The Relationship between Periodontitis and Cardiovascular Disease

Jonathan Krupka

Jonathan Krupka graduated in June 2017 with a B.S. degree in Biology.

Abstract

The relationship between periodontal disease and cardiovascular disease has been the subject of much research in recent years. The aim of this study is to review and analyze the relevant literature regarding this relationship, with an emphasis on determining a presence of periodontal bacteria from the periodontal pocket in atheromatous plaques, and to explore the biological role of inflammatory mechanisms that may link periodontitis and cardiovascular disease. Although there seems to be conflicting reports, the overall consensus confirms the presence of periodontal bacteria, such as Porphyromonas gingivalis, in atheromatous plaques. Additionally, the presence of systemic markers of cardiovascular disease in patients with periodontitis, such as acute phase proteins, proinflammatory cytokines, and markers of procoagulant state, has been confirmed. These confirmations could indicate a role for periodontal pathogenic bacteria in atherosclerosis disease process. Additionally, these findings give rise to possible mechanisms linking the two diseases.

Introduction

As early as the early 1900's, oral sepsis and tooth extractions were suggested as causes of cardiac infection. However, due to the lack of compelling scientific evidence, the idea of oral disease as a cause of systemic illness was basically disregarded. That focus was revived in the early 1990's after reports of the connection between periodontal disease (PD) and cardiovascular disease (CVD). Although many subsequent studies have postulated positive associations between PD and CVD, others have maintained that no such correlation exists. Additionally, several potential mechanisms have been proposed describing how PD could cause systemic inflammation, initiate or exacerbate atherogenesis, and possibly lead to cardiovascular catastrophes such as myocardial infarction (MI) or stroke. The purpose of this article is to review the relevant articles, predominant theories, and proposed mechanisms relating periodontitis and atherosclerotic vascular disease. Specifically, does the inflammatory PD contribute causally to heart disease and stroke, or are these two conditions coincidentally associated?

Methods

The information gathered in this paper has been collected from numerous sources including databases such as GoogleScholar, Touro Library, and PUBMED. The information was read, analyzed and compared to determine each study's validity and authority.

Results and Discussion:

Defining PD and CVD

CVD, or more specifically atherosclerotic vascular disease, affects the heart and the blood vessels. Coronary heart disease (CHD)- also referred to as coronary atherosclerosis, or simply heart disease- is a subset of CVD and is characterized by dysfunction of the arteries supplying blood to the muscle tissue of the heart, depriving it of sufficient amounts of blood. Atherosclerosis, or the hardening and narrowing of the arteries, silently and slowly blocks arteries, putting blood flow at risk. CHD includes blockage of blood vessels (thrombosis) and can eventually cause acute myocardial infarction (heart attack). CVD is the number one cause of death in the United States and other industrialized countries, and is among the major causes of mortality worldwide. Traditionally, CVD has been attributed to risk factors such as treated and untreated systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and body-mass index. However, these factors only occur in about half of all patients that experience heart attacks. For example, 40% of CHD deaths occur in patients who have cholesterol levels that are lower than the population average. This has led researchers to investigate additional causes of CHD, including bacterial induced inflammation (Taylor, et. al. 2009).

Periodontitis is a bacteria-induced, chronic inflammation of the gingival tissue in response to dental plaque accumulation. PD is always preceded by gingivitis, an earlier and less severe form of gum disease, though not all cases of gingivitis will progress to PD. Untreated PD leads to deepening of the gingival sulcus, which evolves into a periodontal pocket, destruction of the connective tissue and bone supporting the teeth, including gingival tissue, periodontal ligament, and alveolar bone. Clinical criteria for PD include bleeding on probing, pocket depth and degree of tooth attachment loss.

