in PD affected individuals than in healthy ones⁷⁴ and PD may represent a potential risk to worsen the stroke condition. Since the close relations between PD and CVD, it has been suggested that PD may have a causative role in determining some CV conditions. Regarding the causality of the correlations mentioned before, several hypotheses have been proposed in literature including endothelial dysfunction, oxidative stress and augmented systemic inflammation in response to bacteremia or cytokines/inflammatory mediators' dissemination from periodontal lesions. However, the biological mechanisms responsible for these conditions remain unknown. Nevertheless, there is a plethora of studies indicating the inflammatory process as the common denominator of PD and CV diseases. Indeed, the oral infectious and inflammatory conditions may favor an intermittent bacteremia, which induces a systemic immune response to pathogens especially towards *Porphyromonas gingivalis*. Then, it has been supposed that bacteria passing through the vascular endothelium and the smooth muscle cells promoting vascular inflammation, low-density lipoprotein (LDL) oxidations and internalization of LDL by macrophages that become foam cells. The presence of individual predisposing factors can accelerate the atherosclerotic process. Supporting this theory, it has been demonstrated that patients affected by PD show significant increase of C-reactive protein (CRP) as well as pro-inflammatory cytokines circulating levels proportionally to its grade of severity. Furthermore, reduction in the levels of systemic inflammation markers such as CRP and serum IL-6 levels were documented in subjects undergoing

periodontal treatment. Moreover, oral pathogens have been found in atherosclerotic plaques and the atherosclerotic microbiome appeared to be more represented in patients affected by PD respect to healthy individuals. A study conducted by Haraszthy *et al.* pointed out the presence of several PD bacteria, identified with polymerase chain reaction (PCR) assay, in almost 80% of carotid endarterectomy specimens. As is known, atherosclerosis and CV diseases recognize an inflammatory pathogenesis too; the CRP role in the atherosclerosis development may be related to its capability to activate the complement and to trigger the formation of foam cells. In this regard, inflammatory markers such as CRP, IL-6 and lipoprotein-associated phospholipase A2 were identified as predictors of increased stroke risk, suggesting that the activation of CV events can be triggered by a systemic inflammation maybe induced or enhanced by PD. The reduction of circulating INF γ and IL-6 were documented in hypertensive patients affected by PD who underwent specific oral treatments with a significant benefit on blood pressure values. A randomized controlled trial, by Tonetti *et al.*, involving subjects with PD showed that intensive periodontal treatment improved the endothelial function at 6 months of follow-up.⁵⁴ Notably, even if the association between PD and CV diseases is unambiguous, their specific underlying mechanisms and the possibility of a causative relation that links these conditions remain under investigation. Moreover, it is necessary to mention that PD, which affect mostly middle-aged subjects and individuals with elevated systemic inflammatory levels, share with atherosclerosis many of its traditional risk factors (age, gender, systolic blood pressure, high-density lipoprotein cholesterol, smoking, diabetes). Therefore, it may be tough to discriminate the potential effect of PD alone in determining the CVD manifestations. However, since PD is a preventable and treatable condition, assuming that it accounts for an additional CV risk factor, its recognition and treatment may significantly reduce the global risk of CV events and the health-care costs. Ultimately, the literature taken into account showed moderate heterogeneity and, to some extent, lack of a uniform adjustment for all confounders, hence this may reduce

the accuracy of our results. Nevertheless, few inaccuracies may be accounted for inconsistencies in the definition of both CVD and periodontitis, as well as in their methods of assessment. In conclusion, the results obtained have to be interpreted with caution and well-designed prospective/randomized controlled studies with a reasonable follow-up are needed to improve our knowledge of the association between PD and CVD.

Limitations of the study

The present umbrella review is characterized by the typical limits of meta-epidemiological studies including the selection bias, the publication bias and the tendency to generalize causal implications where only no-causal associations exist. Despite these limitations, this umbrella review provides a tool to recognize and further support the association between cardiovascular and periodontal disease.

Conclusions

Despite the unambiguous association between PD and CVD, the specific underlying mechanisms and the possibility of a causative relationship that links these conditions remain unclear and yet under investigation. Further prospective/randomized-controlled studies with a reasonable follow-up are needed to improve our knowledge about the real bi-univocal association between PD and CVD.

Key messages

- Periodontal disease and cardiovascular diseases are among the most common pathologies in the world and their relationship has long been studied but not clearly defined. Both conditions lead to a chronic inflammatory process with degenerative characteristics and their association is now well established, but the real biunivocal correlation between these two pathological conditions is not completely understood.
- Periodontal disease resulted to be associated with a higher risk of developing

cardiovascular diseases (acute coronary syndrome, acute myocardial infarction) and cerebrovascular diseases (ischemic stroke); however, the CVD risk reduction of events related to the treatment of periodontitis are yet to be investigated.

- The relationship between CVD and PD provides heterogeneous data. A causal relationship between CVD and PD cannot be fully established. Further research with properly designed long-term follow-up studies are needed in order to examine various pathophysiological aspects of their association.

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