Universidad Europea

*TRABAJO DE FIN DE GRADO*

*Grado en Odontología*

# ASSOCIATION BETWEEN PERIODONTAL DISEASE AND HEART DISEASE

**Madrid, curso 2020/2021**

134

## Summary

**Introduction:** Periodontal disease is a chronic inflammatory process affecting the periodontium of the dentition. It is characterized by bacterial accumulation causing inflammation of the gingiva, called gingivitis, and it is called periodontitis when there is a destruction of the periodontium. The immune response against the inflammation may generate a disproportionate amount of pro-inflammatory mediators which may spread through the bloodstream influencing the initiation and/or progression of heart disease. The most common heart pathology is coronary heart disease which causes about 7.2 million deaths worldwide a year. **Objectives:** This bibliographic review aimed to evaluate if periodontal disease is a causative risk factor for the development of coronary heart disease, moreover, to describe the biological interconnection of periodontal disease and the pathogenesis of coronary heart disease, assess the risk of coronary heart disease when presenting periodontitis, and to evaluate periodontal therapy effect of preventing coronary heart disease. **Methodology:** For the redaction of this bibliographic review work, 29 scientific articles published between 2005 and 2020 in scientific journals have been analysed. The comprehensive search was carried out using PubMed, Medline, MDPI, Crai library, NIH, and Google Scholar databases. **Conclusion:** Periodontal disease shows to be an individual risk factor for coronary heart disease, augmenting the chance with 25%, but no causal relationship was found. The interconnection could be due to systemic migration of bacteria (direct pathway) or by systemic inflammation (indirect procedure) affecting the epithelial layer of the arterial walls. Periodontal therapy decreases the number of periodontal bacteria and inflammation, which in turn decreases the systemic inflammations. With this, it may indicate that the increased risk of coronary heart disease in periodontal patients may be neutralized through periodontal treatment, but further studies are needed to confirm this hypothesis.

# Resumen

**Introducción**: La enfermedad periodontal es un proceso inflamatorio crónico que afecta al periodonto de la dentición. Se caracteriza por la acumulación de bacterias que provocan la inflamación de la encía, denominada gingivitis, y se denomina periodontitis cuando hay destrucción del periodonto. La respuesta inmune contra la inflamación puede generar una cantidad desproporcionada de mediadores pro-inflamatorios que pueden extenderse a través del torrente sanguíneo influyendo en el inicio y/o progresión de la enfermedad cardíaca. La patología cardíaca más común, es la enfermedad coronaria que causa alrededor de 7,2 millones de muertes en todo el mundo al año. **Objetivos**: Esta revisión bibliográfica tuvo como objetivo evaluar si la enfermedad periodontal es un factor de riesgo causal para el desarrollo de enfermedad coronaria, además, describir la interconexión biológica de la enfermedad periodontal y la patogenia de la enfermedad coronaria, evaluar el riesgo de enfermedad coronaria cuando se presenta periodontitis, y evaluar el efecto de la terapia periodontal para prevenir la enfermedad coronaria. **Metodología**: Para la redacción de este trabajo de revisión bibliográfica, se han analizado 29 artículos científicos publicados entre 2005 y 2020 en revistas científicas. La búsqueda exhaustiva se llevó a cabo utilizando las bases de datos PubMed, Medline, MDPI, biblioteca Crai, NIH y Google Scholar. **Conclusión**: La enfermedad periodontal muestra ser un factor de riesgo individual para la enfermedad coronaria, mostrando un aumento del 25%, pero no se encontró una relación causal. La interconexión podría deberse a la migración sistemática de bacterias (vía directa) o por inflamación sistémica (procedimiento indirecto) que afecta la capa epitelial de las paredes arteriales. La terapia periodontal disminuye la cantidad de bacterias periodontales y la inflamación, lo que a su vez disminuye las inflamaciones sistémicas. Con esto, es posible indicar que el mayor riesgo de enfermedad coronaria en pacientes periodontales puede

neutralizarse mediante el tratamiento periodontal, pero se necesitan más estudios para confirmar esta hipótesis.

# Index

# 1. Introduction

## 1.1 Periodontal disease

Before going into the possible destructive disease of the supporting tissues of the teeth, also called the periodontium, it is important to define periodontal health first. The newest classification of 2017 says that periodontal health may be defined at one site in the mouth and in the whole mouth, furthermore, it can be at an intact or reduced periodontium. Reduction of the periodontium may be non-periodontal related, an example may be crown-lengthening, or related to a patient which has had periodontitis. Gingival health, for both types of periodontium, has been defined as no more than 10% of sites with gingival bleeding on probing and probing depth of 3 mm or less. It has been permitted a probing depth of 4 mm in patients with reduced periodontium, but there cannot be any bleeding on probing, if that were the case it would mean the chance of recurrent periodontitis. A probing depth of more than 3 mm in buccal or lingual/palatal indicates periodontitis if affecting 2 or more teeth, and if interdental probing show 2 mm or more at non-adjacent teeth sites of 2 or more teeth (1).

Periodontal disease is a continuous inflammatory process that affects the periodontium (gingiva, periodontal ligament, root cement, and alveolar bone) of the dentition (2-4). This polymicrobial, complex disease, is caused by a tangled relationship between microbial challenge, host genetics and response, and other modifying factors developing a bacterial biofilm on the tooth surface (2, 3). This dysbiotic plaque film made of the accumulation of microorganisms causes an inflammatory response called gingivitis. This inflammation is limited to the soft tissues surrounding the teeth and is a reversible process with the removal of the microbial biofilm. The chronic and progressive inflammation is called periodontitis, which irreversibly affects the periodontium. Periodontitis results in the progressive

destruction of the supporting tissue with the formation of periodontal pockets, gingival recession, and attachment loss, which eventually can result in the loss of the teeth (2, 5).

A patient diagnosed with periodontitis will always remain a periodontal patient, but the state of the disease varies from controlled, remission (inflamed gingiva), and uncontrolled where there is a recurrence of the condition. There are three types of periodontitis classified: periodontitis, necrotizing periodontitis and periodontitis as a consequence of systemic disease. The disorder can be divided into stages (figure 1) and grades (figure 2); initial-, moderate-, severe- and advanced stages and slow-, moderate- and rapid grade of progression (1).


**Figure 1: Periodontitis score in stages** (Extracted from Zabalegui et. al. New Classification of Periodontal and Peri-implant Disease) (1).

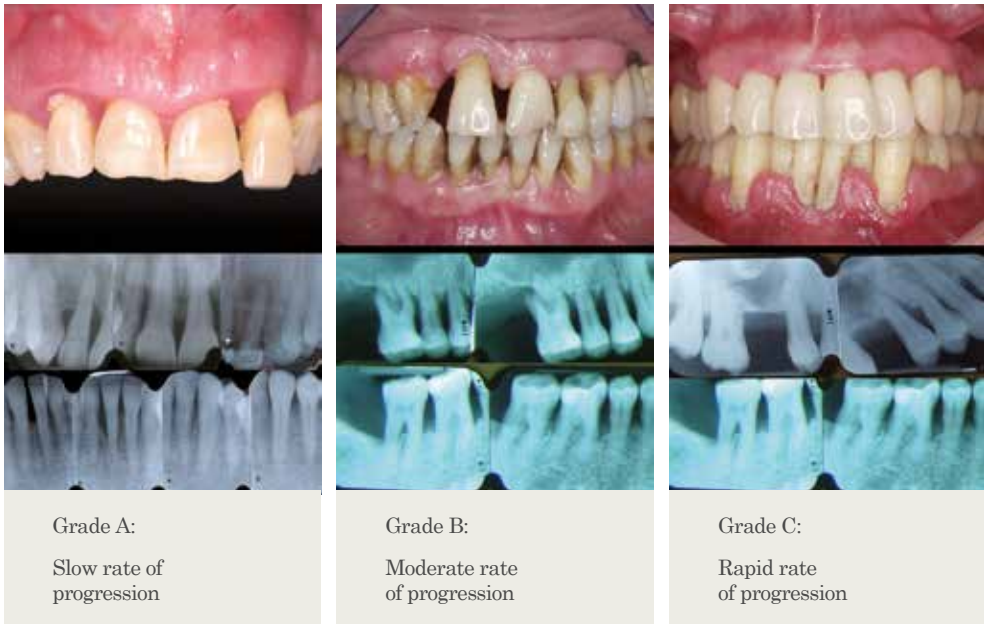



**Figure 2: Periodontitis score in grades**. (Extracted from Zabalegui et. al. New Classification of Periodontal and Peri-implant Disease) (1).

As gingivitis leads up to periodontitis, does not mean that all cases of gingivitis develop into periodontitis; its progression is mainly due to genetics and risk factors dictating the severity of the inflammatory response making some more susceptible than others (2, 3).

When the microbial biofilm on the tooth is not eliminated and is left to accumulate, it will lead to biological changes with the appearance and accumulation of gram-negative anaerobic bacterial species such as *Porphyromonas gingivalis, Treponema denticola,* and *Tannerella forsythia*. These anaerobic bacteria are known as the "red complex" and are constantly associated with periodontitis making them specific risk factors (2, 6).

The risk factors of developing periodontitis can be divided into two groups: we have the modifiable (environmental), which includes smoking tobacco, bad oral hygiene, diabetes mellitus, stress, and low socioeconomic position; and then we have the non-modifiable (genetical), which include old age and hereditary (2, 6, 7).

Even though the bacterial growth and organization in the microbial biofilm initiate periodontitis, the destructive process is mainly due to a host-mediated inherent and adaptative immune response mechanism, which is intensified in disease-susceptible individuals (2, 3, 6, 8). The activation of the immune response mediated by leukocytes in the gingiva is accountable for the creation of unbalanced amounts of pro-inflammatory mediators such as cytokines generating tissue oedema, and matrix metalloproteinases advocating the destruction of the periodontal connective tissues (2, 8, 9) (figure 1).

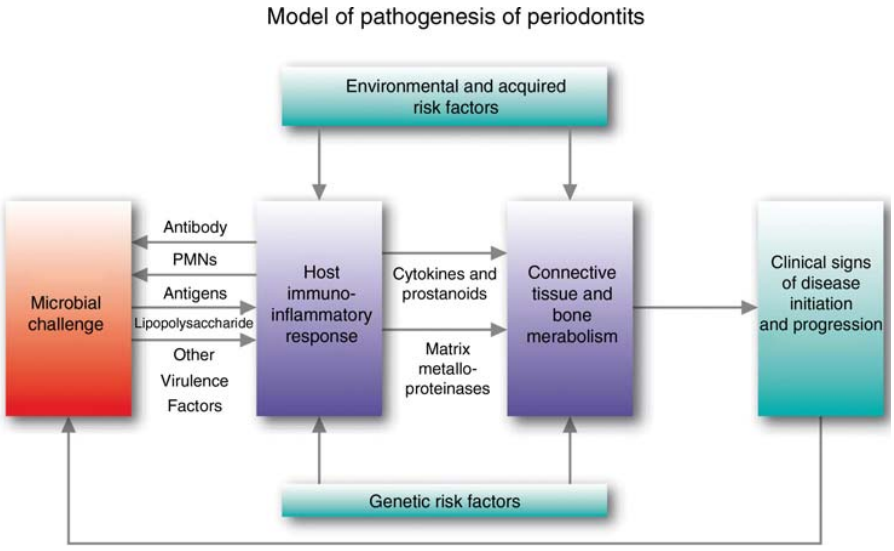



**Figure 3: Model of pathogenesis of periodontitis** (extracted from Sanz et. al. European workshop in periodontal health and cardiovascular disease). Periodontitis is mainly due to microorganisms, but the host-mediated immune-inflammatory response, regulated by both biological and environmental risk factors, is the main cause of periodontal destruction. (8).

The analysis of the prevalence and graveness of periodontal disease was conducted on a report from 2009-2012 by the United States National Health and Nutrition Examination Survey (NHANES). The report included a study group of 7066 adults 30 years of age or

older, and it showed that 46% had periodontitis and 8.9% presented severe periodontitis. Furthermore, it manifested that the prevalence and graveness of periodontitis were higher in males and was increased with the risk factors mentioned earlier (2).

According to the World Health Organization (WHO), signs and symptoms of gingivitis are seen among most children, and initial stages of periodontal disease are more commonly seen among adults. They also show that 5-15% of most populations' present severe periodontitis and early-onset aggressive periodontitis affects 2% of the youth (10).

This disease is a health problem affecting about 20-50% of the individuals worldwide, in both developed and developing countries. It shows to have a higher prevalence among young adults, adults, and elderly making it a public health concern (7).

The mouth is seen as a portal to the body, and the periodontal tissues do not have any protective shield which puts it in constant direct contact with bacteria (2, 11). There are several studies done on the possible link between periodontal disease and its effect on the different body systems (2, 5-7, 11, 12). The chronic inflammation of periodontitis is a constant potential source for infection which can metastatically spread its oral microbial toxins through the bloodstream causing transient bacteraemia, injuries and/or inflammation (11-13).

There have been done associations between periodontal disease and systemic diseases like cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease, respiratory diseases, diabetes mellitus, and osteoporosis in the past years (2, 5, 11, 12). Its association with systemic disease is explained by a decrease of resistance to infections by the host or the dysfunction of the connective tissue of the gums and/or an increase in the individuals' susceptibility to inflammation-induced destruction (12).

There has been shown evidence of a bi-directional relationship between periodontitis and systemic disease, which means that having one of these conditions as mentioned in the paragraph above, may increase the incidence and severity of having periodontal disease by altering the hosts' immune response to the periodontal bacteria and their antigens (5, 6, 11).

## 1.2 Heart disease

Cardiovascular disease (CVD) comprises a broad diversity of conditions affecting the heart and the vascular system of the body, including myocardial infarctions, stroke, infective endocarditis, atherosclerosis, peripheral artery disease, etc. (14). Cardiovascular diseases are the leading cause of death globally, causing death to about 17.9 million individuals each year (15).

Heart disease is the common name used for pathologies, both structural and functional, affecting the heart (16). Coronary heart disease has been defined as the most common disorder affecting the heart, others are infective endocarditis, congenital heart disease, congestive heart failure, heart rhythm problems, amongst others (17, 18).

Coronary heart disease, also called ischemic heart disease or coronary artery disease, affects and cost the lives of about 7.2 million people worldwide a year, and it consists of the accumulation of plaque and fatty substances in the arterial intima, narrowing or blocking the coronary arteries supplying blood to the heart. This build-up in the coronary arteries is called atherosclerosis, and it can happen in the whole cardiovascular system (16, 18-20).

This condition has many risk factors in its pathogenesis, and the more one individual presents the higher is the probability of acquiring the disease (16). The most common risk factors are hypertension, high low-density lipoprotein (LDL) cholesterol, low high-density

lipoprotein (HDL) cholesterol, diabetes mellitus, elderly, overweight, family history and genetics, and poor oral hygiene (6, 7, 11, 19).