Evidence of Correlation Between CVD and PD

Many studies have been conducted assessing the possible connection between CVD and PD. The results have varied, and at times proposed conflicting views. The fact that oral pathogens can come to lesions far from the oral cavity has been proven by Lockhart, et. al.. The authors showed how poor oral hygiene or dental disease are risk factors for developing bacteremia after a simple tooth brushing or after a single tooth extraction. One hundred and ninety-four patients participated in the study. The authors assayed blood samples before, during and after the toothbrushing or single tooth extraction to identify Infective Endocarditis (IE)- associated bacteria. The authors found that oral hygiene and gingival disease indices were strongly correlated with IE-related bacteremia after toothbrushing. Patients with a mean plaque and calculus score of 2 or more had an increased risk of 3.78 and 4.43-times for developing bacteremia. Thus, we see that it is easy for bacteria in the oral cavity to enter that blood stream. This, as well as other similar studies, present a strong basis for the idea that oral pathogens can make their way to regions far from the oral cavity (Lockhart, et. al. 2009). Additionally, many studies show that bacteremia is present after oral examination and probing Loos, 2006).

Siddeshappa, et. al. (2016) conducted a study to determine whether nonsurgical periodontal therapy can impact various hematological parameters in patients with periodontitis. Traditionally, the total number of white blood cells (leukocytes) and erythrocyte sedimentation rates in peripheral blood has been used as diagnostic measures to determine whether or not a patient suffers from an infection or an inflammatory disease. Leukocytes become more numerous through the innate immune system response to periodontal bacteremia. The suggestion has been made that higher numbers of leukocytes makes the blood more viscous. Additionally, cells may adhere to the endothelial lining of the blood vessels causing decrease of blood flow. Furthermore, periodontitis has been associated with an increase in plasma fibrinogen and platelet activation which increase the risk of atherosclerosis and CVD. The aim of the study was to investigate the effect of nonsurgical periodontal therapy on total leukocyte count (TLC), differential leukocyte count (neutrophils, lymphocytes, eosinophils, basophils, and monocytes), erythrocyte sedimentation rate (ESR), and the total platelet count on patients with periodontitis. Thirty patients were selected for the study. The results of this experiment were that a decrease in clinical parameters of PD (ex. plaque index, gingival index, etc.) was accompanied by a statistically significant change in TLC, platelet count and ESR. The authors concluded that there is a decrease in hematological parameters after nonsurgical periodontal therapy, which may also reduce the risk of atherosclerosis (Siddeshappa, et. al. 2016).

In a similar vein, animals with experimentally induced periodontitis had more extensive accumulation of lipids in the aorta than did those without t. There was a positive correlation between the severity of PD and the extent of lipid deposition (Jain, et. al. 2003)., A study of 711 subjects, suggestaaed that tooth loss is a marker of past periodontal disease, and is related to subclinical atherosclerosis. Among those with 0 to 9 missing teeth, 46% had carotid artery plaque, and among those with ≥10 missing teeth, carotid artery plaque prevalence was about 60% (Desvarieux, et al. 2003).

However, such correlations are vague and broad. The above studies merely show increased atherosclerotic suseptability. This can be due to an overall systemic increase of inflammatory organisms. A more direct demonstration of correlation can be had by discovery of specific periodontal oral cavity bacteria in the atherosclerotic lesion. Such findings would show that inflammatory PD contributes causally to heart disease and stroke, and that these two conditions are not merely coincidentally associated. Research in this area is more questionable, and not as consistent in its results.

In a study conducted in 2004, 52 patients were studied who were scheduled for carotid endarderectomy to ascertain the presence of periodontal bacteria DNA, including that of Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia, and Tannerella forsythensis, in carotid atheromatous plaque. In subgingival plaque samples of 19 test patients, T. forsythensis, F. Nucleatum, P. intermedia, P. gingivalis and A. actinomycetemcomitans were found. However, no periodontal DNA was detected by PCR in any of the carotid samples. The authors concluded that the presence of periodontal DNA in atheromatous plaques could not be confirmed by this study, and thus no correlation could be established between species associated with periodontal disease and putative bacteria contributing to atheromatous plaques (Cairo, et. al. 2004). This study brings into question the causality relationship of periodontitis and gingival disease to CVD.

