Link Between Periodontal Inflammation and Cardiovascular Risk. Literature Review

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Abstract

For dental practice, it is necessary to highlight the relevance of periodontal inflammation and oral microorganisms in the development and progression of atherosclerosis and cardiovascular diseases in general, focusing on PI as a causal factor of CVD due to the great complexity and interaction that present the Gram-negative bacteria characteristic of chronic periodontal disease with the vast vascularization of the stomatognathic system. Recent findings describe the association at the cellular and molecular level between periodontal and cardiovascular diseases, although the specific causal correlation as a determining risk factor has not been established. Periodontal disease has been associated with several systemic diseases, and atherosclerosis has become very important in recent years. The possibility of an association has been documented in several field investigations, and this one refers to a systemic bacteremia caused by poor oral hygiene, which in turn can cause bacterial growth on the atherosclerotic plaques located in the coronary arteries, which possibly It will worsen the patient's clinical picture and prognosis, so it is crucial that clinicians understand the association between periodontal and cardiovascular disease to determine a patient's risk of CVD. Comprehensive treatment for gingival inflammatory conditions and reestablishing a healthy periodontium may help reduce widespread inflammation that plays an important role in preventing cardiovascular disease, although most researchers say future research is needed to establish a causal relationship, which only experimental studies could unmask.

KeyWords: Periodontal Disease, Periodontal Inflation, Cardiovascular Disease

1. Introduction

Cardiovascular disease (CVD) comprises a wide range of disorders including diseases of the heart muscle and vascular system supplying the heart, brain and other vital organs, such as coronary heart disease and stroke, which are the leading causes of mortality worldwide, killing 17.1 million people per year. There are a variety of risk factors involved in the pathogenesis of CVD, such as smoking, hypertension and hyperlipidemia. Numerous successful treatment modalities have been developed that are based on these etiological or risk factors. However, in modern society, people are increasingly exposed to such factors, and the aforementioned therapies are still not enough, so the incidence of CVD increases year by year.(1)(2)

Recently, acute or chronic infections have been classified as an etiological factor in CVD; Infections that accelerate inflammation and promote vascular thrombosis are thought to be a secondary pathogenic pathway. Among these infections, periodontitis may be the most common. It is defined as an infectious disease that causes inflammation within the supporting tissues of the dental organ, resulting in a progressive loss of insertion and alveolar bone. (3)

There are two reasons why periodontitis and CVD are thought to be related. First, levels of systemic

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inflammation increase when there is moderate or severe periodontitis, and when treatment for this condition is initiated, there is a clear reduction in clinical signs, with decreased levels of systemic inflammatory mediators. The second reason is related to the complexity of periodontal bacteria, which can invade damaged periodontal tissue, enter the bloodstream and further disrupt the cardiovascular system. Several periodontal pathogens, such as *Porphyromonas gingivalis, Bacteroides forsythus, Prevotella intermedia and Aggregatibacter actinomycetemcomitans* have been detected in carotid atheromas by polymerase chain reaction. Experimental studies have shown that the presence of these periodontal pathogens and oral bacteria in atheromas could induce platelet activation and aggregation through collagen-like cells.(4)

The objective of this literature review is to identify the mechanisms of action of the various periodontopathogenic microorganisms, present in the supporting tissues through which they create alterations at the periodontal level that lead to systemic conditions, focusing on cardiovascular diseases such as arteriosclerosis, coronary heart disease, stroke and atrial fibrillation, and describe the ideal treatment for a heart patient. in the dental office

2. Methods

Protocol

The protocol was designed in accordance with Cochrane standards for systematic reviews. Search criteria met Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA) guidelines

Inclusion and exclusion criteria

The inclusion criteria were: studies published in the last 8 years, conducted on adults with periodontal diseases and their association in cardiovascular diseases, conducted worldwide, written in Spanish, English, French or Portuguese, correlating periodontal diseases with cardiovascular diseases, demonstrating the bacterial load of species in samples of subgingival plaque, as well as research associated with subclinical thickening of the carotid intimal layer.