Symptoms of coronary heart disease differ from patient to patient, where some might have severe symptoms and some none at all. When not presenting any symptoms, the disorder is not detected before the patient starts having chest pain (angina), heart attack (myocardial infarction), or an unexpected cardiac arrest. Between the male and female sex, there is a difference in the experience of symptoms. Females are less likely to have chest pain than the male sex, and they suffer more likely symptoms such as dizziness, fatigue, nausea, pressure or tightness in the chest, and stomach pain. It is also more common for females to be asymptomatic. In general, when coronary heart disease has been present for many years, the patient may present manifestations such as angina, difficulty breathing during physical activity, neck ache and fatigue (16).

The diagnosis of coronary heart disease is established by the symptoms the patient presents, medical and family history, patients' risk factors, as well as the results from tests and procedures performed. Due to women having fewer symptoms, and not being the same as men's, the diagnosis and treatment will be delayed. The tests performed for the diagnosis include blood tests, where they check the levels of low- and high-density lipoprotein cholesterol, sugar, and C-reactive protein, which are indicators of inflammation, and other tests to perform are electrocardiogram (EKG), coronary calcium scan, stress test, etc (16).

The treatment includes healthy life changes for the heart: healthy weight and diet, physical activity, cessation of smoking, stress level control, and good sleep. Medication and/or an invasive procedure might be indicated depending on the severity of the disease (16).

With the understanding of periodontal disease and the importance of heart disease, this text will focus on their association, with the hypothesis that presenting periodontal disease can be a causative risk factor for developing coronary heart disease and that periodontal therapy may reduce or even prevent that risk.

# 2 Objectives

Heart disease has a wide spectre of different conditions. The most common one, coronary heart disease, has several studies conducted on its connection with chronic dental inflammation/periodontitis (6, 13, 19). With this information, the **main objective** of this text is:

1. To evaluate if periodontal disease is an individual causative risk factor for the development of coronary heart disease.

And with the **secondary objectives** as following:

2. To describe the biological interconnection of periodontal disease and the pathogenesis of coronary heart disease.
3. To assess the risk of coronary heart disease when presenting periodontitis.
4. To evaluate the effect of periodontal therapy on preventing coronary heart disease.

# 3 Methodology

To assess the association between periodontal disease and coronary heart disease, numerous scientific articles, journals, books, reliable web pages, and previous lessons on the subject of periodontal disease were consulted. Briefly, the definition and prevalence of periodontal disease was made, as well as for coronary heart disease, with a short connection between the oral cavity and the human body. Further on, the existing literature was used to draw the associations between the two diseases answering the studies objectives.

For the comprehensive search PubMed, Medline, MDPI, Crai library of the European University of Madrid, the National Institute of Health (NIH), and Google Scholar were searched for publications with “periodontal disease”, “periodontitis”, “heart disease”, “coronary heart disease”, “atherosclerosis” as keywords and in combination with “association”, “risk factor”, “oral health”, “biomarkers”, “connection” in the title of the study. There were certain criteria on which sources were valid, they had to be published in the last 20 years, with a greater focus on the ones issued the past 10 years to ensure they contained the most relevant and updated data, and they had to be written in English language.

The literature was read and analysed in detail to extract the association between the two diseases from each article. There was a total of 29 sources collected for the bibliographical research.

When analysing periodontal disease severity and prevalence in various populations it differs due to bias and the lack of agreement on the clinical criteria used to determine the presence of the condition (inter-examiner variability) as for the classification of the disease changing through the years (2, 7, 21). Furthermore, failure to record the attachment loss, which is the determinant factor for destructive periodontal disease, limits the result of studies

as it reflects the oral health status as well as a present or previous long-lasting inflammation and infection (21).

Limitations are also found in the different types of studies conducted, some with higher bias than others, such as case-control studies have a lower risk of bias than cross-sectional studies. Furthermore, some do not take into account the effect of the many other different risk factors for acquiring coronary heart disease other than having periodontal disease. The number of the individuals included in the studies, their ethnicity, age, and location of the study also show to arise limitations in the results of the studies analysed for this bibliographical review (6, 27).

# 4 Discussion

Periodontitis is a well-known local inflammatory disorder that presents the possibility of generating a systemic inflammation by metastatically spreading its bacteria and pro-inflammatory mediators, which could facilitate the initiation and progression of coronary heart disease (22). The association between these two diseases has been discussed for many years, and to understand their connection, it is necessary to acknowledge the elements of coronary heart disease (5-8, 12-14, 19-22, 26).

## 4.1 Elements of coronary heart disease

Coronary heart disease, also reported as an inflammatory disorder, permits the accumulation of lipoproteins in the arterial walls by the presence of "hallmarks" which are considered hypercoagulation, hypercholesterolemia, hyperglycaemia/hyperinsulinemia, inflammation and hypertension (22). The inflammation "hallmark" plays a crucial role in the initial atherosclerotic lesion to the formation of thrombi.

The disorder ranges from angina pectoris to myocardial infarction. Angina is determined as ischemia to the heart muscle causing a reduction in the oxygen supply and halting of aerobic metabolism which if continued, can result in cell death. And myocardial infarction is the death of heart cells due to blood flow restriction caused by obstructive stenosis or thrombosis (21, 22).

The blood vessels are lined with a shield made of endothelial cells, separating the blood flooding through the arteries with the vessel wall; with this resisting the attachment of white blood cells such as T-lymphocytes and monocytes (22). The initiation of the atherosclerotic lesion has been traced back to an adverse change in this endothelial barrier, where the cells may express vascular cell adhesion molecule-1 (VCAM-1) upon irritating

stimuli of increased serum pro-inflammatory cytokines, admitting the aggregation of monocytes and T-lymphocytes to the vascular endothelial cell wall. Once adhered, the monocytes enter into the tunica intima with the help of monocyte chemoattractant protein-1, and T-lymphocytes with interferon-γ, as an immune response to an endothelial injury, making the early atherosclerotic lesion (22).

Inside the tunica intima monocytes differentiate into tissue macrophages, which play an important role in the initiation, maintenance, and resolution of inflammation. These cells convey cell surface receptors to continue the uptake of modified lipoproteins and they transform into lipid-laden foam cells (main cell in atherosclerotic plaque) (22, 24, 25). At this point, the inflammation may continue its progression by macrophages pro-inflammatory aspect, and the further uptake of monocytes and T-lymphocytes will consequently increase the size of the lesion. As it grows, it can either narrow the arterial lumen (stenotic) or not (non-stenotic) (22).

As the atherosclerotic lesion is being formed, there is a relocation of smooth muscle cells, the ones producing collagen and elastin, from the tunica media into the tunica intima. These cells have the purpose of making a fibrous cap cover over the lesion, preventing its necrotic core to come in contact with the bloodstream. Inside the necrotic core, one can locate dead foam cells, which are highly coagulative. There is a possibility of macrophages triggering the apoptosis of these smooth muscle cells by excreting proapoptotic tumour necrosis factor-α (TNF-α) and nitric oxide, thereby thinning and weakening the fibrous cap by the insufficient collagen production (22). The failure of the fibrous cap puts the lipid-rich, highly coagulative, necrotic core in contact with the coagulation proteins in the blood, triggering a hypercoagulative state that generally leads to the formation of a thrombus and its possible migration (embolus) (21, 22).

## 4.2 Systemic inflammation, pro-inflammatory biomarkers and periodontal pathogens

Systemic inflammation is known to provoke the pathogenesis of coronary heart disease; to draw this connection with periodontal disease, biomarkers can be used (22). A biomarker is defined as "*a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease*", and they are measurable, making them useful to identify underlying systemic inflammation (22, 26). With the help of biomarkers, we can permit a more specific identification of the origin of patients suffering from coronary heart disease, enabling one to differentiate similar cases with different pathogenesis (22).

Inflammation markers found to show relative importance regarding coronary heart disease risk are high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), TNF-α, growth-differentiation factor-15 (GDF-15) and a decrease in osteoprotegerin (OPG) (22).

Studies on the association of the two diseases have indicated that periodontitis may directly, with periodontal bacteria present in the bloodstream, or indirectly, by systemic inflammation and its subsequent immune response, affect the atherosclerotic pathophysiology and thus alter coronary heart disease risk (12, 23).

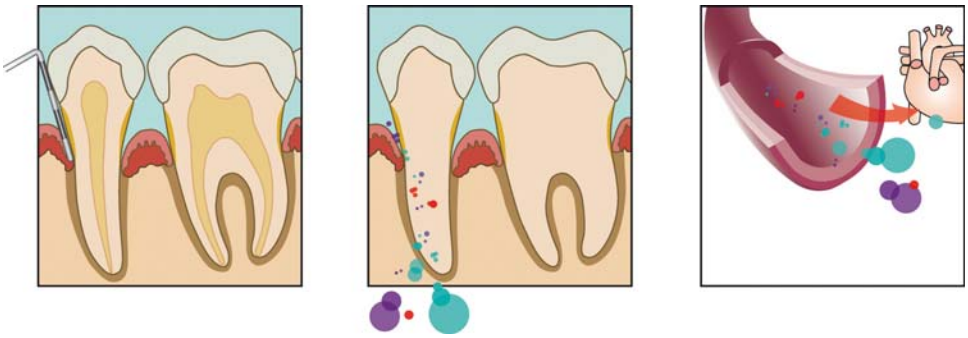


**Figure 4: Model of the association between periodontal disease and coronary heart disease** (8).

Serum tests of patients with periodontitis have indicated higher systemic levels of hsCRP and IL-6, and neutrophils immoderate discharge of IL-1, IL-8, IL-6, and TNF-α (8, 12, 23). High-sensitivity C-reactive protein plays a vital role in endothelial cell dysfunction and gives insight into the link between periodontal disease and coronary heart disease (5, 6). Cytokine manufacturing (TNF-α, IL-1 and IL-6) can in severe cases when the periodontal inflammation has spread to the alveolar bone, cause attachment loss by increasing the amount of receptor activator of nuclear factor-κβ (RANK) and the subsequent reduction of osteoprotegerin (13, 22). The function of osteoprotegerin is to preserve the bone, and RANK serves as an inducer of bone resorption, thereby, with this relationship, we may measure the graveness of inflammation caused by periodontitis (13, 22).

Etiologically, daily activities such as mastication, toothbrushing and flossing, and dental procedures as scaling and root planning (SRP), tooth extraction and periodontal probing, liberate endotoxins from the bacterial biofilm into the bloodstream, causing bacteraemia (2, 5, 8, 23). The number of bacteria present in the subgingival plaque in periodontal pockets of healthy areas is around 1,000, and in periodontitis affected areas there are more than 100,000,000 (2). Thus, when presenting periodontal inflammation, the risk of bacteraemia increases by the elevated volume of bacterial concentration (5, 8). Normally this bacteraemia is removed fast by the non-specific immune system, but there is the chance of the periodontal bacteria or their endotoxins to adhere and/or invade an atheroma and further advance the formation of atherosclerotic lesions (2).

### 4.3 Biological interconnections of periodontal disease and coronary heart disease

Periodontal pathogens such as *A. actinomycetemcomitans, P. gingivalis* and *T. forsythia* have been isolated and detected in atheromatous plaque and have also been found to interact with endothelial cells lining the vessel walls (2, 5, 22, 23). With constant bacteraemia induced by gram-negative periodontal bacteria, and the circulating endotoxins, it may eventually result in endothelial dysfunction in the arterial walls, this making the assumed direct procedure of periodontal-induced atherosclerotic lesions (8, 23).

Oral microbes such as *P. gingivalis, T. denticola, T. forsythia* and *Fusobacterium nucleatum* can provoke pro-inflammatory cytokine manufacturing, hypercoagulability, monocyte stimulation, and the release of C-reactive proteins from the liver (5, 8, 23). Furthermore, these bacteria also induce the production of toll-like receptor 2 (TLR2) and oxidative stress reaction in the epithelial cells (23). *P. gingivalis* and *A. actinomycetemcomitans* have also shown to induce the formation of antibodies, and that the combined response of these serum antibodies against the bacteria has a role in the activation of monocytes and cytokine production (5, 23). In this way, the oral germs can affect the pathogenetic association between periodontal disease and coronary heart disease in an indirect way by pathogenic microbial imbalance provoking systemic inflammation and an immune reaction leading to epithelial dysfunction of the coronary arterial walls (23).

In a research project performed by Marc J. Mathews, an integrated model was made on coronary heart disease, containing its pathogenesis, biological markers, individual health factors and medications (13, 22). The model was made of a great literature investigation and used to draw the association of non-traditional health factors on coronary heart disease (22). Since the main focus of this bibliographic review was to show the conditions' association

with periodontal disease, any other health factor not relevant for that connection was not included.

To understand better the interconnection between these two pathologies, in the integrated model they studied different causative pathways periodontal disease could give rise to coronary heart disease (13, 22). One of the first pathways mentioned was how *P. gingivalis* has the ability to increase platelet activity through a TLR2-dependent mechanism, which may result in hypercoagulation, a known coronary heart disease hallmark (13, 22).

Another pathway shows that the augmented reactive oxygen species associated with periodontitis can have the effect of increasing the oxidation of LDL cholesterol, which makes it easier for the macrophages to ingest cholesterol and their subsequent transformation into lipid-laden foam cells. The increased amount of reactive oxygen species plays also an important role in linking systemic inflammation and periodontal disease with the activation of nuclear factor-κβ, and the subsequent inflammatory response with cytokines and growth factors. With the presence of circulating *P. gingivalis*, the systemic inflammation may continue to increase with the augmentation in the serum levels of C-reactive proteins, fibrinogen, TNF-α and IL-6 (13, 22).

The increase of C-reactive protein, fibrinogen, glucose levels, monocytes and T-lymphocytes, and total cholesterol belong to the acute phase response of the body, which is caused by the systemic inflammatory mediators produced by periodontal inflammation (2).

With the increased release of pro-inflammatory cytokines from the inflamed periodontal tissues, there might be augmentation in the insulin resistance, which consequently will impair insulin's effects of vasodilation (13, 22). The loss of the vasodilation effect might indicate an increase in vasoconstriction of the arteries. This may lead to hypertension, and

further complications such as hyperglycaemia and/or hyperinsulinemia, which are all hallmarks for the pathogenesis of coronary heart disease (22).

Showing to these different pathways it is clear that there are pathogenetic links of the continuous inflammatory process of periodontal disease and coronary heart disease, either through a direct or indirect pathway (13, 22).