Other studies have produced results indicating a small number of matching pathogens. A study was conducted to isolate and identify bacteria from the periodontal pockets of different patients and to compare them with the microorganisms detected in atheromatous plaques obtained from the same patients. Clinical isolates were obtained from 12 patients with periodontal wounds and atheromatous plaques. These samples were then used to identify periodontal bacteria using polymerase chain reaction (PCR) assays. The results were as follows. From the 12 patients studied, 9 presented different periodontopathic species. In two patients Actinobacillus actinomycetemcomitans, a gram-negative coccobacillus, was present in the periodontal pockets and the respective atheromatous plaques. The authors were unable to explain the mysterious absence of P. intermedia and P. gingivalis growth in atheroma samples, even though these bacteria are usually present in periodontal samples. The authors concluded that the presence of A. actinomycetemcomitans in both the atheromatous plaque and the periodontal pockets of the same patients could indicate a role for periodontal pathogenic bacteria in the atherosclerosis disease process (Padilla, et. al. 2006). Similarly another investigation was aimed at testing the validity of the translocation hypothesi and its role in promoting plaque development. The authors used 16s cloning and sequencing, to determine the microbial diversity of the subgingival environment and atheroma plaques of patients concomitantly suffering from periodontitis and obstructive coronary artery atherosclerosis (OCAA). Subgingival biofilm and coronary balloons used in percutaneous transluminal coronary angioplasty were collected from 18 subjects presenting with generalized moderate to severe periodontitis and OCAA. DNA was extracted and the gene 16S was amplified, cloned and sequenced. The authors results were similar to those obtained by Padilla, et al.. They observed significant differences in microbial diversity between the two environments. While subgingival samples mostly contained the phylum Firmicutes, in coronary balloons, Proteobacteria was predominant. Additionally, the most commonly detected genera in coronary balloons were Acinetobacter, Alloprevotella, Pseudomonas, Enterobacter, Sphingomonas and Moraxella, while in subgingival samples Porphyromonas, Filifactor,

Veillonella, Aggregatibacter and Treponema were found. Despite such diversity, 17 identical phylotypes were found in atheroma and subgingival samples, indicating possible bacterial translocation between periodontal pockets and coronary arteries (Serra e Silva Filho, et. al. 2014). Again, these findings are seemingly small pieces of data regarding the overwhelming question of a periodontal-atherosclerotic connection. Nevertheless, several studies do indicate a strong correlation with respect to Porphyromonas gingivalis (P gingivalis). Porphyromonas gingivalis has been strongly associated with adult periodontitis. This bacterium is a Gram-negative, nonmotile, obligate anaerobe that can invade and infect epithelium, endothelium, and vascular smooth muscle cells. Another group used ApolipoprotienE knockout (apoE–/–) mice which were orally administered the periodontal disease pathogen Porphyromonas gingivalis. The P. gingivalis was detected in the blood and aortic tissue of the mice. The mice challenged with P. gingivalis presented with an increase in atherosclerotic plaque, as well as expression of the innate immune response markers Toll-like receptors (TLR)-2 and TLR-4 in the aortic tissue (Gibson, 2004).