The exclusion criteria were: Studies older than 8 years, conducted on animals, without statistical analysis, in a language other than Spanish, English, French or Portuguese, as well as analytical research that does not associate periodontal inflammation with cardiovascular diseases.

Study eligibility and data extraction

We screened the full texts of potentially relevant studies to answer the research question. A matrix was generated for data extraction from selected studies. The matrix had the following fields: authors, year of publication, country, average age, type of research.

Search strategy

A bibliographic, documentary, exploratory and non-experimental qualitative research was carried out through a search of articles in databases. We reviewed 172 scientific articles obtained by entering the terms "Periodontal Disease", "Cardiovascular Diseases" and "Periodontal Inflammation" in a period of 8 years, we searched the following databases from 2014 to March 14, 2022: 1) MEDLINE through PubMed, 2) Scielo 3) Elsevier through ScienceDirect 4) Cochrane.

A total of 172 articles were reviewed, 131 studies were excluded based on the title, 15 based on the information found in the abstract and 15 after reading the articles in full text. Finally, 30 studies were included in the review. The flowchart can be seen in Figure 1.

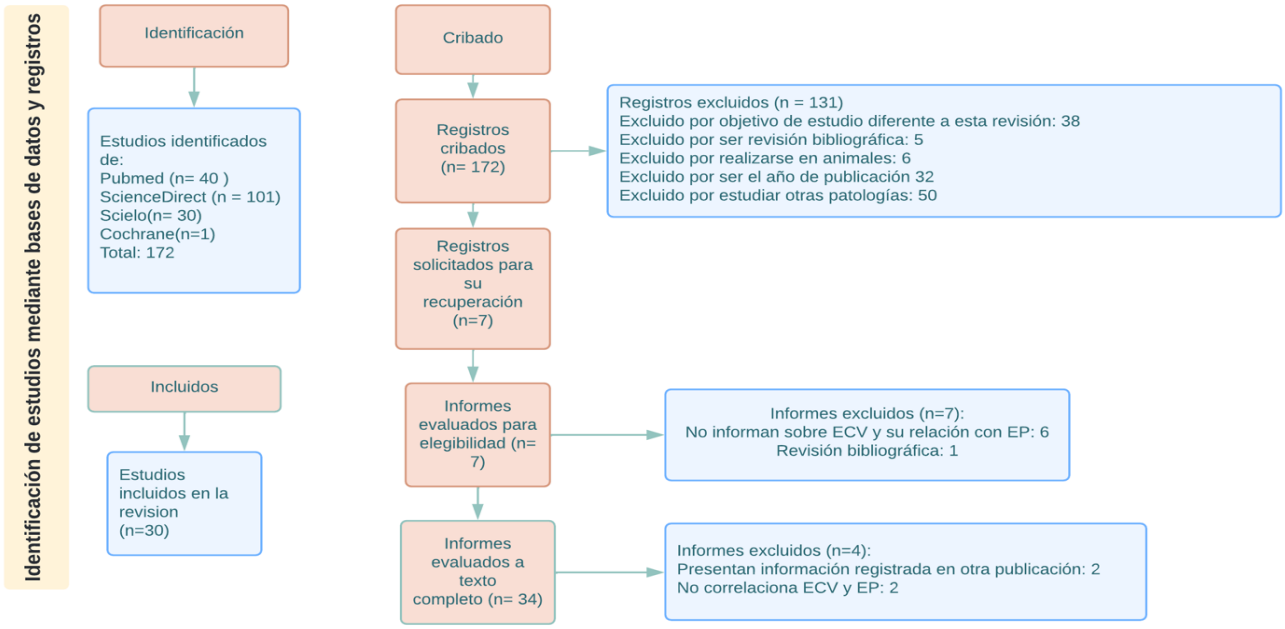

Figure 1. Flowchart of this review.

