Relationship between periodontal disease and hyperlipidemia related to vascular events

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ABSTRACT

INTRODUCTION: The association between oral health and vascular disease has been recently studied and it can be seen that periodontal disease can influence health at all. On the other hand, atherosclerosis is a progressive disease with accumulation of fibrotic and inflammatory elements resulting in endothelial lesions, and increase of incidence when associated to chronic inflammations. It is known the association between Porphyromonas gingivalis and heart diseases, as this microorganism has been found in atheroma plaques, as other periodontal pathogens.

OBJECTIVE: Search information in literature that confirms the relationship between periodontal disease and hyperlipidemia associated to vascular disease.

METHODS: For this article revision, an online search has been made in scientific libraries such as the Virtual Library in Health (BVS, Bireme); PubMed; Digital Brazilian Theses and Dissertations (BDTD) from 2000 to 2014, using as key words periodontal disease, vascular disease, hyperlipidemia.

CONCLUSION: It has been confirmed by some authors the relation between periodontal disease and hyperlipidemia, otherwise, some contradictory results due to risk factors such as age, food intake and social and cultural factors. Mechanisms in which these factors acts in this progression still have not been clear.

Key words: Periodontal diseases; Heart diseases; Hyperlipidemias

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Inter-relação entre doença periodontal e hyperlipidemia relacionados a eventos vasculares

RESUMO

INTRODUÇÃO: Associação entre saúde bucal e doença cardiovascular tem sido, recentemente objeto de estudo e tem demonstrado que a doença periodontal pode influenciar na saúde sistêmica do indivíduo. Por sua vez, a aterosclerose é uma doença progressiva caracterizada pelo acúmulo de elementos fibrosos e inflamatórios provenientes de injúrias endoteliais, conferindo aumento na incidência quando associado com doenças inflamatórias crônicas. Sabe-se da associação entre Porphyromonas gingivalis e doença cardiovascular, uma vez que este microorganismo já foi encontrado em placas de ateromas, assim como outros periodontopatógenos.

OBJETIVO: Verificar dados na literatura que confirmam correlação da influência da doença periodontal sobre a hiperlipidemia associada a eventos relacionados a doença cardiovascular.

METODOLOGIA: Este trabalho de revisão de literatura, foi realizado a partir de uma busca online em bases de dados científicos, Biblioteca Virtual em Saúde (BVS), (Bireme); PubMed; Digital Brasileira de Teses e Dissertações (BDTD) no período de 2000 a 2014, utilizando como palavras chave doença periodontal, cardiopatias, hiperlipidemias.

CONCLUSÃO: Foi encontrado na literatura autores que confirmam a correlação entre a doença periodontal e hiperlipidemia associado a doença cardiovascular, entretanto há divergências no resultados devido os fatores de riscos serem influenciados por idade, alimentação, sócio-cultural, entre outros. Os mecanismos pelos quais estes fatores agem no desenvolvimento da progressão deste desfecho, ainda não estão esclarecidos.

Palavras-chave: Doenças periodontais; Cardiopatias; Hiperlipidemias
INTRODUCTION

The periodontal medicine represents a new paradigm and it has as its main goal relate the periodontal diseases (PD) as a risk factor to the general health conditions of the person, systemic diseases and recurrent infection [1, 2]. Currently cardiovascular diseases are the main causes of mortality in modern society. Risk factors as PD maybe one of the most important in the development of heart diseases more than smoking itself [3].

On the last two decades, the chronic inflammation appeared as a factor that directly interacts with the cardiovascular disease affecting in all levels of the disease since the begging to the progression until thrombotic complications of the atherosclerosis [4].

Atherosclerosis is a progressive disease characterized by the accumulation of lipids, fibrous and inflammatory elements from a vascular endothelial injury. These abnormalities can be from nutrition, mechanical forces as hypertension, or metabolic, such as the hyperlipidemias, glycosylated proteins associated with diabetes mellitus, lipids or oxidative modified proteins and possible viral and bacterial infections, exogenous toxins found in tobacco [5]. The atherosclerosis cannot be considered a degenerative consequence of aging, but an inflammatory condition, and genetic-environmental risk factors can also be related [6]. The inflammatory diseases are exacerbated through the activation of the white blood cells increasing the cytokines concentration and other inflammatory mediators damaging the walls of arteries and accelerating the atherosclerotic process [7-9].

Many mechanisms correlating inflammatory chronic conditions and the acceleration of the atherosclerotic process are suggested in the literature. The damage mediated by cytokines of the vascular endothelial, activation of immune cells and the activation of the coagulation cascade have been assigned to these events [10].