In order to determine whether recurrent intravenous injections of P. gingivalis, mimicking periodontitis-associated bacteremia, promotes coronary artery and aortic atherosclerosis the researchers chose pigs for this experiment since they develop coronary lesions that closely simulate human disease. Showed Thirty-six pigs were sensitized with 109 killed P gingivalis subcutaneously. Four weeks later all sensitized pigs in the group to be challenged started intravenous injections three times a week for 5 months with 106 to 107 units of P gingivalis while controls received saline. Pigs were euthanized 2 weeks after the last injection, and coronary arteries and aortas were analyzed. The results were significant. The authors found that the pigs that received intravenous P gingivalis challenges demonstrated a >100-fold increase in anti–P gingivalis antibody levels. This was in conjunction with the result that pigs challenged with recurrent P gingivalis bacteremia develop significantly larger coronary and aortic atherosclerotic lesions than those that were not challenged. The average coronary and aortic intimal areas were between≈3 times and ≈5.9 times larger than controls, a significant difference. These lesions were predominantly composed of smooth muscle cells. In addition, hypercholesterolemic pigs likewise challenged with recurrent P gingivalis bacteremia develop larger coronary and aortic atherosclerotic lesions, both having an intimal area that was ≈2.2 times larger than controls. Brodala, N et al. summarized their results in Table 1 and Table 2.

Additional significant information was reported by the authors. We mentioned previously the lack of evidence showing periodontal bacteria within the atheromatous legions. Previous studies only showed a correlation between the two diseases. Brodala, et al. discovered the following. P gingivalis ribosomal DNA was detected in the carotids (5 of 5) and the aortas (4 of 5) from the 5 P gingivalis-treated pigs on the low-fat diet and the aortas of all 7 P gingivalis–challenged pigs on the high-fat diet. However, none of the aortas or carotids from saline-challenged control pigs, whether sensitized or not, had amplifiable P gingivalis ribosomal DNA. The authors themselves note two limitations in their study. Firstly, the pig model used does not entirely and accurately replicate the bacteremia of oral origin from inflamed human periodontal tissues. Nonetheless, as seen previously in rodents, the P gingivalis–challenged pigs

Low-Fat Diet	Aorta		Coronary Arteries		
	Intimal Area, μm2	Intimal Area as % Medial Area	Intimal Area, μm2	% Luminal Narrowing by Intima	Intimal Area as % Medial Area
Group 1. P gingivalis A7436–challenged	982.7±217.5	8.06±2.5	192.09±93.92	5.25±0.89	5.45±2.19
Group 2. P gingivalis FDC381–challenged	768.5±318.3	5.08±1.10	158.19±33.45	4.56±0.85	3.83±0.83
Group 3. P gingivalis A7436–sensitized controls	364.3±184.5	1.1±0.5	11.2±7.4	0.4±0.22	0.38±0.24
Group 4. Unsensitized controls	203.6±247.1	1.15±1.46	48.9±29.1	1.3±1.0	1.7±1.3

TABLE 1. Aortic and Coronary Artery Atherosclerosis Morphometry in Pigs Fed a Low-Fat Diet

High-Fat Diet	Aorta	Coronary Arteries			
	Intimal Area, μm2	Intimal Area as % Medial Area	Intimal Area, μm2	% Luminal Narrowing by Intima	Intimal Area as % Medial Area
Group 5. P gingivalis A7436–challenged	4584±3371	17.7±11.5	1536±1917	34.9±21.5	26.9±18.7
Group 6. Unsensitized controls	1976.6±1014.7	7.9±4.0	695.1±804.5	16.3±15.7	11.8±10.4

TABLE 2. Aortic and Coronary Artery Atherosclerosis Morphometry in Pigs Fed a High-Fat Diet

developed an anti–P gingivalisantibody response as a consequence of P gingivalis challenges in association with increased atherosclerosis. Second, the number of pigs was not sufficient to exclude an effect of gender in this study. Data that was not available at the time of this study suggests that human males have a greater prevalence of asymptomatic carotid disease than females with comparable severity of periodontitis. This study does not account for such differences (Brodala, et al. 2005).