3. Results

The oral cavity being a large reservoir of bacterial colonies, is prone to bacteremia when the host's immune system is compromised, there is a wide variety of systemic pathogens that being encapsulated in the periodontal pocket can be exacerbated, the products of the same apart from affecting the periodontal support tissues are able to invade other systems through the bloodstream, compromising the cardiovascular system.(5) (6)
Specifically, chronic periodontal disease affects 20% to 50% of the world's population, especially in unfavorable socioeconomic and demographic populations with little access to health services, and in recent years a high and accelerated risk of cardiovascular diseases has been reported in patients who previously suffered from chronic periodontal disease, regardless of traditional risk factors such as obesity, hypertension. Smoking and age, there is evidence of its association with cardiovascular disease, stroke, myocardial infarction (MI), atherosclerosis, acute coronary syndrome and atrial fibrillation.(6) (5)(7)

Periodontal microbiota involved in cardiovascular disease

Within the varied ecosystem of the oral cavity, microorganisms form the polymicrobial biofilm made up of several crowns, which typically sits on the dentin surface and promotes inflammation of periodontal tissues, when there is a deficit in the quality of toothbrushing. At first the colonizers of the gingival sulcus are aerobic bacteria that are gradually relegated by facultative or strict anaerobic bacteria by 90%, while the gram-negative percentage rises to 75% as well as the spirochetes, within this large set of microorganisms that are closely related to the processes of periodontal inflammation are: (8)(9)*Porphyromonas gingivalis, Campylobacter rectus, Tannerella forsythia, Prevotella intermedia, Aggregatibacter actinomycetemcomitans,* and *Fusobacterium nucleatum*(10) . The stomatognathic system by its anatomy and nutrition of its structures, has an abundant vascularization and the epithelium of the groove is relatively thin and friable, this combined with the pro-inflammatory cytokines (TNF-α, IL-1β, IFN-y and PGE) that can reach high concentrations in the periodontal tissue, making it susceptible to the spread of bacterial inflammatory products along with the inflammatory molecules of the periodontium and infiltrate the blood circulation. (11)(12)
In the face of the aggression of microorganisms, a highly complex protection mechanism called inflammation acts, this mechanism is responsible for the identification, control, regulation and elimination of pathogens with the sole purpose of protecting the tissue even with risk of collateral damage.(6)
This is reflected in the mechanisms used by neutrophils and macrophages, on the one hand neutrophils are white blood cells that have the main function of phagocytizing extracellular pathogens, in a periodontal lesion histopathology refers that neutrophils form a fence between the binding epithelium and the pathogen-rich biofilm, which acts as a solid antimicrobial structure and as a unified phagocytic mechanism, It is presented as a double-edged sword since overexcitation causes tissue damage, extension and compromise of PID, the CD14 antigen acts as another defense mechanism specialized in the inflammatory response, but it is deteriorated in the presence of (13)*Porphyromonas gingivalis* which produces a proteolytic enzyme called gingipain, capable of producing the proteolysis of the CD14 molecule and therefore the suppression of the immune system, as this molecule is a leukocyte lipopolysaccharide receptor facilitating the colonization of the gingival fold. (14)

Atherosclerosis and Periodontal Disease

According to data collected by the World Health Organization, atherosclerosis is considered the largest epidemic in the world and it is currently estimated that periodontal disease is the main causative agent of this infection. Atherosclerosis is caused by the involvement of endothelial cells, this type of cells fulfill functions such as secretion of molecules, control of vascular tone, hemostasis, coagulation and inflammatory response, atherosclerosis involves the entry of bacteria of periodontal origin into the bloodstream, which helps the atheromatous process and disturbs the inflammatory process. (15)(16) (14)
The periodontopathogenic bacterial microbiota, mainly Gram-negative bacteria when passing into the bloodstream becomes a contingent thrombogenic agent, having the ability to adhere and aggregate platelets by molecular mimicry, this occurs in the union of own and foreign peptides to the body interacting with each other, resulting in the activation of T and B cells, which also binds by mimicry of the binding sites to type I and III collagen. Inflammation is measured through C-reactive protein (CRP) that generates alterations at the systemic level, along with TNF α, IL-1, 6 and 8, the aforementioned are the markers that fluctuate with each other to generate atheromatous plaque and its subsequent rupture.(14)(16)