The systemic inflammation caused by periodontal disease, as mentioned, may also have the effect of hyperinsulinemia/hyperglycaemia, a sign of Diabetes Mellitus type II, and by having diabetes mellitus, there is a greater risk of getting periodontal disease and for its worsening due to complications of the condition (5, 22). With this knowledge, it is possible to state that acquiring or presenting periodontal disease, could be used as a sign of elevated risk for coronary heart disease and feasible diabetes mellitus type II, and that being diagnosed with diabetes mellitus, type I or II, may have the consequence of causing periodontal disease and subsequently increase the risk of coronary heart disease (22).

### 4.4 Direct periodontal-induced atherosclerotic lesions studies

To analyse the direct relationship between periodontal disease and coronary heart disease, the pathogenic bacteria present in the periodontal biofilm have to be present in the atherosclerotic plaque (atheroma). In an article written in 2006, it was mentioned an investigation on the direct effect of periodontal disease by the presence of five different periodontal microbes in the atheromatous plaques. The investigation was conducted by Cairo et al. and they detected the presence of periodontal pathogens in carotid atheroma by the use of polymerase chain reaction tests (PCR). Results from the study showed to, from highest to lowest in percentage, *T. forsythia* (previously called *T. forsynthesis*) in 79%, *F. nucleatum* in 63%, *P. intermedia* in 53%, *P. gingivalis* in 37%, and *A. actinomycetemcomitans* in 5% (5).

In another article written in 2014 by Rath et al., a case-control study was conducted to analyse the presence of *P. gingivalis, A. actinomycetemcomitans, T. forsythia* and *T. intermedia* in both periodontal and atheromatous plaque, to also draw the direct connection between periodontal disease and coronary heart disease. The selected cases in the study were patients who had undergone coronary endarterectomy procedure (a total of 7 patients), and the controls were randomly selected outpatients of the Department of Dental Surgery. To determine the presence of the bacteria, they as well used polymerase chain reaction tests (PCR) (27).

In the case group, the results of the PCR examination of periodontal plaque showed the presence of *P. gingivalis* and *T. forsythia* in 100% of the samples, and *A. actinomycetemcomitans* and *T. intermedia* in 71.43%. The combination of *P. gingivalis*, *A. actinomycetemcomitans* and *T. forsythia* was detected more prevalently than the four pathogens together, showing to 57.14% of the samples (27).

The PCR of the atheromatous plaque indicated the presence of *T. forsythia* in 100% of the samples, 71.43% samples with *P. gingivalis*, 42.86% with *A. actinomycetemcomitans*, and *T. intermedia* was not detected. This microorganism trio, *P. gingivalis*, *A. actinomycetemcomitans* and *T. forsythia,* were present in 42.86% of the samples, and the duo of *P. gingivalis* and *T. forsythia* in 28.57%. In the control group, *A. actinomycetemcomitans* was not detected, and only 7.14% of the samples indicated the presence of *P. gingivalis, T. forsythia* and *T. intermedia* (27).

With this case-control study, they found that *T. forsythia* was present in all samples done on periodontal plaque and atheromatous plaque, and *T. intermedia* only detected in periodontal plaque. Furthermore, *P. gingivalis* was found in all periodontal plaques and in 5 out of the 7 patients with atheromatous plaque, and *A. actinomycetemcomitans* was detected

in the atheromatous plaque when present in periodontal plaque. These findings show a direct association between periodontal bacteria contributing to the formation of atherosclerotic lesions leading to coronary heart disease (27).

**Table 1:** Percentage (%) of periodontal bacteria present in atheromatous plaque in four different studies (5, 27).

| | **Haraszthy et al.** (2000) | **Ishihara et al.** (2004) | **Cairo et al.** (2006) | **Rath et al.** (2014) |
|---|---|---|---|---|
| ***T. forsythia*** | 30% | 5.9% | 79% | 100% |
| ***P. gingivalis*** | 26% | 21.6% | 37% | 71.43% |
| ***A. actinomycetemcomitans*** | - | - | 5% | 42.86% |
| ***T. intermedia*** | 14% | - | 53% | 0% |
| ***F. nucleatum*** | - | - | 63% | - |

Hyphen (-) denotes not included in the study.

Comparing the results from the two studies mentioned with other two studies, one done by Haraszthy et al. in the year 2000 and another by Ishihara et al. done in 2004, we can see that the results are compatible (27) (Table 1). It shows that *T. forsythia* was detected in all four of the studies with a greater amount in the two newest ones, and *P. gingivalis* was also identified in a fair amount in the three first studies and in a higher amount, with 71.34%, in the last one by Rath et al. (5, 27). The infection with *A. actinomycetemcomitans* in periodontal disease was only first drawn as an increased risk of coronary heart disease in 2005, and it was therefore not included in the two first studies done by Haraszthy et al. and Ishihara et al (5).

## 4.5 Epidemiological association studies

Over the past two decades, several studies have been conducted on the effect of periodontal disease on the cardiovascular system. It has mainly been performed studies of such kind as case-control, cross-sectional, and prospective cohorts on the connection of the two pathologies, and they have drawn up evidence showing the association between periodontal disease and coronary heart disease (8). In epidemiological studies, when the odds ratio and relative risk (risk ratio) is higher than 1, it shows there will be a positive association or risk (28).

A systemic review conducted by Bahekar et al. in 2007, taking into account age, gender, diabetes mellitus and tobacco smoking, included all three types of studies, where the cohort studies indicated that subjects with periodontal disease had a 1.14 times greater chance of acquiring coronary heart disease than the individuals with healthy periodontium. They also showed an odds ratio of 2.22 in the case-control studies, and in the cross-sectional studies, they showed a relative risk of 1.59 for developing coronary heart disease when presenting periodontal disease (8, 14).

Another meta-analysis which only included prospective cohort studies showed a relative risk between 1.24 and 1.34 for developing coronary heart disease (8).

In a similar analysis on several studies on the association, they showed an odds ratio of 2.35 and relative risk of 1.34, meaning an increase in the odds and risk for periodontally affected individuals of developing coronary heart disease. Another study indicated an increased risk of 19% in individuals with periodontal disease, which increased to 44% when over the age of 65, for the development of cardiovascular disease (7).

With the results from all these meta-analysis and systemic reviews, it shows evidence of periodontal disease being an independent risk factor for coronary heart disease, although it

is not very high, with about 24-35% increase of its chance (8). It was also well demonstrated in another research that was conducted over 14 years on 9760 study subjects that the risk of acquiring coronary heart disease when presenting periodontitis had an increased chance of 25% (27). By calculating the mean of the different relative risks and odds risk obtained, it shows a relative risk of 1.32, and an odds risk of 2.28.

### 4.6 Therapeutic effect of periodontal treatment on coronary heart disease

Individuals with moderate to severe periodontitis that have been connected with increased systemic inflammation, and migration of periodontal bacteria systemically, have shown to have an increased risk for the development of coronary heart disease. The treatment of periodontal disease may show a therapeutic effect on patients with coronary heart disease by lowering the clinical signs of the periodontal disease and its consequent systemic inflammation (22, 27).

When performing periodontal therapy, such as scaling and root planning, there is a decrease in the serum levels of IL-6 and there is also a reduction in the antibodies against the gram-negative bacteria, as well as the amount of high-sensitivity C-reactive protein and TNF-α (2, 23). Also, periodontal therapy lowers significantly the level of fibrinogen, thereby lowering the risk of thrombi formation. Another positive effect is that there will not be an increased activity of the platelets by the lowered concentration of *P. gingivalis*, decreasing the hypercoagulation hallmark (23).

To measure atherosclerotic progression and if it is improving, the intima media thickness and flow-mediated dilation are useful in addition to the lowered serum levels of inflammatory mediators (2, 14, 23).

There have been studies postulating that periodontal treatment and management have the effects of preventing the formation of atherosclerotic lesions or lowering the risk of cardiovascular events (damaging incidents to the heart muscle). A study conducted in 2009 showed an improvement of the intima media thickness in atherosclerotic lesions 12 months after periodontal treatment (2, 11, 23). This reduction was very small, and it had a great chance of being due to measurement inaccuracy. Another study showed an improvement of about 2% after six months in the flow-mediated dilation with periodontal treatment, whereas a meta-analysis done on 3 different studies gave a result of 6.64% improvement (2).

Research has shown a decrease in endothelial dysfunction, meaning an improved flow-mediated dilation, and lowered systemic inflammation. But unfortunately, there is no good evidence, nor are there well enough conducted trials that can indicate improvement or preventive effects of periodontal therapy on atherosclerotic events such as myocardial infarction and stroke, but the risk may be reduced by maintaining good overall oral health (2, 14, 23). Both periodontal disease and coronary heart disease are chronic, and it takes several years for an atherosclerotic lesion to appear, which means that by the time periodontal therapy is started, the formation of atheromatous plaque in the coronary arteries may already have happened (14).

Additional studies are needed to show if there is a connection between periodontal therapy and the prevention or reduction of atherosclerotic lesions and possible future cardiovascular events in coronary heart disease patients (27).

## 4.7 Additional information

As already mentioned earlier, periodontally induced bacteraemia caused by daily activities (chewing, tooth-brushing, flossing, etc.) may contribute to the damaging inflammatory process on the epithelial cell layer of the cardiovascular tissues giving rise to atherosclerosis, and latterly infective endocarditis (29).

Infective endocarditis is an infection of the heart and the heart valves endocardium, and it affects mostly already damaged cardiac valves, more commonly the mitral valve, then secondly the aortic and then not so commonly, the pulmonary valve (14, 29). It is a heart disease that has the dentist, patient and the cardiologist concerned. The link between this heart condition and periodontal bacteria is well known but hard to stablish. It is determining for the connection to have a damaged surface, such as of the endocardium, and a high load of bacteria. When presenting periodontitis there is an increased risk of bacteraemia due to the high vascularization of the periodontium and its close relationship with the bacterial biofilm. With this information, it is evident that patients at risk of developing infective endocarditis will benefit from periodontal therapy and good oral hygiene, by this means removing and controlling periodontal infection (gingivitis and periodontitis) which in turn reduces the origin of microorganisms and its possible consequent bacteraemia. Nevertheless, there are no apparent benefits to performing periodontal treatment prior to cardiac valve surgery (29).

With the knowledge that periodontal disease can cause bacteraemia and increased serum levels of inflammatory mediators, proteins, and lipids, the disorder does not only bring a higher risk of heart diseases but also many other systemic health problems (27). And as mentioned earlier, the well-known pancreases disorder diabetes mellitus is one of many diseases with connection to periodontal disease (2, 5, 11, 13, 22).

# 5 Conclusion

1. With this bibliographic review the association between periodontal disease and heart disease, coronary heart disease to be more specific, has been drawn. The results have not indicated a causal relationship, but it has shown that periodontal disease is a risk factor on its own for the development of coronary heart disease. There is a possibility of periodontal disease being a causal risk factor for the development of coronary heart disease due to the link of systemic inflammation which is a well-known hallmark for the pathogenesis of atherosclerotic lesions, but there is no evidence indicating that there is a causal relationship, and further studies are needed to show for such causative connection.
2. The association between the two pathologies is due to bacteraemia and systemic inflammation where the connection can be of a direct pathway: by constant exposure to periodontal pathogens and endotoxins in the blood, or by indirect procedure: by systemic inflammation and the release of systemic inflammation mediators. Both direct and indirect procedures may lead up to endothelial dysfunction in the coronary arterial walls and a consequent immune reaction, this making up the periodontal-induced atherosclerotic lesions. However, there may be some uncertainty because both diseases have the same risk factors which may give casual results. And with both diseases being of inflammatory origin, it may be the chance that the parameters measured, instead of being of periodontal disease induced systemic inflammation, their origin is of coronary heart disease itself, or it may even be due to the total inflammatory burden and not just caused by a single bacterial infection.
3. Periodontitis increases the risk of atherosclerosis formation in the coronary arteries by bacteraemia and systemic inflammatory mediators such as pro-inflammatory

cytokines, high-sensitivity C-reactive protein, uncontrolled discharge of IL-1β, IL-8, IL-6 by neutrophils, and TNF-α.With this, there is an increased risk of 25% and a mean relative risk of 1.32, and a mean odds risk of 2.28 for developing coronary heart disease when diagnosed with periodontitis.

4. Studies have shown that with periodontal therapy there will be a resulting decrease in the serum levels of pro-inflammatory mediators and a normalization of the platelet activity, indicating that the increased risk of coronary heart disease in periodontal patients may be neutralized through periodontal treatment. It has also been shown that periodontal treatment improves endothelial function, but it does not exist a study showing clear evidence that it may prevent or improve atherosclerotic events, nor even future cardiovascular events, therefore, further studies are needed to confirm this hypothesis.

# 6 Responsibility

The present bibliographical review is looking into the association between periodontal disease and coronary heart disease. The biological interconnection of the two diseases have been explained and that by maintaining good oral health it might be possible to prevent bacteraemia and its systemic consequences. With the understanding of the interconnection, it may help dentists and medical doctors in preventing coronary heart diseases by early detection of both pathologies and encouragement of maintaining good oral health. Since periodontal disease is preventable, treatable and indicated as a risk factor for the development of atherosclerosis in the coronary arteries, it will have a big impact on its prevention and also on maintaining overall good health.

