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REVIEW

Oral Sciences

Periodontal Disease and C-Reactive Protein - Association with Cardiovascular Risk

GUIMARÃES, Maria do Carmo Machado, ARAÚJO, Valéria Martins de, LA ROQUE, Priscyla de, ALENCAR, D`angela Marise G. de, RAULINO, Fernanda Franco, COSTA, Ana Maria, AMORIM, Rivadávio Fernandes Batista de. Periodontal Disease and C-Reactive Protein - Association with Cardiovascular Risk. Oral Sci., Jan/Apr. 2010, vol.2, no.1, p. 55-59.

ABSTRACT - Cardiovascular disease is the main cause of death in the contemporary western world and traditional risk factors do not completely explain its development. Plausible mechanisms have been proposed to explain the relationship between periodontal disease and cardiovascular disease, since both diseases present complex etiological factors, combining genetic and environmental influences. Several studies indicate that cell and molecular components of inflammatory and immunological events due to periodontal infection may contribute to develop cardiovascular disease. Among these components, C-reactive protein, an important acute phase reagent with pro-inflammatory properties, whose levels are high in periodontal infection and also a significant indicator of atherosclerosis may explain in part the association between periodontitis and cardiovascular disease. This protein and some other components of periodontal infection involved in this possible association are discussed in this revision of the literature.

KEYWORDS - Cardiovascular disease, atherosclerosis, periodontal disease.

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Received January 13, 2009
Accepted February 2, 2009

Introduction

Cardiovascular disease, atherosclerosis and their complications such as infarction, stroke, transitory ischemia and peripheral vascular disease are diseases prevalent in developed countries. In spite of continuous preventive efforts directed to the risk factors, there has not been variation in cardiovascular disease mortality in developed countries. In Brazil, approximately 260 thousand people die from cardiovascular problems per year (1).

Among the several physiological and behavioral factors responsible for triggering the disease, the outstanding factors are: arterial hypertension, smoking, diabetes mellitus, obesity and hyperlipidemia. Furthermore, age, sex, sedentary lifestyle, stress and family history are normally associated with heart diseases.

Infectious agents such as herpes simplex virus and cytomegalovirus were related to the development of atherosclerotic lesion (2). These infectious agents may alter the anticoagulant phenotype of the endothelial cells to pro-coagulant phenotype (3).

The inflammatory response induced by pathogens of chronic infection is an important mechanism in which the

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infection predisposes to the atherosclerotic processes (4). The probable access of pathogens of periodontal disease and release of lipopolysaccharide (LPS) and other soluble components in the conjunctive tissue and bloodstream (5) has strengthened the evidence of association between periodontal disease and cardiovascular disease (6). Furthermore, evidences suggest that the increase in the levels of the systemic markers of inflammation, such as C-reactive protein (CRP) and interleukin-6 (IL-6), is associated with cardiovascular diseases (7).

Literature Review and Discussion

Evidences of association between periodontal disease and cardiovascular disease

Several studies have investigated the association of the periodontal disease with cardiovascular disease.

In 1989, Matilla, et al (8), when assessing patients who had myocardial infarction, they concluded that the oral health of these patients was significantly worse than patients from control group, without cardiac problems.

The first prospective study about the inter-relation between periodontitis and coronary diseases (9) included 9760 individuals. The authors reported that individuals with periodontitis had 25% increased risk for cardiovascular disease compared with those with little or no periodontal disease. The analysis was restricted to men under the age of 50 revealed that those with periodontitis as well as the edentulous ones were 70% more prone to develop cardiovascular disease when compared with men with minimum periodontal disease. The risk of death was significantly higher for patients who had periodontitis when compared with patients who have cardiopathies with healthy periodontium. Although they concluded that periodontal disease is associated with an increased risk of cardiovascular disease, they emphasized that the association may be merely accidental, since many patients with cardiac problems showed precarious hygiene and were not concerned with matters related to health.

To investigate the plausible relationship between periodontitis and coronary disease, several studies were published, and although a great number of these studies reported the association between periodontal disease and cardiovascular disease (10-14), some studies did not find a significant correlation between the two diseases (15, 16).

Periodontopathogenic bacteria, exclusive in the oral cavity, may disseminate into the bloodstream causing inflammations. Genetic tests for microbial identification applied in 50 atheromas revealed that 44% were positive for DNA of at least one of the tested periodontal pathogens (Tannerella forsythensis, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Prevotella intermedia). According to the authors, these bacteria, conducted by the blood, install themselves on the vascular walls and may be part of the atherosclerosis pathogenesis (6).

There are several hypotheses that explain the association between periodontal disease and atherosclerosis. The theory of bacterial invasion presupposes a direct action of periodontal bacteria and their toxins in the endothelium, which has been partially proved by the microbiological findings in the atheromatous plaques (17).

Haraszthy et al; Stelzel et al (6,18) demonstrated the presence of genetic material of gingival pocket bacteria in atheromatous plaques examined. The most frequently identified microorganisms were Tannerella forsythensis and Porphyromonas gingivalis.

In 1998, Deshpande et al (19) first demonstrated that Porphyromonas gingivalis was capable of invade the bovine aortic and cardiac endothelium.