Periodontal Disease and Coronary Heart Disease

There is evidence to suggest that increasing the severity of periodontal disease carries a proportionally higher risk of coronary heart disease by approximately 24 to 35%. In addition, studies have also looked at the relationship between periodontal disease and aortic vascular inflammation, which in turn is a substitute for coronary heart disease. In addition, a recent study explored the relationship between periodontal involvement and coronary artery calcification and found that periodontal involvement exhibits positive, linear correlation with the presence of coronary

artery calcification.(17) (18) (19)

Periodontal Disease and Stroke

Periodontal disease was first shown to be linked to an increase in the thickness of the intima-media layer of the carotid artery in a cohort at high risk of atherosclerosis. Subsequent studies have shown that up to 31.3% of patients with periodontal disease have unilateral carotid calcifications demonstrating an increase in subclinical carotid disease. Other studies have shown that periodontal disease is associated with higher levels of circulating CRP compared to controls and that the thickness of the intima-media layer of the carotid artery is greater in patients with periodontal disease. In addition, a case-control study showed a significant relationship between stroke and periodontal index. Chronic periodontitis was found to be associated with lacunar infarctions and linked to elevated CRP and TNF levels. (20) (21)

Periodontal Disease and Atrial Fibrillation

Several studies show that inflammation has a potential role in the development of atrial fibrillation, associated with disorders of the coagulation cascade and the spread of thrombosis. (22) . Patients with periodontal disease have been associated with elevated systemic inflammation, as well as a higher incidence rate of atrial fibrillation, it is estimated that patients with periodontal inflammatory processes are more likely to suffer from AF by 9.5%. A study conducted in an animal model showed that periodontitis was associated with increased immune activation in the atrial myocardium, which in turn alters the electrophysiological properties of the atrium(23). (24).

Endothelic dysfunction

Endothelial dysfunction is an independent predictor of cardiovascular events and precedes the development of atherosclerosis and other CVDs. This pathological process is usually caused by the reduced bioavailability of endogenous molecules, such as nitric oxide (NO), a gas transmitter that restricts platelet aggregation, inhibits the binding of leukocytes to endothelial cells, and prevents the expression of adhesion molecules. (25) (26)

Several lines of evidence suggest a link between periodontitis and endothelial dysfunction and demonstrate that, in human subjects affected by periodontitis, endothelial dysfunction without cardiovascular risk factors or with hypertension was due to a marked reduction in nitric oxide (NO) bioavailability and systemic inflammation. Similarly, a potential correlation between salivary concentration of nitric oxide (NO) and endothelial dysfunction in patients with periodontal disease was recently demonstrated. (27) .

It should be noted that several reports have suggested that endotoxins and antigens secreted by periodontal bacteria may play an important role in the pathogenesis of endothelial dysfunction, for example, it has been shown that periodontal bacteria can directly affect the positive regulation of several chemoattractants and adhesion molecules of endothelial origin that stimulate the binding of leukocytes to the surface of endothelial cells, a clear example is Porphyromonas gingivalis itself which is capable of inducing a robust expression of the endothelial monocyte chemoattractant protein-1 (MCP-1), thus enhancing the formation of atheromatous plaques.

This same periodontopathogen can induce a significant increase in the expression and release of endothelin-1 (ET-1). Importantly, ET-1 acts as a vasoconstrictor factor and high levels of this molecule are associated with the onset of CVD. According to this body of evidence, periodontal treatment alone or antibiotic supplementation has been shown to improve endothelial dysfunction. (28).

Limitations and effects of the treatment of Periodontal Disease and Cardiovascular Disease

Although there have been many hypotheses and pathophysiological findings to support the association between periodontal disease and cardiovascular disease, the link may not be causal. It has previously been reported that at least part of the association between periodontal disease and cardiovascular disease is explained by adjusting for traditional risk factors such as smoking, diabetes mellitus, age and socioeconomic conditions. In addition, periodontal therapy (scraping, root planing, antibiotic treatment) has been shown to reduce levels of pro-inflammatory markers (CRP, TNF-α and IL-6), further corroborating that the periodontium is a source of these inflammatory mediators. However, this has not been proven in a large randomized clinical trial. To date, pilot case-randomized control studies, investigation of periodontitis and vascular events, compared single scraping of the entire mouth and root planing with community care alone in 301 patients with stable cardiovascular disease for 6 to 25 months, presented results that were inconclusive and the study was underpowered. The association between Periodontal Disease and Cardiovascular Disease events was present but not significant. (25) (7) (26)(27)