# 7 Bibliography


1. Zabalegui I, Serrano J, Pascual A, Adriaens L, Sanz I. Periodoncia clínica. New Classification of Periodontal and Peri-implant Disease. Scientific journal of the Sociedad Española de Periodoncia. 2019[cited 23 February 2021];(15):1-132.
2. Craig R, Kamer A. A Clinician's Guide to Systemic Effects of Periodontal Diseases. New York: Springer-Verlag Berlin Heidelberg; 2016[cited 9 November 2020].
3. Bostanci N, Belibasakis G. Pathogenesis of Periodontal Diseases: Biological Concepts for Clinicians. Stockholm: Springer International Publishing AG; 2018[cited 9 November 2020].
4. Víla P. Basic Periodontology Review. Lecture presented at; 2019[cited 9 November 2020]; UEM.
5. Kim J, Amar S. Periodontal disease and systemic conditions: a bidirectional relationship. Odontology. 2006[cited 9 November 2020];94(1):10-21. Available at: https://doi.org/10.1007/s10266-006-0060-6
6. Friedewald V, Kornman K, Beck J, Genco R, Goldfine A, Libby P et al. The American Journal of Cardiology and Journal of Periodontology Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease. J Periodontal [Internet]. 2009 [cited 16 November 2020];80(7):1021-1032. Available at: https://doi.org/10.1902/jop.2009.097001
7. Nazir M. Prevalence of periodontal disease, its association with systemic diseases and prevention. Odontology [Internet]. 2017 [cited 9 November 2020];11(2):72-80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5426403/#!po=28.8462

8. Sanz M, D'Aiuto F, Deanfield J, Fernandez-Avilés F. European workshop in periodontal health and cardiovascular disease—scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature. European Heart Journal Supplements [Internet]. 2010 [cited 19 November 2020];12: B3-B12. Available at: https://doi.org/10.1093/eurheartj/suq003
9. Checchi V, Maravic T, Mazzoni A, Bellini P, Generali L, Consolo U et al. The Role of Matrix Metalloproteinases in Periodontal Disease. Int J Environ Res Public Health [Internet]. 2020 [cited 19 November 2020];17(14):1-13. Available from: https://doi.org/10.3390/ijerph17144923
10. Petersen P. What is the burden of oral disease? [Internet]. World Health Organization. 2000 [cited 9 November 2020]. Available from: https://www.who.int/oral_health/disease_burden/global/en/
11. Gude D, Koduganti R, Pothini L. Mouth: A portal to the body. Dent Res J (Isfahan) [Internet]. 2012 [cited 16 November 2020];9(6):659–664. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3612210/
12. Arigbede A, Osagbemiro Babatope B, Kolude Bamidele M. Periodontitis and systemic diseases: A literature review. J Indian Soc Periodontal [Internet]. 2012 [cited 16 November 2020];16(4):487–491. Available at: https://doi.org/10.4103/0972-124X.106878
13. Mathews M, Mathews E, Mathews G. Oral health and coronary heart disease. BMC Oral Health [Internet]. 2016 [cited 16 November 2020];16(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5111198/#!po=67.0213
14. Persson G, Persson R. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol [Internet]. 2008 [cited 19 November

2020];35(8):362–379. Available from: https://doi.org/10.1111/j.1600-051X.2008.01281.x

15. Cardiovascular Diseases [Internet]. World Health Organization. 2020 [cited 19 November 2020]. Available from: https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1
16. Coronary Heart Disease [Internet]. National Heart, Lung and Blood Institute. [cited 11 November 2020]. Available from: https://www.nhlbi.nih.gov/health-topics/coronary-heart-disease
17. Heart disease [Internet]. National Cancer Institute. [cited 11 November 2020]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/heart-disease
18. Coronary heart disease [Internet]. National Cancer Institute. [cited 11 November 2020]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/coronary-heart-disease
19. Sikka M, Sequeira P, Acharya S, Bhat M, Rao A, Nagaraj A. Poor oral health in patients with coronary heart disease: a case–control study of Indian adults. Journal of the New Zealand Medical Association [Internet]. 2020 [cited 11 November 2020];124(1347):53-62. Available from: https://pubmed.ncbi.nlm.nih.gov/22237568/
20. Humphrey L, Fu R, Buckley D, Freeman M, Helfand M. Periodontal Disease and Coronary Heart Disease Incidence: A Systematic Review and Meta-analysis. J Gen Intern Med [Internet]. 2008 [cited 2020 Nov 11];23(12):2079-2086. Available at: https://doi.org/10.1007/s11606-008-0787-6
21. Zanella S, Pereira S, Barbisan J, Vieira L, Saba-Chujfi E, Haas A et al. Periodontal disease, tooth loss and coronary heart disease assessed by coronary angiography: a

cross-sectional observational study. Jurnal of Periodontal Research [Internet]. 2016 [cited 4 December 2020];51:221–227. Available from: http://doi.org/10.1111/jre.12301

22. Mathews MJ. A systems engineering approach to coronary heart disease. North-West University [Internet]. 2015 [cited 2020 Jan 1]. Available from: https://repository.nwu.ac.za/handle/10394/18953
23. Byun S, Lee S, Kang S, Choi H, Hong S. Cross-Sectional Analysis of the Association between Periodontitis and Cardiovascular Disease Using the Korean Genome and Epidemiology Study Data. International Journal of Environmental Research and Public Health. 2020 [cited 10 February 2021];17(14):5237. Available at: http://doi.org/10.3390/ijerph17145237
24. Yu X, Fu Y, Zhang D, Yin K, Tang C. Foam cells in atherosclerosis. Clinica Chimica Acta [Internet]. 2013 [cited 2 February 2021];424:245–252. Available at: http://dx.doi.org/10.1016/j.cca.2013.06.006
25. Fujiwara N, Kobayashi K. Macrophages in Inflammation. Current Drug Target - Inflammation & Allergy [Internet]. 2005 [cited 2 February 2021];4(3):281-286. Available at: http://doi.org/10.2174/1568010054022024
26. Biomarker [Internet]. National Cancer Institute. 2021 [cited 9 February 2021]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biomarker
27. Rath S, Mukherjee M, Kaushik R, Sen S, Kumar M. Periodontal pathogens in atheromatous plaque. Indian Journal of Pathology and Microbiology [Internet]. 2014 [cited 14 February 2021];57(2):259. Available at: http://doi.org/10.4103/0377-4929.134704

28. Sanchez J. Epidemiology in dentistry (I). Lecture presented at; 2020 [cited 31 March 2021]; UEM.
29. Carinci F, et.al. Focus on periodontal disease and development of endocarditis. Journal of Biological Regulators and Homeostatic Agents. 2018;32(2):143-147.

# Annexes

**Source number 1**

Scientific journal of the
Sociedad Española de Periodoncia
International Edition

Period I, Year V, n.º 15
Editor: Ion Zabalegui

2019 / 15

# periodoncia clínica

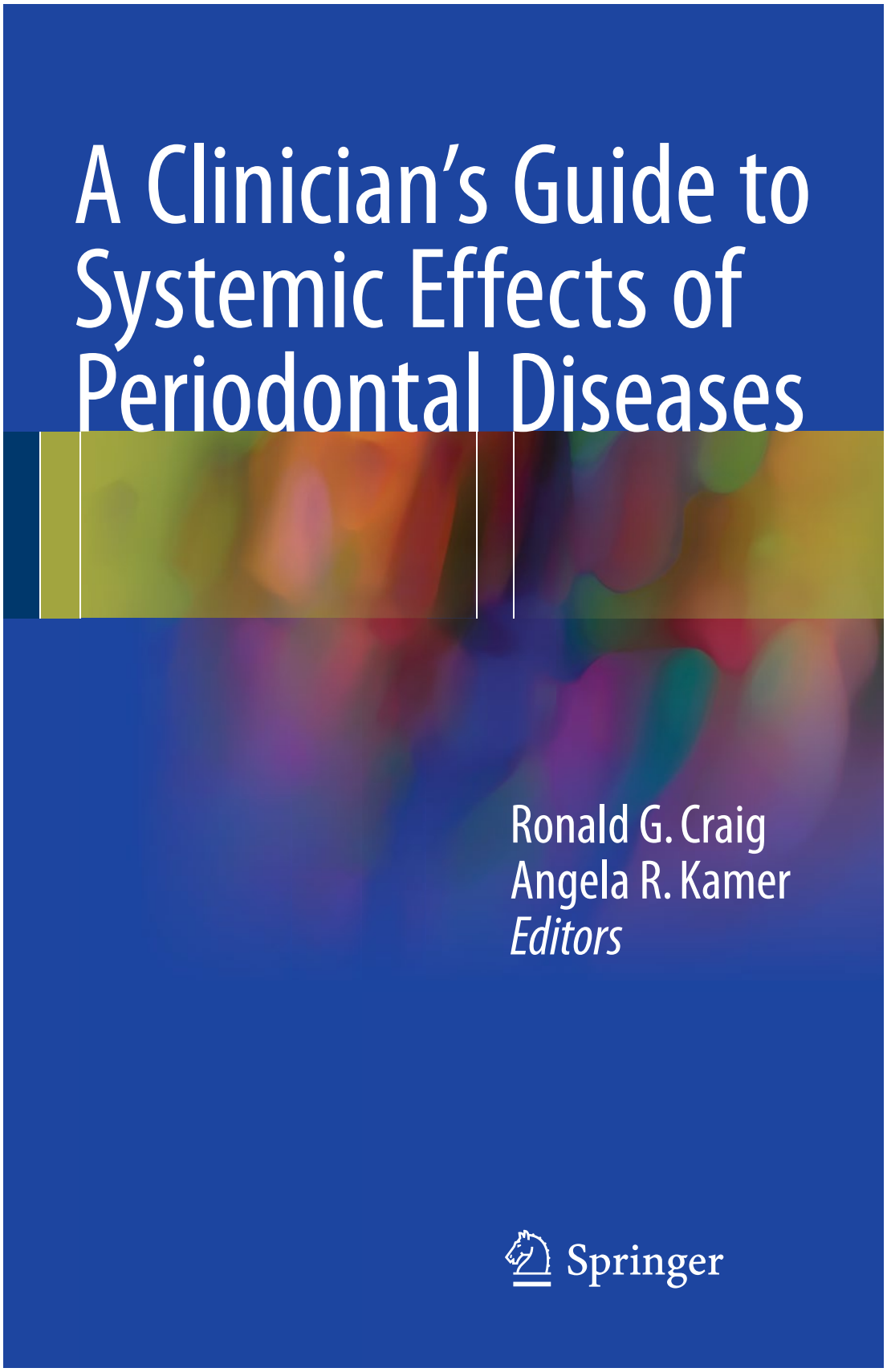
## NEW CLASSIFICATION OF PERIODONTAL AND PERI-IMPLANT DISEASES

Guest editors:
Mariano Sanz y Panos N. Papapanou

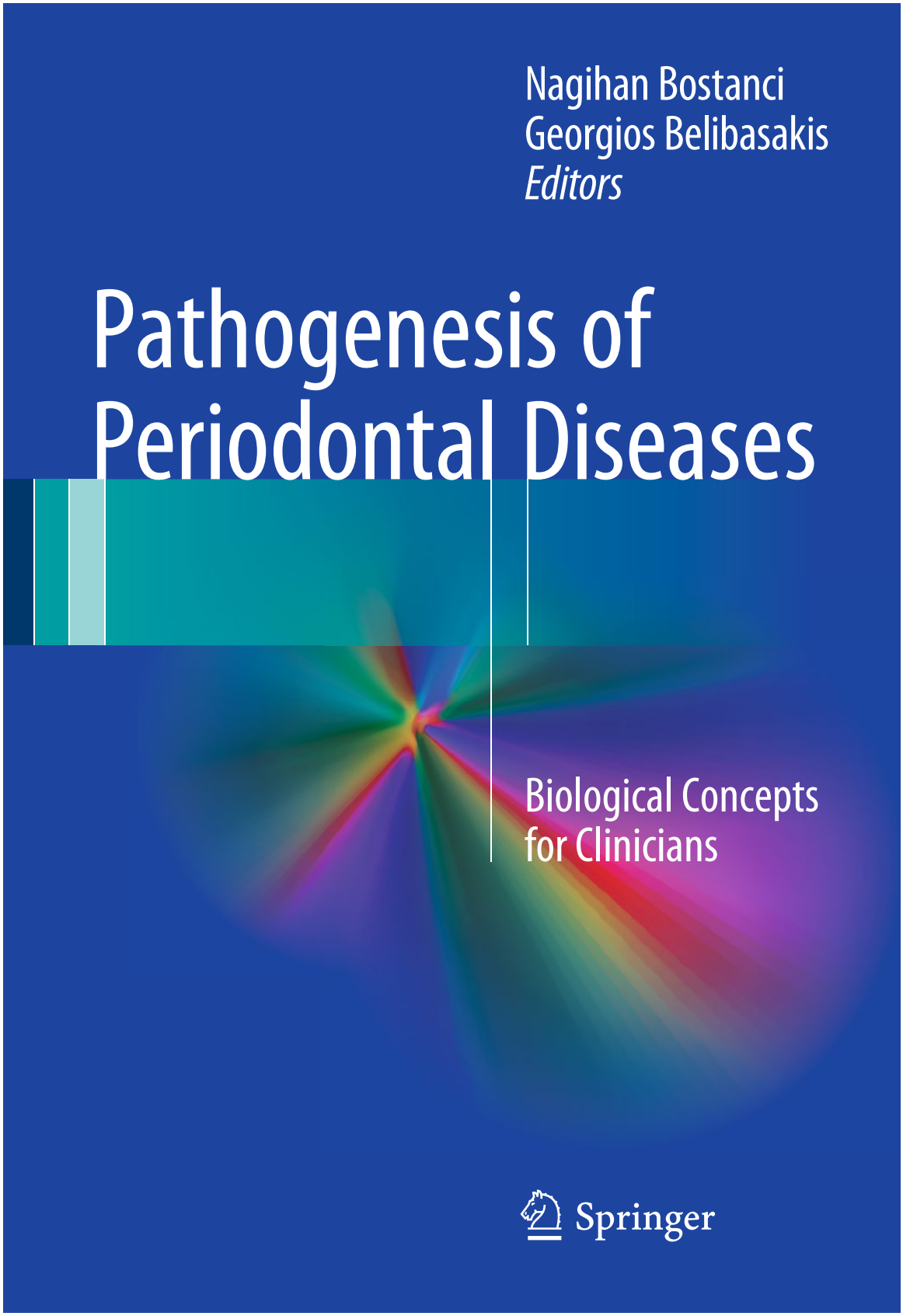
new classification of periodontal and peri-implant diseases

SEPA
SOCIEDAD ESPAÑOLA
DE PERIODONCIA
Y OSTEOINTEGRACIÓN

**Source number 2**



**Source number 3**



**Source number 5**



Published in final edited form as:
*Odontology*. 2006 September ; 94(1): 10–21.

# Periodontal disease and systemic conditions: a bidirectional relationship

**Jemin Kim** and
*Boston University Goldman School of Dental Medicine, Department of Periodontology and Oral Biology, Boston, MA, USA*

**Salomon Amar**
*Boston University Medical Center, 700 Albany Street, W201E, Boston, MA 02118, USA Tel. +1−617−638−4983; Fax +1−617−638−8549 e-mail: samar@bu.edu*

## Abstract

For decades, physicians and dentists have paid close attention to their own respective fields, specializing in medicine pertaining to the body and the oral cavity, respectively. However, recent findings have strongly suggested that oral health may be indicative of systemic health. Currently, this gap between allopathic medicine and dental medicine is quickly closing, due to significant findings supporting the association between periodontal disease and systemic conditions such as cardiovascular disease, type 2 diabetes mellitus, adverse pregnancy outcomes, and osteoporosis. Significant effort has brought numerous advances in revealing the etiological and pathological links between this chronic inflammatory dental disease and these other conditions. Therefore, there is reason to hope that the strong evidence from these studies may guide researchers towards greatly improved treatment of periodontal infection that would also ameliorate these systemic illnesses. Hence, researchers must continue not only to uncover more information about the correlations between periodontal and systemic diseases but also to focus on positive associations that may result from treating periodontal disease as a means of ameliorating systemic diseases.