Other systemic markers also present evidence that periodontitis can lead to a systemic inflammatory response. Loos, (2006) outlines several systemic effects of periodontitis. He writes that in severe periodontitis, characterized by extensive plaque buildup, bacteremia occurs frequently, leading to leakage of lipopolysaccharides, a major component of periodontopathogens. Additionally, Loos was involved in several studies which investigated the presence of systemic markers of cardiovascular disease in patients with periodontitis. The author took peripheral blood from patients and analyzed the presence and levels of white blood cells, red blood cells and thrombocytes. He also analyzed the presence of important marker molecules such as acute phase proteins, proinflammatory cytokines, and markers of procoagulant state. The suggestion is that increased numbers of white blood cells may make the blood more viscous and increase blood rheology. Additionally, white blood cells tend to stick to the inside of blood vessels, particularly where there is inflammation. This may contribute to reduced blood flow which in turn increases the risk of microthrombus formation. The author writes that he found that the highest number of white blood cells were present in patients with severe periodontitis, the lowest numbers were found in control groups, and subjects with moderate periodontitis presented levels in between. Thus, the presence of elevated WBC's in the blood stream due to periodontitis is evident. We can then postulate that such inflammatory markers can exacerbate an atherosclerotic lesion.

The presence of other systemic markers of inflammation in periodontitis is also evident. One of the important markers of CVD is proinflammatory cytokines. In particular, interleukin-6 (IL-6) is produced by monocytes, neutrophils, endothelial cells, and B cells, and stimulates the hepatocytes to produce acute phase reactants. The author found that in general, patients with severe periodontitis had much higher levels of IL-6 than the controls. In many controls the levels of IL-6 could not be detected at all. Additionally, when patients with aggressive periodontitis were treated, IL-6 levels decreased, highlighting the correlation between periodontitis and IL-6 levels.

C-reactive protein (CRP) is another systemic marker of periodontitis. CRP is one of several acute phase proteins produced in the liver. The liver produces these acute phase proteins in response to infection or an inflammatory process, mainly due to elevated IL-6. CRP acts as a substance that binds to foreign microorganisms or cells, making them more susceptible to phagocytosis, also known as an opsonization. What is especially important is that CRP is associated with CVD. The relative risk of CVD is increased 90% when CRP levels are equal to or more than 2 mg. Thus, a possible mechanism would also be associated with these findings (Loos, 2006).

Evidence of the Role of Inflammation in CVD

Until recently, most believed that atherosclerosis was an arterial collection of cholesterol, complicated by smooth muscle cell accumulation. According to that theory, endothelial denuding injury led to platelet aggregation and release of platelet factors which would trigger the proliferation of smooth muscle cells within the arterial wall. It is now widely accepted that a major component of CVD in general, and atherosclerosis in particular, involves numerous components of the adaptive and innate immune systems leading to an inflammatory response within atheromatous lesion. A brief synopsis of these findings follows.

The innate immune system plays a major role in the inflammatory response in atherosclerosis. Considerable evidence supports the notion of early involvement of the monocyte/macrophage, the most prominent cellular component of the innate immune system, in atherosclerosis. Observations in human arterial samplings have identified monocyte recruitment as an early event in atherogenesis. Additionally, recent examinations of monocyte recruitment in mouse atherosclerotic lesions have shown that monocyte entry into the atherosclerotic lesion continues throughout lesion maturation. High levels of proinflammatory monocytes in mice are recognized by the high levels of a marker known as Ly6C, or Gr-1, and may correspond to a human monocyte subset marked by the presence of P-selectin glycoprotein ligand (PSGL) These proinflammatory monocytes express high levels of proinflammatory cytokines and other macrophage mediators. Recent studies have also highlighted the possible participation of mast cells, which exhibit numerous functions implicated in atherogenesis. For example, mast cells are known to release certain serine proteinases, histamine and leukotrienes, and heparin, a cofactor in atherogenesis. An additional area of evidence links thrombosis with inflammation. Thrombin may induce the expression of proinflammatory cytokines (Libby Peter, 2009).

The adaptive immune system also contributes to the inflammatory response in atherosclerosis. T lymphocytes populate atherosclerotic plaques and can be stimulated by certain heat shock proteins, components of plasma lipoproteins and other molecules. These T cells, upon further stimulation, produce cytokines and trigger inflammation. Additionally, biomarkers, such as highly sensitive C-reactive protein (CRP), apolipoprotein B (ApoB), and lipoprotein (a) amongst others, have been identified in conjunction with atherosclerosis predictability (Libby Peter, 2009) (Wong , 2012).