According to the cytokine theory, inflammatory mediators released by the cells of the immune system are the key for damage of the vascular wall of the endothelium. Bacterial endotoxins such as LPS, are connected to CD14 receptors on monocytes, macrophages and endothelium cells. The TLRs receptors present on the macrophage, monocyte and granulocyte surfaces recognize bacterial endotoxins, initiate intracellular signaling and mediate the transcription of the factor responsible for releasing pro-inflammatory and pro-aggregated cytokines such as PGE-2, IL-1, IL-2 and TNF- . These cytokines activate the arachidonic acid cascade and initiate synthesis of the thrombogenic agents such as leucotrien (LTB4) and LTC4 released

by erithrocytes and granulocytes. They also lead to the synthesis of prostaglandins PGE-1 and 2 by leukocytes and myocytes on the vascular wall and thromboxane A2 by platelets. These compounds stimulate chemataxis of monocytes and macrophages and adhesion to endothelial cells, which leads to the accumulation of intracellular lipids and the formation of spongy cells (20).

The plasma of patients with chronic inflammatory diseases has high levels of fibrinogen and C-reactive protein (CRP). TNF- activates the secretion of IL-6 that stimulates the liver to produce CRP and synthesis coagulation factors, inducing the formation of micro arterial thrombosis, and consequently leads to cardiovascular diseases (21).

The autoimmune theory emphasizes the importance of HSP65 protein (heat shock proteins) expressed in some pathogens such as Porphyromonas gingivalis, Prevotella intermedia and Aggregatibacter actinomycetemcomitans. This protein produces anti-hsp65/60 antibodies present in the saliva of patients with periodontitis and generates an autoimmune process of cross-reaction with the HSP 60 endothelial protein leading to endothelial cell damage and exposure to inflammatory factors (17).

Role of the C-reactive protein in periodontitis and cardiovascular disease

Periodontitis seems to have an important infectious and inflammatory load, which may increase hepatic synthesis of CRP, an acknowledged and accepted factor of risk for acute myocardial infarction (22). This protein is an indicator of an acute phase that increases specially during inflammatory and infectious processes. Very high levels of this protein indicate an increase in the risk of infarction and stroke. Patients with periodontal disease who treated with root scraping and planning showed a significant reduction of C-reactive protein and IL-6. Those patients who responded to scraping presented a decrease of C-reactive protein four times greater when compared with those patients with poor clinic response (21, 23).

Seinost et al, 2005 (24), assessed the endothelial function in 30 patients with severe periodontitis and compared them with 31 controls without the disease. Before periodontal intervention the artery dilation mediated by the flow was significantly low in patients with periodontal disease compared with controls. Patients who responded to periodontal treatment had better dilation mediated by the brachial artery flow and concentration of C-reactive protein. In the study about the association between cardiovascular and periodontal diseases, it was observed that healthy individuals concerning both conditions had a mean level of CRP of 1.14g/ml, while individuals with both diseases had a mean level of 8.7g/ml. The authors also noted a reduction of 65% in the level of CRP three months after treatment of the periodontal disease (23).

However, Ide et al, 2003 (16), did not find any significant association in the change of systemic inflammatory and cardiovascular markers such as C-reactive protein, sialic acid, TNF- , IL-6 and IL- in systematically healthy patients with periodontal disease, after non-surgical therapy. Furthermore, Montebugnoli et al, 2005 (15), did not find a statistically significant difference for the homeostatic factors, except for the decrease of C-reactive protein 3 months after scraping in patients with coronary disease history. Yamazaki et al, 2005 (25), observed in Japanese patients that the level of IL-1 and IL-6 was similar to patients with advanced chronic periodontal disease and controls. The C-reactive protein was slightly increased in patients, but the levels detected were lower than those found in other populations.

Conclusion

Several studies suggest the association between periodontal disease and atherosclerosis, which include data from original publications, systemic reviews, narrative review and meta-analysis. Nevertheless, evidences regarding causality are still insufficient to establish a causal relationship between periodontal disease and cardiovascular alterations. Since these diseases have several common characteristics, other studies which control the misleading factors for both diseases are necessary. Studies suggest that periodontal therapy improves predictive factors of cardiovascular disease such

as serological biomarkers and vascular function. However, the modulator effect of periodontal treatment in cardiovascular risk factors, up to the present, has not yet been established.

Resumo

GUIMARÃES, Maria do Carmo Machado, ARAÚJO, Valéria Martins de, LA ROQUE, Priscyla de, ALENCAR, D`angela Marise G. de, RAULINO, Fernanda Franco, COSTA, Ana Maria, AMORIM, Rivadávio Fernandes Batista de. Doença Periodontal e Proteína C-Reativa – Associação com Risco de Doença Cardiovascular. Oral Sci., Jan/Apr. 2010, vol.2, no.1, p. 55-59.

A doença cardiovascular constitui a principal causa de morte no mundo ocidental contemporâneo e fatores de risco tradicionais não explicam completamente o seu desenvolvimento. Mecanismos plausíveis têm sido propostos para explicar a relação entre doença periodontal e doença cardiovascular, uma vez que ambas as doenças apresentam fatores etiológicos complexos, combinando influências genéticas e ambientais. Diversos estudos indicam que componentes celulares, moleculares dos eventos inflamatórios e imunológicos decorrentes da infecção periodontal podem contribuir para o desenvolvimento da doença cardiovascular. Entre estes componentes, a proteína C reativa, importante reagente de fase aguda com propriedades pró-inflamatória, cujos níveis se apresentam elevados na infecção periodontal e também significativo marcador de aterosclerose pode explicar, em parte, a associação entre periodontite e doença cardiovascular. Esta proteína e alguns outros componentes da infecção periodontal envolvidos nesta provável associação serão apresentados na presente revisão da literatura.

Palavras-chave: Doença cardiovascular, aterosclerose, doença periodontal.

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