### Keywords

Periodontal diseases; Systemic diseases; Cardiovascular diseases; Diabetes; Adverse pregnancy outcomes; Osteoporosis

## Etiology and pathogenesis of periodontal disease

Periodontal disease refers to the inflammatory processes that occur in the tissues surrounding the teeth in response to bacterial accumulations, or dental plaque, on the teeth. The bacterial accumulations cause an inflammatory response from the body. The chronic and progressive bacterial infection of the gums leads to alveolar bone destruction and loss of tissue attachment to the teeth. Periodontal disease has many states or stages, ranging from easily treatable gingivitis to irreversible severe periodontitis. Periodontal disease is increased by several risk factors: cigarette smoking; systemic diseases; medications such as steroids, anti-epilepsy drugs and cancer therapy drugs; ill-fitting bridges; crooked teeth and loose fillings; pregnancy; and oral contraceptive use. In addition to these variables, any medical condition that triggers host

Correspondence to: Salomon Amar.

**Source number 6**

J Periodontol • July 2009

# Editors' Consensus Report

## *The American Journal of Cardiology* and *Journal of Periodontology* Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease♦

**Vincent E. Friedewald,* Kenneth S. Kornman,† James D. Beck,‡ Robert Genco,§ Allison Goldfine,‖ Peter Libby,¶ Steven Offenbacher,# Paul M. Ridker,** Thomas E. Van Dyke,†† and William C. Roberts‡‡**

***Acknowledgment:*** *This Editors' Consensus is supported by an educational grant from Colgate-Palmolive, Inc., New York, New York, and is based on a meeting of the authors held in Boston, Massachusetts, on January 9, 2009.*

***Disclosure:*** *Dr. Friedewald has received honoraria for speaking from Novartis, East Hanover, New Jersey. Dr. Kornman is a full-time employee and shareholder of Interleukin Genetics, Waltham, Massachusetts, which owns patents on genetic biomarkers for chronic inflammatory diseases. Dr. Genco is a consultant to Merck, Whitehouse Station, New Jersey. Dr. Ridker has received research support from AstraZeneca, Wilmington, Delaware; Novartis; Pfizer, New York, New York; Roche, Nutley, New Jersey; Sanofi-Aventis, Bridgewater, New Jersey; and Abbott Laboratories, Abbott Park, Illinois. Dr. Ridker has received non-financial research support from Amgen, Thousand Oaks, California. Dr. Ridker is a co-inventor on patents held by Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. Dr. Ridker is a research consultant for Schering-Plough, Kenilworth, New Jersey; Sanofi-Aventis; AstraZeneca; Isis, Carlsbad, California; Novartis; and Vascular Biogenics, Tel Aviv, Israel. Dr. Van Dyke is a co-inventor on patents held by Boston University, Boston, Massachusetts, that relate to inflammation control, including consulting fees. Dr. Roberts has received honoraria for speaking from Merck, Schering-Plough, AstraZeneca, and Novartis. All other individuals in a position to control content disclosed no relevant financial relationships.* J Periodontol 2009;80:1021-1032.

The organization of the health professions into specialties and subspecialties according to body organs and systems is often more pragmatic than scientific. The human organism is a single unit composed of a seemingly infinite number of biologic processes so intertwined that abnormalities of almost any of its parts or processes have profound effects on multiple other body areas, exemplified in this document by the common and complex theme of *inflammation*. In recent years, the immune system, once believed to be only a vital defense against infection and a promoter of healing—except in the instances of a few uncommon connective tissue disorders—is now recognized as a significant active participant in many chronic diseases, including hypertension, diabetes mellitus, arthritis, inflammatory bowel disease, psoriasis, and the two diseases addressed in this Editors' Consensus: atherosclerotic cardiovascular disease (CVD) and periodontitis.

This aim of this document is to provide health professionals, especially cardiologists and periodontists, a better understanding of the link between atherosclerotic CVD and periodontitis and, on the basis of current information, an approach to reducing the risk

* Associate Editor, *The American Journal of Cardiology;* Research Professor, University of Notre Dame, Notre Dame, IN; and Clinical Professor, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston, TX.
† Editor-in-Chief, *Journal of Periodontology,* and Chief Scientific Officer, Interleukin Genetics, Waltham, MA.
‡ Distinguished Professor and Associate Dean for Research, University of North Carolina School of Dentistry, Chapel Hill, NC.
§ Distinguished Professor, Departments of Oral Biology and Microbiology, University at Buffalo, State University of New York, Amherst, NY.
‖ Associate Professor, Harvard Medical School, and Section Head of Clinical Research, Joslin Diabetes Center, Boston, MA.
¶ Chief, Cardiovascular Medicine, Brigham and Women's Hospital, and Malinckrodt Professor of Medicine, Harvard Medical School, Boston, MA.
# Distinguished Professor of Periodontology and Dental Research, University of North Carolina School of Dentistry, Chapel Hill, NC.
** Eugene Braunwald Professor of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA.
†† Professor and Program Director, Postdoctoral Periodontology, and Director, Clinical Research Center, Boston University, Goldman School of Dental Medicine, Boston, MA.
‡‡ Editor-in-Chief, *The American Journal of Cardiology* and *Baylor University Medical Center Proceedings*; Executive Director, Baylor Heart and Vascular Institute, Baylor University Medical Center; and Dean, A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, TX.

♦ **Published simultaneously in *The American Journal of Cardiology.*** doi: 10.1902/jop.2009.097001

Source number 7

IJHS

Review Article

# Prevalence of periodontal disease, its association with systemic diseases and prevention

**Muhammad Ashraf Nazir**

Department of Preventive Dental Sciences, University of Dammam College of Dentistry, Dammam, Kingdom of Saudi Arabia

**Address for correspondence:**
Muhammad Ashraf Nazir,
Department of Preventive Dental Sciences, University of Dammam College of Dentistry, Dammam, Kingdom of Saudi Arabia.
E-mail: manazir@uod.edu.sa

**WEBSITE:** ijhs.org.sa
**ISSN:** 1658-3639
**PUBLISHER:** Qassim University

## ABSTRACT

Periodontal diseases are prevalent both in developed and developing countries and affect about 20-50% of global population. High prevalence of periodontal disease in adolescents, adults, and older individuals makes it a public health concern. Several risk factors such as smoking, poor oral hygiene, diabetes, medication, age, hereditary, and stress are related to periodontal diseases. Robust evidence shows the association of periodontal diseases with systemic diseases such as cardiovascular disease, diabetes, and adverse pregnancy outcomes. Periodontal disease is likely to cause 19% increase in the risk of cardiovascular disease, and this increase in relative risk reaches to 44% among individuals aged 65 years and over. Type 2 diabetic individuals with severe form of periodontal disease have 3.2 times greater mortality risk compared with individuals with no or mild periodontitis. Periodontal therapy has been shown to improve glycemic control in type 2 diabetic subjects. Periodontitis is related to maternal infection, preterm birth, low birth weight, and preeclampsia. Oral disease prevention strategies should be incorporated in chronic systemic disease preventive initiatives to curtail the burden of disease in populations. The reduction in the incidence and prevalence of periodontal disease can reduce its associated systemic diseases and can also minimize their financial impact on the health-care systems. It is hoped that medical, dental practitioners, and other health-care professionals will get familiar with perio-systemic link and risk factors, and need to refer to the specialized dental or periodontal care.

**Keywords:** Periodontal disease, epidemiology, risk factors, systemic disease, preventive strategy

## Introduction

Periodontal disease is a chronic inflammatory disease of periodontium and its advanced form is characterized by periodontal ligament loss and destruction of surrounding alveolar bone.[1] It is the main cause of tooth loss and is considered one of the two biggest threats to the oral health.[1,2] There are approximately 800 species of bacteria identified in the oral cavity[3] and it is hypothesized that complex interaction of bacterial infection and host response, modified by behavioral factors such as smoking, can result in periodontal disease.[4]

The aim of the review is two-fold: (1) To evaluate the prevalence of periodontal disease in different populations, risk factors, and its association with systemic diseases and (2) to discuss the strategies and measures to prevent and control periodontal disease.

## Prevalence of Periodontal Disease

Periodontal disease is the most common oral condition of human population.[5] The prevalence and incidence statistics of periodontal diseases vary because of bias, case misclassification, and the number of teeth and the sites examined.[6] According to the Canadian Health Measures Survey 2007-2009, the measurement of loss of periodontal ligament attachment is considered the gold standard in reporting the prevalence of periodontal disease.[7] National Health and Nutrition Examination Survey (NHANES) determined the attachment loss (AL) and probing depth (PD) at six sites of all teeth (excluding third molars) for the estimation of periodontal disease in the U.S.[8]

The world Health Organization (WHO) has maintained global oral health data bank using community periodontal index (CPI).[9] This global oral health data from large epidemiological studies from different countries were gathered to show the distribution of periodontal disease in adolescents, adults and elderly populations (Figures 1-3).[9] CPI index score ranges from 0 to 4 and describes the periodontal condition of individuals at population level. CPI score 0 represents no periodontal disease; score 1 means gingival bleeding on probing; score 2 shows the presence of calculus and bleeding; score 3 indicates shallow periodontal pockets of

**Source number 8**

European Heart Journal Supplements (2010) **12** (Supplement B), B3–B12
doi:10.1093/eurheartj/suq003

# European workshop in periodontal health and cardiovascular disease—scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature

**Mariano Sanz[1]*, Francesco D'Aiuto[2], John Deanfield[3], and Francisco Fernandez-Avilés[4]**

[1]*Department of Periodontology, Faculty of Odontology, University Complutense of Madrid, Plaza Ramon y Cajal, Madrid 28040, Spain*
[2]*Periodontology Unit, University College London Eastman Dental Institute, London, UK*
[3]*Cardiothoracic Unit, University College London, Great Ormond Street Hospital, London, UK*
[4]*Department of Cardiology, Hospital Gregorio Marañón, University Complutense de Madrid, Madrid, Spain*

**KEYWORDS**
Periodontal diseases;
Cardiovascular disease;
Oral health;
Systemic inflammation;
Cardiovascular events;
Periodontal pathogens

In the last 10 years, a rising number of epidemiological investigations have studied the possible association between chronic oral infections and cardiovascular diseases (CVD). These studies were based on the hypothesis that periodontal diseases (PD), may confer an independent risk for CVD. There is, however, still controversy whether these associations are causal or whether there are common aetiological factors common to both diseases (residual confounding). The objective of this paper was to review the possible association between PD and CVD on both the epidemiological association and the possible preventive and treatment implications.

Although the reported epidemiological studies have shown a significant, albeit week associations, we still lack properly designed clinical trials demonstrating that these chronic infections are independent factors of cardiovascular risk. The use of surrogate variables assessing the infective load and measures of subclinical atherosclerosis have clearly shown, not only a significant pathogenic relationship, but also a significant impact after periodontal therapy.

From a public health perspective, if further studies consistently identify PD as a risk factor for CHD and treatment studies show benefit, the implications are significant, since PD is mostly avoidable and treatable when not prevented. In addition, good preventive dental care has multiple other benefits, particularly on quality of life. Furthermore, identifying individuals at higher risk for CHD than predicted by traditional risk factors could facilitate treatment of risk factors known to decrease CHD events in high-risk individuals and this might be significant given the high prevalence of PD in the population and the common problem of CHD.

* Corresponding author. E-mail: marianosanz@odon.ucm.es

**Source number 9**

International Journal of
*Environmental Research and Public Health*

MDPI

*Review*

# The Role of Matrix Metalloproteinases in Periodontal Disease

**Vittorio Checchi [1,*], Tatjana Maravic [2], Pierantonio Bellini [1], Luigi Generali [1], Ugo Consolo [1], Lorenzo Breschi [2] and Annalisa Mazzoni [2]**

[1] Unit of Dentistry and Oral-Maxillo-Facial Surgery, Department of Surgery, Medicine, Dentistry and Morphological Sciences with Transplant Surgery, Oncology and Regenerative Medicine Relevance, University of Modena and Reggio Emilia, 41125 Modena, Italy; pierantonio.bellini@unimore.it (P.B.); luigi.generali@unimore.it (L.G.); ugo.consolo@unimore.it (U.C.)
[2] DIBINEM, University of Bologna, 40100 Bologna, Italy; tatjana.maravic2@unibo.it (T.M.); lorenzo.breschi@unibo.it (L.B.); annalisa.mazzoni@unibo.it (A.M.)
* Correspondence: vittorio.checchi@unimore.it; Tel.: +39-059-422-4314

Received: 26 April 2020; Accepted: 6 July 2020; Published: 8 July 2020

check for updates

**Abstract:** This review provides a detailed description of matrix metalloproteinases (MMPs), focusing on those that are known to have critical roles in bone and periodontal disease. Periodontal disease is an inflammatory process initiated by anaerobic bacteria, which promote the host immune response in the form of a complex network of molecular pathways involving proinflammatory mediators such as cytokines, growth factors, and MMPs. MMPs are a family of 23 endopeptidases, collectively capable of degrading virtually all extracellular matrix (ECM) components. This study critically discusses the available research concerning the involvement of the MMPs in periodontal disease development and progression and presents possible therapeutic strategies. MMPs participate in morphogenesis, physiological tissue turnover, and pathological tissue destruction. Alterations in the regulation of MMP activity are implicated in the manifestation of oral diseases, and MMPs comprise the most important pathway in tissue destruction associated with periodontal disease. MMPs can be considered a risk factor for periodontal disease, and measurements of MMP levels may be useful markers for early detection of periodontitis and as a tool to assess prognostic follow-ups. Detection and inhibition of MMPs could, therefore, be useful in periodontal disease prevention or be an essential part of periodontal disease therapy, which, considering the huge incidence of the disease, may greatly improve oral health globally.

**Keywords:** matrix metalloproteinases; MMP; collagenases; periodontal disease

## 1. Introduction

Periodontitis is an inflammatory disorder that causes tissue and bone loss as a consequence of various interactions between the host immune response and pathogenic bacteria [1]. This inflammatory process is originated by plaque biofilm that causes the loss of periodontal attachment, resulting, in the most severe cases, in tooth loss [2–4]. Though anaerobic bacteria are considered the starting agents, the disease progression is induced by the host response, which can be influenced by environmental and behavioral factors [5]. The disease development involves various interacting molecular pathways made of proinflammatory mediators such as growth factors, cytokines, matrix metalloproteinases (MMPs), and their inhibitors and regulators [6].

Several pieces of evidence suggest that MMPs comprise the most important pathway in tissue destruction associated with periodontal disease due to their role in the pathological breakdown of extracellular matrix (ECM) within periodontal tissues. The MMPs and their tissue inhibitors (TIMPs)

# Source number 11



## Mouth: A portal to the body

Dilip Gude, Rekha Rani Koduganti, [...], and Lakshmi Radhika Pothini

### Abstract

Periodontal disease is now increasingly believed to play a significant part in various systemic conditions. Likewise these systemic diseases and their severity have been found to have an impact on the morbidity of periodontal disease. A number of mechanisms specific to such interlink have been proposed and later established in numerous studies. The disorders with such bidirectional link with periodontal disease include cardiovascular, respiratory, neurological, and connective tissue diseases. The periodontal – systemic interlink has a vibrant effect on the management aspects and is of paramount topical interest to clinicians. We review the pertaining literature (Google scholar and pubmed).