Besides that, inflammatory events can also induce changes in the metabolism of lipoproteins, increasing LDL levels (low density lipoproteins).

Khovidhunkit et al. (2000) [11] declare that infections and inflammations can change the metabolism of lipoproteins and produce a wide range of variations on the plasma concentrations, including the growth of triglycerides and the reduction of HDL (high density lipoproteins).

Patients with chronic inflammatory diseases such as Periodontitis, Rheumatoid Arthritis, Psoriasis, Systemic Lupus Erythematosus, Respiratory and Urinary Tract Infections, have a growth on the incidence of atherosclerotic events [12-14]. The AAS is a drug widely used for pain control, and it is also used for primary or secondary prevention of myocardial infarction and ischemic strokes, due to its effect of reducing the platelet adhesion [15]. The using frequency of AAS in a hospital level and clinic has been of 17.7% in primary prevention (people aged>40 years old with at least two risk factors) and 98% in secondary prevention (patients with strokes history, acute myocardial infarction and/or angina pectoris) causing a reduction in cardiovascular events that can be up to 40% [16].

It is understood that this is an area that needs new research, that can contribute for a better understanding between the influence of the periodontal disease related with hyperlipidemia and as a consequence heart diseases, being that the reason that stimulated us to elaborate the present review.

This literature review had as goal, find data in the literature that correlate the influence of the periodontal disease with the hyperlipidemia associated to events related to cardiovascular disease.

METHODS

It has been executed a non-systematic review in the period from 2000 to 2014, which the data bases were from the Virtual Library in Health (BVS, Bireme); PubMed; Digital Brazilian theses and dissertations (BDTD). Using as descriptors: periodontal diseases, heart diseases, hyperlipidemias.

LITERATURE REVIEW

The periodontal disease is formed by the initial inflammation of the gingival tissue, related to the adhesion of the biofilm on the teeth surface, through the lack of bacterial plaque control. The biofilm and the dental calculus are factors that contribute to the development of the PD, being very prevalent in adults and youth all over the world [18].

The periodontitis starts by the migration of the junctional epithelium, that gets characterized by the presence of a periodontal pocket [19]. Periodontitis is a highly prevalent disease in the dental field, and its clinical signs are checked in middle-aged patients. It is observed in this disease a chronic inflammatory picture with tissue destruction of the supporting tissue of the tooth, which can cause the movability and dental loss [20].

The cardiovascular disease is a heart and blood vessels disorder that involves the increase of blood pressure, coronary disease, congestive heart failure and myocardial infarction. It is highly prevalent and cause of death [21].

Periodontal disease and atherosclerosis show common etiopathogenic mechanisms. Aetiologically, it is known that both conditions have in common complex causes, genetic predisposition and risk factors [22].

There is much evidence that PD can influence in systemic health, having an important role on the development of heart disease, due to the fact that it predisposes the individual to chronic infections, which induces a systemic inflammatory response, increasing the inflammatory markers, and so the prevention and the treatment of the periodontal infection can reduce the mortality and morbidity associated to cardiac diseases [23, 24].

The various forms of PD have similar mechanisms of tissue destruction, such as healing and regeneration, although
they differ in etiology, natural study, progression and in the response to the therapy. The pathological mechanisms are proinflammatory cytokines, interleukin (IL-1) and the tumor necrosis factor – alpha (TNFα) which induce an increase in the production of prostaglandin (PGE2) and matrix metalloproteinase (MMP), that destroy the extracellular matrix of the gingiva, the periodontal ligament, and alveolar bone resorption [1]. Studies have shown that the inflammation participates in every evolution stage of the atherosclerosis, increasing the levels of inflammatory markers such as cytokines, total white blood cell count, CRP (C-reactive protein), among others. In patients with PD it has been considered as markers the level of CRP (C-reactive protein), inflammatory and immunological mediators (especially IL-6), as a risk for cardiovascular diseases, due to the fact that in both diseases it is observed a high level of these markers [25].

The C-reactive protein is one of the present proteins in acute and sensible inflammatory states, being used in the evaluation of patients with inflammatory disorders, as an auxiliary in diagnosis, therapeutic control and development of several other diseases [26].