4. Discussion

In this literature review, the importance of the link between periodontal inflammation and cardiovascular diseases was highlighted, since the periodontopathogenic microbiota, when passing into the bloodstream, is capable of evading the patient's immune system, specifically neutrophils that are sometimes not able to recognize pathogens and specifically the main etiological agent of periodontitis, *the Porphyromonas gingivalis* which has a notorious thrombotic capacity.(28)

Cardiovascular and periodontal diseases, despite presenting a cause-effect link, presents certain factors that predispose an individual to suffer greater

susceptibility to cardiovascular diseases, within which we find, obesity, hypertension, age and smoking habit being a latent factor within most of the investigations examined, the same factor that is predisposing for both cardiovascular and periodontal disease independently, and represents a link between both pathologies, influencing CVD in patients with PD.(29)

Although Vincent E. Friedewald states that periodontal disease has no relationship with CVD, it has been shown in several experimental studies that, if there is a positive relationship between both pathologies (35), for example Xiaoru Qin in his cohort study states that PD is modestly associated with the risk of cardiovascular diseases; In the same study it is shown that this type of synergy between pathologies presents a predisposition for sex being the female gender predisposing to suffer the myocardial infarction related to PD, Pazmino VFC, proposes that this phenomenon presents its genesis in the hormonal changes that women suffer in certain stages of their lives combined with the oral hygiene they practice. (30) (31)

Raydén states that scaling and root planing combined with antibiotic treatment is effective in treating patients with cardiovascular diseases who have periodontal conditions, and shows that it reduces the levels of (CRP, TNF-α and IL-6), on the other hand Liu W. states that treatment with scaling and root planing, is completely effective in combating chronic periodontal disease in patients with CVD regardless of the use of antibiotics, Berth supports this conjecture, and states that periodontal treatment should be administered in several short sessions, and generalized treatment at the level of the entire alveolar ridge can be performed in a maximum period of 24 hours, but reiterates that this technique represents a period of prolonged generalized inflammation that could trigger an acute inflammatory response associated with a transient deterioration of endothelial function, Graziani endorses this therapeutic norm since it raises the question of whether performing longer sessions of periodontal treatment could contribute to an individual's inflammatory risk and increase their short-term risk of suffering from CVD.(25)(32)(33)(34)

Xiaoru Qin et al. affirms that despite the relevance that the subject has taken in recent years, it has several limitations to affirm whether PD has a direct relationship to CVD, this due to the great heterogeneity of studies that exists presented a greater number of bibliographic reviews in relation to experimental studies, That is why it suggests the elaboration in specific of a greater number of cohort studies to corroborate the direct interrelation between both pathologies. (30)

5. Conclusion

A positive association between periodontal disease and cardiovascular disease has been demonstrated, in which inflammation plays a key role as a mediator. While most of the previously evaluated studies provide important outcomes in relation to CVD, such as myocardial infarction, heart failure, stroke or mortality related to cardiovascular disease and PD, there is very limited evidence evaluating the impact of periodontal therapy in the prevention of cardiovascular disease, and it is insufficient to generate implications for practice. Further trials are needed before reliable conclusions can be drawn.

From our perspective, future research should focus on the use of cutting-edge technology that provides comprehensive results such as technical imaging, such as positron emission tomography, nuclear magnetic resonance imaging, echocardiography and coronary computed tomography to detect subclinical atherosclerosis and evaluate how it can be related to PD.

Since periodontitis is a chronic condition, a long-term approach, rather than a one-time treatment, is likely needed to achieve sustained improvement in periodontal health. It has not yet been established whether treatment of periodontal disease reduces disease and cardiovascular events.

Randomized clinical trials involving standardized periodontal disease definitions and standardized periodontal interventions are required to demonstrate that PD treatment is beneficial for CVD risk reduction, with increasing research into the role of periodontal disease in CVD, periodontal disease may potentially become a risk factor for CVD.

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