**Keywords:** Inter-link, periodontal disease, systemic

### INTRODUCTION

Periodontal disease and the systemic interlink, although well researched in the scientific community, is not niversally cognizant among clinicians. There is a dire need to bring the awareness about the inter-relationship as it has far-reaching effects on management aspects. Periodontitis as a manifestation of systemic diseases is one of the seven categories of periodontitis as defined by the American Academy of Periodontology (1999) classification system.[1] The association of periodontitis between various systemic diseases is explained by decreased host resistance to infections or dysfunction in the connective tissue of the gums and/or increasing patient susceptibility to inflammation-induced destruction. A literature review (Google scholar and pubmed) of evidence-based associations between periodontal disease and various systemic disorders is presented.

### PERIODONTAL DISEASE AND DIABETES

There is abundant evidence that diabetes increases the risk of periodontal disease and likewise the latter has shown to increase insulin resistance thereby perturbing glycemic control.

In diabetes, impaired neutrophil function may undermine the eradication of bacteria in the periodontal pocket, leading to periodontal inflammation and destruction. The key factors behind such impairment such as monocyte upregulation and stimulation of NF-κB may be secondary to AGE (advanced glycation end products) and R (receptor)-AGE reciprocity.[2] In a study, it was shown that the oxidative stress in periodontitis compounds the release of proinflammatory cytokines such as interleukin-1beta (IL-1β), and IL-6 and tumor necrosis factor-alpha (TNF-α).[3] The degree of glycemic control has also shown to correlate with the severity of epriodonitis. Periodontitis-affected diabetes patients having HbA1c levels more than 8% demonstrate twice the normal levels of IL-1ß in gingival crevicular fluid.[4]

Known to have a bidirectional relationship, periodontitis predisposes to increased levels of inflammatory markers such as matrix metalloproteinases (MMP), TNF-α, IL-1β, IL-6 and prostaglandin $E_2$ in diabetes.[5] The effect of adequate periodontal therapy on glycemic control was studied and it was concluded that the therapy correlated with definite improvement in mean HbA1c values (from 8% to 7.1%), in levels of TNF-α and fasting insulin.[6] Likewise those with HbA1C levels greater than 9% sported severe periodontitis with higher probing pocket depths and more sites with loss of attachment than those with lesser HbA1c levels.[7]

Insulin resistance is believed to be perpetuated by fibrinogen, C-reactive protein, and plasminogen activator inhibitor-1.[8] Diabetics also manifest perturbed pH of saliva and its buffering capacity, levels, and activity of peroxidase, increased incidence of dry mouth, need for the prevention of caries and prosthetic corrections.[9,10]

### PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

Periodontal disease is an established risk factor conferring about 24-35% increase in the risk of coronary heart disease (CHD).[11]

# Source number 12



## Periodontitis and systemic diseases: A literature review

Abiodun O. Arigbede, B. Osagbemiro Babatope, and M. Kolude Bamidele

### Abstract

Studies have revealed possible link between periodontitis and different systemic diseases. There is need to review this interesting subject. The aims are: to provide a comprehensive literature that can easily be consulted, on the subject; to draw the attention of health practitioners to the impact of oral health on the general well-being; and to emphasize the need for a deeper interaction between medical and dental training. The Medline database was searched for relevant literature by combining each of the following terms, "oral health," "oral infection," "periodontitis," with "systemic diseases." Manual library search and review of bibliographies of published literature were also conducted. Periodontitis is a constant potential source of infection and has been considered as a separate risk factor for some cardiovascular, respiratory, endocrine, musculoskeletal, and reproductive system related abnormalities. Oral health impacts on the general well-being, and if comprehensive health care is ever to be achieved, oral health should not be seen as a separate, distant, and less important area of health, which is totally unrelated to lifespan and its quality.

**Keywords:** Oral health, periodontitis, systemic diseases

### INTRODUCTION

Not too long ago, literature evidence began to suggest a possible link between chronic inflammatory periodontitis and a number of systemic diseases.[1–4] A chronic oral infection such as periodontitis is a constant potential source of infection and has been considered as a separate risk factor for cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease, respiratory diseases, and low birth weight.[5] In addition, periodontitis has been described as a potential risk for increased morbidity and mortality for diabetes, insulin resistance, rheumatoid arthritis, obesity, osteoporosis, and complications of pregnancy.[2,3] In fact, a case of pyogenic liver abscess caused by periodontal bacteria had been reported.[5]

Some of these conditions may in turn increase the incidence and severity of periodontal disease by modifying the body's immune response to periodontal bacteria and their by-products.[6] Evidence suggests a bi-directional relationship between periodontitis and systemic diseases.[6] The possible mechanisms or pathways linking oral infections to secondary systemic effect are: metastatic spread of infection from the oral cavity as a result of transient bacteremia, metastatic injury from the effects of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral micro-organisms.[4,6,7]

There is tendency for medical and dental specialists to see patient management from regional rather than systemic point of view. In the light of the ever increasing available facts on the role of oral infections like periodontitis on multifarious systemic disorders, it has become necessary to undertake a literature review on the subject. The aims are: to provide a comprehensive literature that can easily be consulted, on the subject; draw the attention of health practitioners to the impact of oral health care on the general well-being; and to emphasize the need for a deeper interaction between medical and dental trainings.

### CHRONIC PERIODONTITIS

Chronic periodontitis, also known as adult periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tissues that support the teeth, i.e. the gingival, the periodontal ligament, cementum, and the alveolar bone.[8,9] Periodontal disease is characterized by periods of exacerbation interspersed with periods of remission and presents a local microbial burden that initiates local inflammation and local tissue destruction.[10]

#### Etiopathology

Periodontitis is an infective condition attributable to certain pathogens, namely, Aggregatibacter actinomycetecomitans, Porphyromonas gingivalis, Bacteroides forsythus, Prevotella intermedia, Campylobacter rectus, Treponema denticola, Fusobacterium nucleatum and so on. Crevicular fluid often contains inflammatory mediators and the oral pathogens associated with periodontitis. The mechanism

**Source number 13**

Mathews *et al. BMC Oral Health* (2016) 16:122
DOI 10.1186/s12903-016-0316-7

BMC Oral Health

RESEARCH ARTICLE Open Access

# Oral health and coronary heart disease

Marc J. Mathews, Edward H. Mathews and George E. Mathews*

**Abstract**

**Background:** It is well documented that there is some correlation between poor oral health in the form of periodontal disease and coronary heart disease (CHD). It is unclear whether this correlation is due to a causal relationship or shared underlying disorder such as inflammation. A suitable integrated model of the CHD pathogenetic pathways relevant to periodontal disease may help to elucidate the association. Such a model is currently not available in literature.

**Methods:** A previously developed integrated model of CHD was used to investigate potential pathogenetic pathways linking periodontal disease to CHD biomarkers.

**Results:** The integrated model was created to provide insight into possible higher-order biological interactions underlying CHD and periodontal disease. In order to simplify these interactions a novel 'connection graph' was developed. It quantitatively illustrates the relationship between periodontal disease and various serological biomarkers of CHD. The pathogenesis of periodontitis shows various possible pathways which could link periodontitis to CHD pathogenesis.

**Conclusion:** An integrated model of CHD was developed which provides a summary of the potential CHD effects of periodontal disease. Further research must refine and validate the model.

**Key words:** Coronary heart disease, Periodontal disease, Biomarkers, Integrated model

## Background

The largest cause of death globally is Coronary heart disease (CHD) [1]. It is also well documented that poor oral health in the form of periodontal disease is associated with an increased risk for CHD [2–6]. Whether this prevalence is directly linked to a causal effect of periodontitis or the effect of a shared underlying disorder such as inflammation has not been determined [7]. It is however clear that although there is a correlation between periodontal disease and CHD, the extent of this correlation and the usefulness thereof are not yet evident [2–7].

It may thus prove beneficial to quantify and elucidate the underlying pathogenetic effect of periodontal disease on the pathogenesis of CHD. Using a previously described integrated model of CHD [8] we therefore investigated the possible interconnectivity of periodontal disease and the pathogenesis and pathophysiological traits attributed to CHD.

The existing model graphically describes all the hypothetical pathogenetic pathways of CHD [8]. Some of these pathways can then be measured by serum biomarkers to give an indication of the degree of risk such a pathway represents. The model was used in this study to holistically review the interconnections between oral health pathogenesis and the pathogenesis of CHD. The theory is that where these conditions overlap there is the possibility for causal interaction which should be investigated in detail.

The vision behind the model is that it could be validated over time by calibrating it on a patient specific basis. Patients can be compared with themselves over time. Once the sample size of patient specific calibrated models is large enough the model could give new insight on the underlying workings of CHD. However, in the absence of existing studies of our model, using patient specific data, this paper attempts to gain some knowledge by looking at population based data. The data are in terms of risk ratios, the incidence of health factors and typical pathogenesis of CHD. Some interesting insights are revealed about possible interconnections of pathogenesis underlying both CHD and periodontal disease.

* Correspondence: 20270046@nwu.ac.za
CRCED, North-West University, P.O. Box 11207, Silver Lakes 0054, South Africa

**Source number 14**

Journal of Clinical Periodontology

Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

*J Clin Periodontol 2008; 35 (Suppl. 8): 362–379 doi: 10.1111/j.1600-051X.2008.01281.x*

Journal of Clinical Periodontology

# Cardiovascular disease and periodontitis: an update on the associations and risk

**Gösta Rutger Persson[1,2,3] and Rigmor Elisabeth Persson[1,3]**

[1]Department of Periodontology, University of Bern, Bern, Switzerland; [2]Department of Periodontology, University of Washington, Seattle, WA, USA; [3]Department of Oral Medicine, University of Washington, Seattle, WA, USA

*Persson GR, Persson RE. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol 2008; 35 (Suppl. 8): 362–379. doi: 10.1111/j.1600-051X.2008.01281.x.*

***Abstract***

**Background:** Associations between periodontitis and cardiovascular diseases have been recognized.

**Material and Methods:** New literature since the last European Workshop on Periodontology has been reviewed.

**Results:** The lack of reliable epidemiological data on disease prevalence makes an assessment of the associations and risks between periodontitis and cardiovascular diseases difficult. Two recent meta-analysis reports have identified associations between periodontitis and cardiovascular diseases (odds ratios: 1.1–2.2). Different surrogate markers for both disease entities, including serum biomarkers, have been investigated. Brachial artery flow-mediated dilatation, and carotid intima media thickness have in some studies been linked to periodontitis. Studies are needed to confirm early results of improvements of such surrogate markers following periodontal therapy. While intensive periodontal therapy may enhance inflammatory responses and impair vascular functions, studies are needed to assess the outcome of periodontal therapies in subjects with confirmed cardiovascular conditions. Tooth eradication may also reduce the systemic inflammatory burden of individuals with severe periodontitis. The role of confounders remain unclear.

**Conclusions:** Periodontitis may contribute to cardiovascular disease and stroke in susceptible subjects. Properly powered longitudinal case–control and intervention trials are needed to identify how periodontitis and periodontal interventions may have an impact on cardiovascular diseases.

Key words: acute coronary syndrome; atherosclerosis; infection; inflammation; periodontitis; review; stroke; therapy

Accepted for publication 20 May 2008

Cardiovascular diseases comprise a variety of heart and vascular conditions including: ischaemia, atherosclerosis, peripheral artery disease, infective endocarditis, and acute myocardial infarction (Karchmer 1997). Cardiovascular diseases are common in many adult populations (Rosamond et al. 2007). Over the last 30 years, the greater life expectancy and changes in diet and exercise habits have resulted in a higher prevalence of obesity, elevated levels of blood cholesterol, hypertension, and diabetes mellitus which are all recognized cardiovascular risk factors. Smoking is another risk factor in cardiovascular disease contributing to the increasing incidence and mortality of cardiovascular diseases (Kuller 2006).

Atherosclerosis, and myocardial infarctions occur as a product of complex combinations of factors (Ross 1997). Myocardial infarctions, stroke, and thromboembolic events result from atherosclerosis and often in combination with a superimposed coronary thrombosis. Development of atherosclerosis begins already in the first or second decade of life, and with clinical manifestations many years later.

A large number of surrogate endpoints of future cardiovascular diseases has been identified. This includes assessments of carotid intima media thickness (IMT), flow-mediated dilatation of the brachial artery, serum biomarkers including high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol fibrinogen, triglyceride, high sensitivity CRP, HbA1c, and systolic/diastolic blood pres-

**Conflict of interest and source of funding statement**

The Clinical Research Foundation for the Promotion of Oral Health (CRF) University of Berne, Switzerland has supported the review. The authors declare no conflict of interests.

The 6th European Workshop on Periodontology was supported by an unrestricted educational grant from Straumann AG.

**Source number 19**

THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

# Poor oral health in patients with coronary heart disease: a case–control study of Indian adults

Mona Sikka, Peter S Sequeira, Shashidhar Acharya, Meghashyam Bhat, Ashwini Rao, Anup Nagaraj

**Abstract**

**Aim** The present study was conducted to quantitate the oral health of coronary heart disease patients and compare them with controls for a valid inference

**Method** A total of 100 medically diagnosed coronary heart disease patients were compared with 100 controls using the World Health Organization (WHO) oral health assessment form. Statistical analysis was done using SPSS (version 10) software.

**Results** Statistically higher mean sextant value for shallow pockets 4–5 mm, CPI (Community Periodontal Index) score 3 and LOA (Loss of attachment) score 1,2 was found for cases as compared to controls ($p \leq 0.05$). Similarly, higher mean DMFT (Decayed-Missing-Filled Teeth) and missing teeth were observed for cases as compared to controls ($p > 0.05$).

**Conclusion** The present study shows a slight increase in the level of mild periodontal disease in coronary heart disease patients as compared to controls, with a non-significant difference in dental caries.

Coronary heart disease is a multifactorial disease claiming, 7.2 million deaths every year.[1] Main factors identified in its pathogenesis are sedentary lifestyle, cigarette smoking, hypertension, high low density lipoprotein (LDL) cholesterol, low high density lipoprotein (HDL) cholesterol, diabetes mellitus, obesity and family history of premature coronary heart disease.[2]

The current evidence (case-control studies[3–15] and longitudinal studies[16–19]) has implicated chronic dental infections (severe periodontal disease) also in its pathogenesis.

The main mechanism postulated is:[20]

- A common genetic predisposition as a result of which the periodontal microflora provides excess lipopolysaccharides and host response inflammatory cytokines, which promotes atherogenesis and thromboembolic events.
- Indirect or host-mediated factors like elevated levels of acute phase proteins such as C-reactive protein and fibrinogen in systemic circulation which are risk factors for coronary heart disease.
- Direct effects of infectious agents like *Porphyromonas gingivalis*, which has been found in carotid and coronary atheromas, and has been shown to induce platelet aggregation and thrombus formation.