Chronic periodontal disease can be considered an etiological predisposing factor to cardiovascular disease [20, 22, 27-29]. Evidence demonstrate that periodontitis causes inflammatory chronic cases and endothelial dysfunction [30], and, specifically Porphyromonas gingivalis, a periodontal pathogen, that increases cholesterol and the atheroma formation [27, 31]. In addition, Porphyromonas gingivalis presents surface proteins that induce a decrease of the immune response in individuals with periodontal disease [32].

This periodontopathogen, induces an endothelial injury through its toxins, and thereafter a systemic inflammatory response [30]. In atheromatous plaques it is verified a presence of two major odontopathogens, Porphyromonas gingivalis and Streptococcus sanguis [32].

The incoming of periodontopathogens and its products in circulation are considered one of the major initial events of the biological events that related periodontitis and cardiovascular disease [21].

Individuals with periodontitis show a higher prevalence of Porphyromonas gingivalis when compared to patients with gingivitis, as shown by Shanker et al., (2013) [30] that evaluated 532 patients with gingivitis and 282 patients with periodontitis. It was also verified a higher occurrence of this pathogen in patients with diabetes and hypertension.

Studies in rats showed a presence of polymicrobial colonization and infection by the periodontopathogens Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola in aorta and the increase of inflammatory markers related to changes in cholesterol and triglycerides [33].

Many patients with atherosclerosis have yet as an aggravating the increase of blood pressure [34-36]. It is known that in hypertensive occur a proliferation of the tunica intima and the elastic lamina with the decrease of the lumen in blood vessels that irrigate the periodontal membrane, increasing the susceptibility of hypertensive patients to the development of periodontal disease [34].

Cardiovascular disease is correlated with hyperlipidemia, since it is affirmed that the beginning of the formation of the atheromatous plaque starts by the focal accumulation of lipids [37]. Balan (2010) [28] compared in his study individuals with coronary heart disease, individuals with periodontal disease and healthy individuals. He verified that the HDL concentrations (high density lipoprotein) were lower in the group with cardiovascular disease, higher in healthy individuals and median in individuals with periodontitis. This study demonstrated that the periodontal infection has effect over the systemic inflammation and the lipid metabolism.

Patients with the periodontal disease, have total cholesterol (TC) and LDL (low density lipoprotein) increased and HDL decreased when compared to healthy patients, verified in laboratorial studies in rats [31, 38]. It is affirmed that low HDL levels can indirectly contribute for the exacerbation of the inflammatory process [20, 21].

It is verified the relationship between periodontal disease and the lipid profile, as verified in a study of 26 patients with chronic periodontitis and a control group. TG (triglycerides), LDL, HDL and cholesterol levels were measured. TG levels were significantly higher in patients with periodontal disease. However the other levels were not very significant [39].

Hyperlipidemia and periodontitis also find a big correlation in the studies of the area, due to the liberation of inflammatory cytokines [38-39]. The LDL invades the endothelial cells, initiating inflammatory reaction [21].

In a systemic inflammatory state, the atherogenic effects can manifest in different levels. In physiological conditions the endothelia produces nitric oxide (NO) which is a vasodilator, avoiding a possible atherothrombosis10 and directly related in mechanisms that control the blood flow and participate of the blood pressure modulation in normotensive and hypertensive individuals. In patients that present hypercholesterolemia there is a bioavailability decrease of nitric oxide due to a high production of free radicals [40].

The endothelial dysfunction results on the decrease of the enzyme nitric oxide synthase (eNOS) and an increase of inducible nitric oxide (iNOS), and so there is an expressive increase on the amount of underlying nitric oxide.

The systemic inflammation induces a secondary dyslipidemia characterized by an increase of triglycerides and a decrease of high density lipoprotein (HDL) [41, 11] modifying the composition of the enzymes and proteins of the HDL particle [42, 43], occurring functional shift, taking pro atherogenic effect [44], can activate the coagulation cascade and vice versa [45]. The systemic inflammation activates the thrombin and the platelets that are deeply connected to the development of the atherothrombosis [46]. After being connected to the endothelia it can liberate a big quantity of inflammatory mediators, adhesion molecules, chemokines and coagulation factors that make the recruitment of white
blood cells to the vascular wall of the endothelial space [47]. This activation of the with blood cells (mostly monocytes) is done by the platelets that activate the P-selectin that is an adhesion factor. These monocytes platelets complexes are sensible for the activation of the platelets [48], which plays a fluke on the instability of the plaque and thrombosis [49].

**DISCUSSION**

Despite the relationship between the periodontal disease and systemic factors related to cardiovascular disease and hyperlipidemia has been studied since 1980, it is observed that there are still doubts in mechanisms that interrelate these pathologies.