Proposed Mechanisms Linking Periodontitis to Cardiovascular Disease

Based on this review regarding systemic effects of periodontitis and inflammatory roles in CVD, we can begin to hypothesize the different mechanisms that link the two diseases. The authors suggest that the host response to bacteremia may vary between patients with periodontitis due to individual variation in inflammatory pathway. It is also possible that inherited genetic variations could enhance these mechanisms.

The authors maintain that a number of inflammatory mediators and markers are present in higher concentrations in the systemic circulation of periodontal patients than in those with healthy oral cavities. There are theoretically two pathways by which this could occur. There are ample data indicating that inflammatory cytokines and other mediators are produced in the periodontal lesion (Siddeshappa, et al. 2016)(Loos, 2006). It has been hypothesized that these mediators could enter into the circulation from the oral cavity. If this occurs, and the mediators achieve adequate concentrations, they would then impact tissues and organs distant from the oral cavity. In particular, these mediators from the periodontium could affect other organs, such as the liver, to initiate an acute-phase response that would impact other organs. The result is that the mediators themselves cause inflammation, as well as stimulate other organs to produce a pro-inflammatory response. This would lead to inflammatory changes in the endothelium such as up-regulation of adhesion molecules and promotion of cytokine production, which directly causes initiation and/or acceleration of atheroma development. It should be noted that there is not strong evidence supporting this mechanism for inflammatory cytokines and other mediators accessing the circulation (Teles, Wang, 2010).

In addition, it has been shown patients with periodontitis have frequent bacteremic incidents and that detectable concentrations of lipopolysaccharides are frequently found in the circulation. Thus, bacteria, or their pro-inflammatory components, may stimulate systemic inflammatory responses as well as local inflammatory responses in atheromatous lesions. This would follow their association with, or modification of serum lipids, engagement of receptors on inflammatory cells and endothelium, invasion of endothelial cells, or seeding of atheromatous lesions with bacteria or bacterial components. Bacteria or their products could then promote inflammatory changes that would contribute to the development or propagation of atheromatous lesions.

There are a number of antibodies that can also effect an inflammatory response. Some of these anti-bodies have been found to react as models of "molecular mimicry," which is defined as the theoretical possibility that sequence similarities between foreign and self-peptides are sufficient to result in the cross-activation of autoreactive cells. This is the case in which antibodies that have arisen due to infection by oral bacteria in the oral cavity make thier way into the systemic blood, engage with the host antigens and regulate their operation. These are cross-reactive antibodies. It is possible that sometimes these antibodies promote cardiovascular disease by exacerbating the endothelial reaction to their presence which causes further endothelial inflammation, or increasing the absorption of lipids into phagocytes.

Several studies indicate that serum concentrations of potentially inflammatory lipids, including LDLs, triglycerides, and very low-density lipoproteins (vLDLs) are elevated in periodontitis patients. These lipid subforms are thought to enter the blood vessel wall more easily, may be more susceptible to modification and therefore more likely to be incorporated in to the atherosclerotic lesion. This would accelerate and promote the development and maturation of the lesions (Schenkein, Loos, 2013).

It is thought that patients who present with periodontal disease are at risk for some or all of the activities outlined above. These mechansims may separately, or in partnership with each other, be implicated in arterial disease in periodontal patients. If these mechanisms work together, their cumulative effects could impact greatly on the severity of the cardiac and arterial disease in the periodontal patient.