# Periodontal Disease and Coronary Heart Disease Incidence: A Systematic Review and Meta-analysis

*Linda L. Humphrey, MD, MPH[1,2,3,4,7,8], Rongwei Fu, PhD[1,4,5], David I. Buckley, MD, MPH[1,2,6], Michele Freeman, MPH[1], and Mark Helfand, MD, MPH[1,2,3,7]*

[1]Oregon Evidence-based Practice Center, Veterans Affairs Medical Center, Portland, OR, USA; [2]Department of Medical Informatics and Clinical Epidemiology, Veterans Affairs Medical Center, Portland, OR, USA; [3]Department of Medicine, Veterans Affairs Medical Center, Portland, OR, USA; [4]Public Health and Preventive Medicine, Veterans Affairs Medical Center, Portland, OR, USA; [5]Emergency Medicine, Veterans Affairs Medical Center, Portland, OR, USA; [6]Family Medicine, Veterans Affairs Medical Center, Portland, OR, USA; [7]Oregon Health & Science University, Hospital and Specialty Medicine, Veterans Affairs Medical Center, Portland, OR, USA; [8]Oregon Health & Science University, Portland, OR, USA.

***BACKGROUND:*** Periodontal disease is common among adults in the US and is a potential source of chronic inflammation. Recent data have suggested an important role for chronic inflammation in the development of coronary heart disease (CHD).

***OBJECTIVE:*** To aid the United States Preventive Services Task Force (USPSTF) in evaluating whether periodontal disease is an independent novel risk factor for incident CHD.

***METHODS:*** Studies were identified by searching Medline (1966 through March 2008) and reviewing prior systematic reviews, reference lists, and consulting experts. Prospective cohort studies that assessed periodontal disease, Framingham risk factors, and coronary heart disease incidence in the general adult population without known CHD were reviewed and quality rated using criteria developed by the USPSTF. Meta-analysis of good and fair quality studies was conducted to determine summary estimates of the risk of CHD events associated with various categories of periodontal disease.

***RESULTS:*** We identified seven articles of good or fair quality from seven cohorts. Several studies found periodontal disease to be independently associated with increased risk of CHD. Summary relative risk estimates for different categories of periodontal disease (including periodontitis, tooth loss, gingivitis, and bone loss) ranged from 1.24 (95% CI 1.01–1.51) to 1.34 (95% CI 1.10–1.63). Risk estimates were similar in subgroup analyses by gender, outcome, study quality, and method of periodontal disease assessment.

***CONCLUSION:*** Periodontal disease is a risk factor or marker for CHD that is independent of traditional CHD risk factors, including socioeconomic status. Further research in this important area of public health is warranted.

J Gen Intern Med 23(12):2079–86
DOI: 10.1007/s11606-008-0787-6


*Received January 16, 2008*
*Revised June 18, 2008*
*Accepted August 28, 2008*
*Published online September 20, 2008*

## BACKGROUND

Coronary heart disease (CHD) is the leading cause of death and morbidity in the US and many developed countries. In the year 2002 nearly 500,000 people died of CHD in the US, and millions of others live with prevalent CHD.[1] Worldwide, CHD kills more than 7 million people each year.[2] It is estimated that in the US in 2006, heart disease cost more than 258 billion dollars in health-related costs and lost productivity.[3] Many risk factors for CHD have been identified, but a significant proportion of CHD is not explained by traditional risk factors. Recently, several lines of evidence have implicated chronic inflammation etiologically in CHD and cardiovascular disease (CVD).[4]

Periodontal disease is a chronic gram-negative anaerobic infection of the tooth-supporting structures with an estimated prevalence of as high as 75% in adults in the US, among whom approximately 20–30% have severe forms of the disease.[5–7] Alveolar bone resorption is both a measure and a consequence of severe periodontal disease. Common signs of periodontal disease that are identified by dentists and may be noted by primary care providers include: tooth loss, gingivitis with gum inflammation and bleeding, excess tartar, infection, decay, tooth mobility, and gum recession with bone loss (Fig. 1). Periodontal disease is associated with elevations of several markers of chronic inflammation,[8–13] and because of evidence implicating chronic inflammation in the etiology of CHD, a etiologic relationship between periodontal disease and CHD has been hypothesized.[4] For these reasons, there has been strong interest in evaluating whether periodontal disease is independently associated with CHD.

In this systematic review and meta-analysis, we evaluate the epidemiologic literature evaluating the possible link between periodontal disease and associated measures of oral health, and CHD, to aid the USPSTF in their review and consideration of screening for non-traditional risk factors for CHD. Identifying individuals at higher risk for CHD than predicted by traditional risk factors could facilitate more aggressive treatment of risk factors known to decrease CHD in high-risk individuals, such as those with hyperlipidemia. Our meta-analysis differs from two prior meta-analyses[14,15] by focusing on population-based prospective studies, more recent literature, systematic evaluation of study quality and by conducting subgroup analyses to explore identified associations.

**Source number 21**

Journal of
PERIODONTAL RESEARCH

*J Periodont Res 2016; 51: 221–227*


JOURNAL OF PERIODONTAL RESEARCH
doi:10.1111/jre.12301

# Periodontal disease, tooth loss and coronary heart disease assessed by coronary angiography: a cross-sectional observational study

**S. M. Zanella[1], S. S. Pereira[2], J. N. Barbisan[3], L. Vieira[3], E. Saba-Chujfi[2], A. N. Haas[1], C. K. Rösing[1]**

[1]Periodontology, Faculty of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil, [2]Periodontology, Faculty of Dentistry, São Leopoldo Mandic University, Campinas, Brazil and [3]Institute of Cardiology of Porto Alegre, Porto Alegre, Brazil

*Zanella SM, Pereira SS, Barbisan JN, Vieira L, Saba-Chujfi E, Haas AN, Rösing CK. Periodontal disease, tooth loss and coronary heart disease assessed by coronary angiography: a cross-sectional observational study. J Periodont Res 2016; 51: 221–227. © 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd*

*Objective and Background:* To evaluate the association between periodontal disease, tooth loss and coronary heart disease (CHD). There is still controversy about the relationship between periodontal disease and tooth loss with vessel obstruction assessed using coronary angiography.

*Material and Methods:* This cross-sectional study included 195 patients that underwent coronary angiography and presented with at least six teeth. Patients were classified into three categories of coronary obstruction severity: absence; one or more vessels with ≤ 50% obstruction; and one or more vessels with ≥ 50% obstruction. The extent of coronary obstruction was dichotomized into 0 and ≥ 1 affected vessels. A periodontist blinded to patient CHD status conducted a full mouth examination to determine mean clinical attachment loss, mean periodontal probing depth and tooth loss. Multiple logistic regression models were applied adjusting for age, gender, hypertension, smoking, body mass index, low-density lipoprotein cholesterol and C-reactive protein.

*Results:* Most patients were males (62.1%) older than 60 years (50.8%), and 61% of them had CHD. Mean periodontal probing depth, clinical attachment loss and tooth loss were 2.64 ± 0.72 mm, 4.40 ± 1.31 mm and 12.50 ± 6.98 teeth respectively. In the multivariable models, tooth loss was significantly associated with a higher chance of having at least one obstructed vessel (odds ratio = 1.04; 95% confidence interval 1.01–1.09) and with vessel obstruction ≥ 50% (odds ratio = 1.06; 95% confidence interval 1.01–1.11). No significant associations were found between periodontal variables and vessel obstruction.

*Conclusion:* Tooth loss was found to be a risk indicator for CHD.

Cassiano K. Rösing, DDS, MS, PhD, Periodontology, Faculty of Dentistry, Federal University of Rio Grande do Sul, Ramiro Barcelos 2492, Porto Alegre 90035-003, Brazil
Tel/Fax: +55 51 33085318
e-mail: ckrosing@hotmail.com

Key words: coronary angiography; coronary disease; periodontal disease; tooth loss

Accepted for publication May 8, 2015

**Source number 22**

# A systems engineering approach to coronary heart disease

**MJ Mathews**
**25890484**

Thesis submitted for the degree *Doctor Philosophiae* in Mechanical Engineering at the Potchefstroom Campus of the North-West University

Promoter: Dr R Pelzer

November 2015

It all starts here ™

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

**Source number 23**

International Journal of
*Environmental Research and Public Health*

MDPI

*Article*

# Cross-Sectional Analysis of the Association between Periodontitis and Cardiovascular Disease Using the Korean Genome and Epidemiology Study Data

**Soo Hwan Byun [1,2], Sunki Lee [3], Sung Hun Kang [4], Hyo Geun Choi [2,5,6,*] and Seok Jin Hong [2,7,*]**

1 Department of Oral & Maxillofacial Surgery, Dentistry, Sacred Heart Hospital, Hallym University College of Medicine, Anyang 14068, Korea; purheit@daum.net
2 Research Center of Clinical Dentistry, Hallym University Clinical Dentistry Graduate School, Chuncheon 24252, Korea
3 Division of Cardiology, Department of Internal Medicine, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Dongtan 18450, Korea; galiard@hallym.or.kr
4 Department of Biomedical Sciences, College of Medicine, Hallym University, Chuncheon 24252, Korea; malice23@nate.com
5 Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang 14068, Korea
6 Department of Otorhinolaryngology-Head & Neck Surgery, Sacred Heart Hospital, Hallym University College of Medicine, Anyang 14068, Korea
7 Department of Otorhinolaryngology-Head & Neck Surgery, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Dongtan 18450, Korea
* Correspondence: pupen@naver.com (H.G.C.); enthsj@hanmail.net (S.J.H.)

Received: 18 June 2020; Accepted: 16 July 2020; Published: 20 July 2020

check for updates

**Abstract:** This cross-sectional study aimed to evaluate the association between periodontitis and cardiovascular disease (CVD) by reviewing and discussing the role of the oral microbiome in periodontitis and CVD. This prospective cohort study used epidemiological data from the Korean Genome and Epidemiology Study from 2004 to 2016. We selected 9973 patients with periodontitis and 125,304 controls (non-periodontitis) from 173,209 participants and analyzed their medical histories to determine the relationship between cerebral stroke/ischemic heart disease and periodontitis. The participants were questioned about any previous history of hypertension, diabetes mellitus, hyperlipidemia, cerebral stroke (hemorrhagic or ischemic), ischemic heart disease (angina or myocardial infarction), and periodontitis. Their body mass index, smoking habit, alcohol intake, nutritional intake, and income were recorded. The Chi-square test, independent *t*-test, and two-tailed analyses were used for statistical analysis. The adjusted OR (aOR) of periodontitis for stroke was 1.35 (95% confidence interval (CI) = 1.16–1.57, $p < 0.001$). The aOR of periodontitis for ischemic heart disease was 1.34 (95% CI = 1.22–1.48, $p < 0.001$). We concluded that periodontitis was associated with CVD and may be a risk factor for CVD. However, further studies are required to determine the association between periodontal treatment and CVD.

**Keywords:** periodontal diseases; risk factor; periodontitis; cardiovascular disease; stroke; ischemic heart disease; inflammation; oral health

# Source number 24

Clinica Chimica Acta 424 (2013) 245–252

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Invited critical review

# Foam cells in atherosclerosis

Xiao-Hua Yu [a], Yu-Chang Fu [c], Da-Wei Zhang [d], Kai Yin [b,*], Chao-Ke Tang [a,b,**]

[a] Life Science Research Center, University of South China, Hengyang, Hunan 421001, China
[b] Institute of Cardiovascular Research, Key Laboratory for Atherosclerology of Hunan Province, University of South China, Hengyang, Hunan 421001, China
[c] Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL 35294-0012, USA
[d] Department of Pediatrics and Group on the Molecular and Cell Biology of Lipids, University of Alberta, Edmonton, Alberta T6G 2S2, Canada

ARTICLE INFO

*Article history:*
Received 25 April 2013
Received in revised form 4 June 2013
Accepted 6 June 2013
Available online 16 June 2013

*Keywords:*
Foam cells
Atherosclerosis
CD36
ACAT1
ABCA1
ABCG1

ABSTRACT

Atherosclerosis is a chronic disease characterized by the deposition of excessive cholesterol in the arterial intima. Macrophage foam cells play a critical role in the occurrence and development of atherosclerosis. The generation of these cells is associated with imbalance of cholesterol influx, esterification and efflux. CD36 and scavenger receptor class A (SR-A) are mainly responsible for uptake of lipoprotein-derived cholesterol by macrophages. Acyl coenzyme A:cholesterol acyltransferase-1 (ACAT1) and neutral cholesteryl ester hydrolase (nCEH) regulate cholesterol esterification. ATP-binding cassette transporters A1(ABCA1), ABCG1 and scavenger receptor BI (SR-BI) play crucial roles in macrophage cholesterol export. When inflow and esterification of cholesterol increase and/or its outflow decrease, the macrophages are ultimately transformed into lipid-laden foam cells, the prototypical cells in the atherosclerotic plaque. The aim of this review is to describe what is known about the mechanisms of cholesterol uptake, esterification and release in macrophages. An increased understanding of the process of macrophage foam cell formation will help to develop novel therapeutic interventions for atherosclerosis.



**Contents**



*Abbreviations:* ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; SR-BI, scavenger receptor BI; SR-A, scavenger receptor class A; ACAT1, acyl coenzyme A:cholesterol acyltransferase-1; nCEH, neutral cholesteryl ester hydrolase; ox-LDL, oxidized low-density lipoprotein; HDL, high-density lipoprotein; apoA-I, apolipoprotein A-I; LDLR, low-density lipoprotein receptor; apoE, apolipoprotein E; CE, cholesterol ester; FC, free cholesterol; LXR, liver X receptor; RXR, retinoid X receptor; PPAR-γ, peroxisome proliferator-activated receptor-γ; ERK1/2, extracellular signal-regulated kinases 1 and 2; PPREs, PPAR response elements; PKB, protein kinase B; PKC, protein kinase C; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinase; RCT, reverse cholesterol transport; PI3K, phosphatidylinositol 3-kinase; AGE, advanced glycation end products.

* Corresponding author. Tel./fax: +86 734 8281852.
** Correspondence to: Institute of Cardiovascular Research, University of South China, Hengyang, Hunan 421001, China. Tel./fax: +86 734 8281853.
*E-mail addresses:* kaiyinby@yahoo.com.cn (K. Yin), tchaoke@yahoo.com.cn (C.-K. Tang).