When reviewing the literature on the relationship between periodontal conditions and the blood levels of lipoproteins in plasma, there are several scientific articles that affirm a positive relationship [37, 50-53, 56]. Including the article by Pejcic et al., (2011) [50] verified that there were not a relationship, and also, a decrease on the lipid level after the periodontal therapy in patients with periodontitis, in a longitudinal study.

Penurmarthy et al., (2013) [38] verified increased levels of TG, TC and LDL in patients with periodontitis, and a decrease in levels of HDL, showing co-relation of these variables with periodontal attachment loss. Oliveira et al., (2010) [53] in addition to finding an increase of LDL and TG in patients with vascular diseases, the study also attempt for a presence of oral pathogens in plaques of coronary arteries.

On the other hand Hagh et al., (2014) [54] found differences statistically significant in LDL and HDL levels in patients with chronic periodontitis. These authors referred to the difference of data in study standards, sample sizes and methodologies.

As Machado et al., (2005) [55] also did not find on the studied population and with the appointed methodology a statistically significant association between hyperlipidemia and periodontal disease. The authors attribute the differences of result to the eating habits, sedentary lifestyle, socio-economic conditions, obesity, age and stress. Lösch et al., (2000) [56] also verified such co-relation in research with 39 individuals, however, the study affirms that the obtained data cannot allow to induce if the periodontal disease and cardiovascular disease present hyperlipidemia and prediabetic states as risk factors in common. Other risk factors in common would be diabetes mellitus, smoking and poor living habits.

Another factor that Lei et al., (2013) [57] attempt to on the study, is that the hyperlipidemia is related to obesity, and that it depends of the studied population and of the eating habits and life of the same. So, obesity is also a risk factor for coronary heart disease [58]. Fentoglu & Bozkurt (2008) [37] attributed the hyperlipidemia to diets rich in saturated fat and metabolic disorders such as type 2 diabetes.

A possible explanation for the inter-relationship hyperlipidemia and periodontitis is that hyperlipidemia causes hyperactivity of the white blood cells, which would induce an increase of the production of oxygen free radicals, inwardly related to periodontitis cases in adults [56]. Besides that, the hyperlipidemia indirectly acts on the modulation of the immune response, acting mostly on the response of macrophages to the bacterial invasion by *Porphyromonas gingivalis* [57].

Regarding the presence of C-reactive protein (CRP) in patients with severe and aggressive periodontitis, studies, as the one by Bezerra et al., cannot establish in high levels of this protein in patients with PD can cause the development or the aggravation of cardiovascular diseases. Braga et al., (2004) [40] affirm that its use in periodontitis is still limited and unspecified.

Fentoglu & Bozkurt (2008) [37] reported that the interrelation between periodontitis and hyperlipidemia generates systemic changes that predispose the individual to oral infections, and once it is established, the systemic condition can be exacerbated, however, there are not clear evidence in the literature if this interrelation is cause-effect, causing the periodontitis to induce to an increase of the lipid metabolism or that the increased lipid levels in blood are risk factors to the development of periodontitis.

The relationship between periodontal disease and atherosclerosis begun being searched in the 60’s. However in the 80’s, scientific studies confirmed this hypothesis [3, 20, 21, 25, 32].

Angeli et al., (2003) [29] on the study could not, confirm such hypothesis. They attribute the difference of the results found on the study to factors related to lifestyle that can confront and chance the way of cardiovascular diseases and its responses.

Togashi et al., (2005) [24] as other authors verified prevalence of periodontal disease in cardiac patients, relating with systemic alterations, wherein, the most prevalent ones were the hypertension and atherosclerosis.

The periodontal disease, as dental caries, has as a primary etiologic factor the accumulation of biofilm. Patients that present cardiovascular diseases show worse oral hygiene conditions when compared to healthy patients, what could be an aggravating to a higher prevalence of periodontal disease in this group. Although the mechanisms still have not been clarified yet, the necessity of control and prevention of these risk factors are more important [18].

The biofilm control is essential in the prevention not only of periodontitis, but also in vascular diseases, since *Porphyromonas gingivalis* and other periodontopathogens can be found in atheromatous plaque [30, 31].

**CONCLUSION**

It was found in the literature authors that confirm the co-relation between the periodontal disease and hyperlipidemia associated with cardiovascular disease, however there are divergences in the results due to risk factor being influenced by age, food intake, socio-cultural conditions, among others. The mechanisms whereby these factors act in the development of the progression of this upshot are not clarified yet.