Conclusion

In conclusion, to date the research does not absolutely prove that periodontitis causes cardiovascular disease. However, as seen above there is strong evidence supporting this idea, and many possible and logical mechanisms have been delineated through which periodontitis with all of its ramifications could effect cardiovascular disease. More recently, patients being admitted for surgeries with no seeming connection to periodontitis, for example hip replacement surgery, have been required to receive authorization from their oral care providers that they do not have any periodontal diseases. This is due to the mounting evidence, over the last few years, that there is indeed a correlation between PD and the rest of the body. Oral care providers should be wary of these problems and should advise their patients accordingly of the importance of oral care, not only with regard to the oral cavity.

References

Brodala, N. M. (2005). Porphyromonas gingivalis bacteremia induces coronary and aortic atherosclerosis in normocholesterolemic and hypercholesterolemic pigs. Arteriosclerosis, Thrombosis, and Vascular Biology 25. 1446–1451.

Cairo, F., Gaeta, C., Dorigo, W., Oggioni, M. R., Pratesi, C., Pini Prato, G., & Pozzi, G. (2004). Periodontal pathogens in atheromatous plaques. A controlled clinical and laboratory trial. journal of periodontal research, 442-446.

Desvarieux, M., Demmer, R. T., Rundek, T., Boden-Albala, B., Jacobs Jr, D. R., Papapanou, P. N., & Sacco, R. L. (2003).

Relationship Between Periodontal Disease, Tooth Loss, and Carotid Artery Plaque: The Oral Infections and Vascular Disease Epidemiology Test (INVEST). Stroke, 2120-2125.

George W. Taylor, W. S. (2009). Associations between Periodontal Disease and Atherosclerotic Cardiovascular Diseases (CVD). Delta Dental Plans Association (DDPA).

Gibson, F. C. (2004). Innate immune recognition of invasive bacteria accelerates atherosclerosis in apolipoprotein E-deficient mice. American Heart Association.

Jain, A., Batista Jr., E. L., serhan, C., Stahl, G. L., & Van Dyke, T. E. (2003). Role of Periodontitis in the Progression of Lipid Deposition in an Animal Model.

Libby Peter, R. P. (2009). Inflammation in Atherosclerosis. Journal of the American College of Cardiology, 54(23).

Lockhart PB, B. A. (2012). Periodontal Disease and Atherosclerotic Vascular Disease: Does the Evidence Support an Independant Association? . The American Heart Association .

Lockhart, P. B.-M. (2009). Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. Journal of the American Dental Association, 140, 1238–1244.

Loos, B. G. (2006). Systemic effects of periodontitis. Int Journal of Dental Hygiene, 34-38.

Padilla, C., Lobos, O., Hubert, E., Gonzalez, C., Matus, S., Pereira, M., . Descouvieres, C. (2006). periodontal pathogens in atheromatous plaques isolated from patients with chronic periodontitis. journal of periodontal research(41), 350-353.

Schenkein, H. A. (2013). Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. Journal of Clinical Periodontology, 51-69.

Schenkein, H., & Loos, B. (2013). Inflammatory Mechanisms linking Periodontal Diseases to Cardiovascular Diseases. Journal of Clinical Periodontology, S51-S69.

Serra e Silva Filho W, Casarin RCV, Nicolela Junior EL, Passos HM, Sallum AW, Gonçalves RB (2014) Microbial Diversity Similarities in Periodontal Pockets and Atheromatous Plaques of Cardiovascular Disease Patients. PLoS ONE 9(10): e109761. https://doi.org/10.1371/journal.pone.0109761

Siddeshappa, S. T., Nagdeve, S., yeltiwar, R. K., Parvez, H., Deonani, S., & Diwan, V. (2016). Evaluation of various hematological parameters in patients with periodontitis after non-surgical therapy at different intervals. Journal of Indian Society Periontology, 20(2), 180-183.

Teles, R., & Wang, C.-Y. (2010). Mechanisms Involved in the Association between Periodontal Diseases and Cardiovascular Disease. John Wiley & sons.

Wong Brian W, M. A. (2012). The Biological Role of Inflammation in Atherosclerosis. Canadian Journal of Cardiology, 631-641.