0009-8981
http://dx.doi.org/10.1016/j.cca.2013.06.006

**Source number 25**

*Current Drug Targets - Inflammation & Allergy*, 2005, *4*, 281-286 

# Macrophages in Inflammation

Nagatoshi Fujiwara* and Kazuo Kobayashi

*Department of Host Defense, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan*

**Abstract**: The inflammatory process is usually tightly regulated, involving both signals that initiate and maintain inflammation and signals that shut the process down. An imbalance between the two signals leaves inflammation unchecked, resulting in cellular and tissue damage. Macrophages are a major component of the mononuclear phagocyte system that consists of closely related cells of bone marrow origin, including blood monocytes, and tissue macrophages. From the blood, monocytes migrate into various tissues and transform macrophages. In inflammation, macrophages have three major function; antigen presentation, phagocytosis, and immunomodulation through production of various cytokines and growth factors. Macrophages play a critical role in the initiation, maintenance, and resolution of inflammation. They are activated and deactivated in the inflammatory process. Activation signals include cytokines (interferon γ, granulocyte-monocyte colony stimulating factor, and tumor necrosis factor α), bacterial lipopolysaccharide, extracellular matrix proteins, and other chemical mediators. Inhibition of inflammation by removal or deactivation of mediators and inflammatory effector cells permits the host to repair damages tissues. Activated macrophages are deactivated by anti-inflammatory cytokines (interleukin 10 and transforming growth factor ß) and cytokine antagonists that are mainly produced by macrophages. Macrophages participate in the autoregulatory loop in the inflammatory process. Because macrophages produce a wide range of biologically active molecules participated in both beneficial and detrimental outcomes in inflammation, therapeutic interventions targeted macrophages and their products may open new avenues for controlling inflammatory diseases.

## INTRODUCTION

Inflammation is a complex, highly regulated sequence of events that can be provoked by a variety of stimuli including pathogens, noxious mechanical and chemical agents, and autoimmune responses. The subsequent cascade of events is characterized by the signs and symptoms of redness, swelling, heat, and pain. The inflammatory response occurs in the vascularized connective tissue, including plasma, circulating cells, blood vessels, and cellular and extracellular components. This corresponds with increased microvascular caliber, enhanced vascular permeability, leukocyte recruitment, and release of inflammatory mediators [1]. Inflammation is the primary process through which the body repairs tissue damage and defends itself against stimuli. In the physiologic condition, the regulated response protects against further injury and clears damaged tissue. In pathologic situation, inflammation can result in tissue destruction and lead to organ dysfunction.

The process of inflammation is divided into acute and chronic patterns. Acute inflammation is of relatively short duration, lasting for minutes, several hours, or a few days, and its main features are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes, predominantly neutrophils. Chronic inflammation is of longer duration and is associated histologically with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis, and tissue necrosis. Many factors participate in the course and histologic features of both acute and chronic inflammation. In inflammation, macrophages have three major function; antigen presentation, phagocytosis, and immunomodulation through production of various cytokines and growth factors [2, 3]. No human has been identified as having congenital absence of this cell line, probably because macrophages are required to remove primitive tissues during fetal development as new tissues develop to replace them. In this article, we will review the role of macrophages in inflammation.

## DEVELOPMENT OF MACROPHAGES

The mononuclear phagocyte system consists of cells that have a common lineage whose primary function is phagocytosis. Monocytes and tissue macrophages in their various forms make up the system [4]. These cells are a system because of their common origin, similar morphology, and common functions, particularly phagocytosis. The cells of the mononuclear phagocyte system originate in the bone marrow, circulate in the blood, and mature and become activated in various tissues (Fig. **1**). The first cell type that enters the peripheral blood after leaving the marrow is incompletely differentiated and is called monocytes. When the monocyte reaches the extravascular tissue, it undergoes transformation into a larger phagocytic cell, the macrophage. In addition to augmenting phagocytotic activity, macrophages have the potential of being activated, a process that results in increased cell size, increased production of lysosomal enzymes, more active metabolism, and greater ability to phagocytose and kill ingested microbes. Once they settle in the tissues, these cells mature and become macrophages. Macrophages may exhibit different morphology and functional properties after activation by external stimuli, including microorganisms. Some develop abundant cytoplasm and are called epithelioid cells because the morphologic similarity to epithelial cells of the skin. Activated macrophages can fuse to form multinucleated giant cells. Epitheliod cells and multinucleated giant cells are the major cellular component of granulomas, a typical phenotype of chronic inflammation [5]. Macrophages are found in all organs and connective tissues and named to designate their location, such as microglial cells in the central nervous system, Kupffer cells in the liver, alveolar macrophages in the lung, and osteoclasts in the bone.

## FUNCTIONS OF MACROPHAGES

Macrophages have at least three major functions: antigen presentation, phagocytosis, and immunomodulation [2, 3]. The functional responses of macrophages in host defense consist of sequential steps; active recruitment of the cells to the site of infection, recognition of microbes, phagocytosis, and destruction of ingested microbes. In addition, macrophages produce biological active molecules that serve many important roles in innate and adaptive immune responses.

### Antigen Presentation

Antigen-presenting cells function to display antigens for recognition by lymphocytes and to promote the activation of lymphocytes. Antigen-presenting cells include dendritic cells and monocytes/macrophages. Macrophages containing ingested microbes present microbial antigens to differentiated effector T lymphocytes. The effector T cells then activate macrophages to kill microbes in association with cytokines. The macrophage-cytokine-T lymphocyte axis plays a critical role in development of cell-mediated immunity against intracellular pathogens, including *Mycobacterium tuberculosis*, *Salmonella typhi*, and *Listeria monocytogenes*. Ingested macrophages play a role in activate/differentiate naïve T lymphocytes to induce primary responses to microbial antigens, although it is likely that dendritic cells act as more effective inducers of the response.

### Phagocytosis

Macrophages ingest materials to eliminate waste and debris (scavenging) and to kill invading pathogens. The microbicidal mechanisms of phagocytes are largely confined to intracellular vesicles (lysosomes and phagolysosomes) to protect the cells themselves from injury. Therefore,

*Address correspondence to this author at the Department of Host Defense, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan; Tel: +81-6-6645-3746; Fax: +81-6-6645-3747; E-mail: fujiwara@med.osaka-cu.ac.jp

Contract grant sponsors: Ministry of Health, Labour and Welfare (Research on Emerging and Re-emerging Infectious Diseases, Health Sciences Research Grants), The Japan Health Sciences Foundation, Ministry of Education, Culture, Sports, Science and Technology, Osaka City University (Urban Research Project), and The United States-Japan Cooperative Medical Science Program against Tuberculosis and Leprosy.

1568-010X/05 $50.00+.00

# Source number 27

Indian Journal of Pathology & Microbiology

**ORIGINAL ARTICLE**
**Year** : 2014 | **Volume** : 57 | **Issue** : 2 | **Page** : 259--264

## Periodontal pathogens in atheromatous plaque

**Saroj K. Rath[1], Manish Mukherjee[2], R Kaushik[3], Sourav Sen[4], Mukesh Kumar[5],**
[1] Department of Periodontology, Army Dental Centre, Research and Referral Hospital, Delhi Cantonment, New Delhi, India
[2] Department of Periodontology and Oral Implantology, Armed Forces Medical College, Pune, India
[3] CTC, Armed Forces Medical College, Gaya, Bihar, India
[4] Department of Microbiology, Armed Forces Medical College, Gaya, Bihar, India
[5] Department of Microbiology, Military Hospital, Gaya, Bihar; Department of Microbiology, AFMC, Pune, India

**Correspondence Address**:
Saroj K. Rath
Department of Periodontology, Army Dental Centre, Research and Referral Hospital, Delhi Cantonment, New Delhi
India

### Abstract

**Background:** There has been increasing attention paid in recent years to the possibility that oral bacterial infection, particularly periodontal disease may influence the initiation and or progression of systemic diseases. These studies confirm the observation that heart disease is the most commonly found systemic condition in patients with periodontal disease. Moreover, the literature has also highlighted substantial evidence indicating the presence of Gram-negative periodontal pathogens in atheromatous plaques. **Aim:** This study intends to investigate the possible association between periodontal health and coronary artery disease by evaluating periodontal status, association between the periodontal plaque and coronary atheromatous plaques for presence of micro-organisms such as, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia,* and *Tannerella forsythia.* **Materials and methods:** A case-control study was designed with seven patients who had undergone coronary endarterectomy for cardiovascular disease and 28 controls. The periodontal examination for cases was performed 1 day before vascular surgery and the controls were clinically examined. The atheromatous plaque sample collected during endarterectomy and the intraoral plaque samples were subjected to polymerase chain reaction for identification of *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia* and *T. forsythia*. **Results:** The presence of periodontal bacteria DNA in coronary atheromatous plaques and sub-gingival plaque samples of the same patients was confirmed by this study. CONCLUSION A correlation was established between putative bacteria contributing to atheromatous plaques and species associated with periodontal disease. One particularly important study to be carried out is the investigation of a possible clinically meaningful reduction in coronary heart disease resulting from the prevention or treatment of periodontal disease.

**How to cite this article:**
Rath SK, Mukherjee M, Kaushik R, Sen S, Kumar M. Periodontal pathogens in atheromatous plaque.Indian J Pathol Microbiol 2014;57:259-264

**How to cite this URL:**
Rath SK, Mukherjee M, Kaushik R, Sen S, Kumar M. Periodontal pathogens in atheromatous plaque. Indian J Pathol Microbiol [serial online] 2014 [cited 2021 Apr 21 ];57:259-264
**Available from:** https://www.ijpmonline.org/text.asp?2014/57/2/259/134704

### Full Text

## INTRODUCTION

Recent studies have proven that periodontal disease can produce numerous changes in systemic health with changes in the blood chemistry with a rise in inflammatory mediators, proteins, and lipids in the serum. [1] There has been increasing attention paid in recent years to the possibility that oral bacterial infection, particularly periodontal disease may influence the initiation and or progression of systemic diseases. Periodontitis has been proposed as having an etiological or modulating role in cardiovascular and cerebrovascular disease, diabetes, respiratory diseases, adverse pregnancy outcome, and rheumatoid arthritis. [2] Several mechanisms have been proposed to explain probable association between periodontitis and systemic diseases, including potential systemic dissemination of locally produced mediators such as C-reactive protein (CRP), interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor-alpha. [3]

The first indication of association between the dental disease and cardiovascular disease (CVD) or atherosclerosis was given in 1963. [4] Since then, there is growing evidence that poor dental health, especially the presence of periodontal disease, increases the risk of occurrence of coronary heart disease (CHD). [1] Studies conducted on different populations have suggested that atherosclerosis and the occurrence of acute myocardial infarction could be linked with chronic oral infections. [5] These studies confirm the observation that heart disease is the most commonly found systemic condition in patients with periodontal disease. Moreover, the literature has also highlighted substantial evidence indicating the presence of Gram-negative periodontal pathogens in atheromatous plaques. [6] Elevated levels of inflammatory molecules, which is seen as a result of periodontitis in long-term can predict increased risk for CVD. [7] Increased numbers of leukocytes have also been associated with CVD. [8]

However, evidence that periodontal infections contribute to or are decisive factors in the development of atherosclerotic plaques is circumstantial, and an epidemiological association is not proof of a causal link between pathogens and CVD, although bacterial presence at the diseased site is one of the requirements to determine a causal relationship. [9] As a result of the high-sensitivity of polymerase chain reaction (PCR) and other molecular methods, the presence of these pathogens within atheromatous plaques can be identified. In recent years, studies have implicated Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Porphyromonas gingivalis and Tannerella forsythia in connective tissue attachment loss and periodontal inflammation.

This study intends to investigate the possible association between periodontal health and coronary artery disease by evaluating periodontal status, association between the periodontal plaque and coronary atheromatous plaques for presence of micro-organisms such as, A. actinomycetemcomitans, P. gingivalis, P. intermedia, and T. forsythia.

## MATERIALS AND METHODS

**Source number 29**

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 32, no. 2 (S1), 143-147 (2018)

# FOCUS ON PERIODONTAL DISEASE AND DEVELOPMENT OF ENDOCARDITIS

F. CARINCI[1*], M. MARTINELLI[2*], M. CONTALDO[3], R. SANTORO[3], F. PEZZETTI[2], D. LAURITANO[4], V. CANDOTTO[5], D. MUCCHI[6], A. PALMIERI[2], A. TAGLIABUE[7**] and L. TETTAMANTI[7**]

*[1]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy; [2]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [3]Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania Luigi Vanvitelli, Naples, Italy; [4]Department of Medicine and Surgery, University of Milano Bicocca, Monza, Italy; [5]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [6]LAB S.r.l., Codigoro, Ferrara, Italy; [7]Department of Medicine and Surgery, University of Insubria, Varese, Italy*

*these authors contributed equally to this work and they are co-first authors
**these authors contributed equally to this work and they are co-last authors

**Abstract Infective endocarditis is a devastating disease with high morbidity and mortality. The link to oral bacteria has been known for many decades and has caused ongoing concern for dentists, patients and cardiologists. The microbiota of the mouth is extremely diverse and more than 700 bacterial species have been detected. Half of them are uncultivable so far. Oral microbiota is not uniform, specific sites exist in the mouth such as tongue, palate, cheek, teeth and periodontal pockets that have their own microbiota. Factors involved in the development of a bacterial endocarditis are difficult to define but a vulnerable surface (i.e. a damaged endocardium) and a high bacterial load in the blood seems to be decisive. The cause of microorganisms, in 90% of cases, are staphylococcus, streptococcus and enterococcus. Oral streptococci belong to viridans group (streptococcus mutans and streptococcus sanguis). As they are part of dental plaque, they could enter the bloodstream causing bacteraemia through daily habits like chewing or tooth brushing. Effective treatment of periodontal infections is important to reduce local inflammation and bacteraemia. In addition, poor periodontal health appears to increase the risk of cardiovascular disease, pulmonary disease, and preterm and low birth weight. Conclusions: Long-standing oral disease prevention protocols reduce the risk of developing periodontal disease. Data suggest that methods used to prevent cases of IE that originate from oral bacteria should focus on improving oral hygiene and reducing or eliminating gingivitis, which should reduce the incidence of bacteraemia after tooth-brushing and the need to extract teeth owing to periodontal disease and caries.**

Infective endocarditis is a devastating disease with high morbidity and mortality. The link to oral bacteria has been known for many decades and has caused ongoing concern for dentists, patients and cardiologists.

Infective endocarditis (IE) is a disease caused by a bacteraemia that affects different organs or tissues, including the oral cavity. Although it has a low incidence, it might imply a potential threat to the life of the affected individual. Predominantly it tends

*Key words: oral disease, periodontitis, bacteria, endocarditis*

*Mailing address:*
Prof. Angelo Tagliabue,
Department of Medicine and Surgery,
University of Insubria, Via Piatti, 10,
21100 Varese, Italy
Tel.: +39.0332-825625 - Fax: +39.0332-825655
e-mail: angelo.tagliabue@uninsubria.it



0393-974X (2018)