UNIVERSIDADE FEDERAL DE UBERLÂNDIA

FACULDADE DE ODONTOLOGIA

HEITOR FARIA DE CASTRO

OXIDATIVE STRESS: A POSSIBLE LINK BETWEEN PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE.

UBERLÂNDIA

2017

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Trabalho de conclusão de curso apresentado a Faculdade de Odontologia da UFU, como requisito parcial para obtenção do título de Graduado em Odontologia

Orientadora: Profª. Dra. Ana Paula de Lima Oliveira

UBERLÂNDIA

2017

SERVIÇO PÚBLICO FEDERAL
MINISTÉRIO DA EDUCAÇÃO
UNIVERSIDADE FEDERAL DE UBERLÂNDIA
GRADUAÇÃO EM ODONTOLOGIA
TRABALHO DE CONCLUSÃO DE CURSO

ATA DA COMISSÃO JULGADORA DA DEFESA DE TRABALHO DE CONCLUSÃO DE CURSO DO (A) DISCENTE **Heitor Faria de Castro** DA FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE FEDERAL DE UBERLÂNDIA.

No dia **03 de julho de 2017**, reuniu-se a Comissão Julgadora aprovada pelo Colegiado de Graduação da Faculdade de Odontologia da Universidade Federal de Uberlândia, para o julgamento do Trabalho de Conclusão de Curso apresentado pelo (a) aluno (a) **Heitor Faria de Castro, COM O TÍTULO: "OXIDATIVE STRESS: A POSSIBLE LINK BETWEEN PERIODONTAL DISEASE AND CARDIOVASCULAR".** O julgamento do trabalho foi realizado em sessão pública compreendendo a exposição, seguida de arguição pelos examinadores. Encerrada a arguição, cada examinador, em sessão secreta, exarou o seu parecer. A Comissão Julgadora, após análise do Trabalho, verificou que o mesmo encontra-se em condições de ser incorporado ao banco de Trabalhos de Conclusão de Curso desta Faculdade. O competente diploma será expedido após cumprimento dos demais requisitos, conforme as normas da Graduação, legislação e regulamentação da UFU. Nada mais havendo a tratar foram encerrados os trabalhos e lavrada a presente ata, que após lida e achada conforme, foi assinada pela Banca Examinadora.

Uberlândia, 03 de julho de 2017

Profa. Dra. Ana Paula de Lima Oliveira *Universidade Federal de Uberlândia – UFU*	Aprovado Aprovado/Reprovado
Profa. Dra. Karla Zancopé *Universidade Federal de Uberlândia – UFU*	APROVADO Aprovado/Reprovado
Prof. Dr. Paulo Vinicius Soares *Universidade Federal de Uberlândia – UFU*	Aprovado Aprovado/Reprovado
Rafael Resende de Miranda *Aluno de doutorado – PPGO/UFU*	Aprovado Aprovado/ Reprovado

Agradecimentos

Em especial a minha família por sempre acreditar, confiar e estar presente em todos os momentos.

À Profa. Dra. Ana Paula Oliveira, muito obrigado pela orientação e ensinametos. Sempre com muita dedicação, seriedade, entusiamo e comprometimento.

À Doutoranda Bruna Cristina Borges, pela disponibilidade, ideias, seriedade e auxilio.

À Universidade Federal de Uberlândia por proporcionar o título de Cirurgião Dentista.

Um muito obrigado a todos professores, funcionariós e amigos da FOUFU, por fazerem parte da minha formação profissional e pessoal.

“Quando a caminhada fica dura, só os duros continuam caminhando.”

Racionais MC’s

SUMÁRIO

Lista de abreviações e siglas:

Aggressive periodontitis (GAgP)

Cardiovascular diseases (CVD)

Chronic granulomatous disease (CGD)

Chronic periodontitis (CP)

Gingival crevicular fluid (GCF)

Low-density lipoprotein (LDL)

Macrophage colony stimulating factor (M-CSF)

Malondialdehyde (MDA)

Monocyte chemoattractant protein-1 (MCP-1)

Nicotinamide adenine dinucleotide phosphate (NADPH)

Nitric oxide (NO)

Reactive oxygen species (ROS)

Scaling and root planing (SRP)

Superoxide dismutase (SOD)

Total antioxidant status (TAS)

Review Article

Oxidative stress: a possible link between periodontal disease and cardiovascular disease

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ABSTRACT

This review examines current literature regarding relation ships between periodontal disease, oxidative stress and cardiovascular disease. Periodontitis refers to the chronic inflammation of gingival tissue associated with extensive dental plaque formation at the tooth and gingival interface. Previous studies have demonstrated an association between periodontal disease and risk of cardiovascular diseases such as atherogenesis and hypertension. Oxidative stress is implicated in the pathogenesis of many diseases and may provide a connection between periodontal disease and cardiovascular disease given that biomarkers related to the development of heart disease have diminished in patients with periodontitis after periodontal therapy. Several studies have examined the involvement of periodontitis and the role of oxidative stress in the initiation and

progression of hypertension. However, the relationship between periodontitis and the development of cardiovascular disease has not been fully elucidated.

INTRODUCTION

Periodontal disease is a group of chronic inflammatory diseases involving the periodontium, the soft tissue and mandibular bone surrounding the teeth. These diseases, including gingivitis and periodontitis, are among the most common dental diseases (1). Periodontitis is attributed to toxic products from pathogenic bacteria plaque and inflammation of gingival tissues elicited by the host response (2,3,4,5). Periodontitis is linked to an increased risk of cardiovascular diseases (CVD). The chronic inflammatory process of periodontitis and the host response provide the basis for the hypothetical association between periodontitis and CVD (6,7).

Oxidative stress is an imbalance between oxidants and anti-oxidants molecules in favor of the oxidants, leading to adisruption of redox signaling and control and/or molecular damage caused by the presence of reactive oxygen species (ROS) (8). The cells have a mechanism of defense systems against oxidative challenge. To maintain a steady-state of metabolites and functional integrity in the aerobic environment, antioxidant defense is organized to prevent, interceptionm and repair damage of tissues (8).

ROS has been identified in a number of normal processes including intracellular oxygen metabolism, immune-mediated pathogen attacks and signal transduction/gene expression pathways and this is also involved in a number of human pathological conditions. Normal cells protect themselves from ROS using both enzymatic and non-enzymatic antioxidants. For example, superoxide dismutase converts superoxide to molecular oxygen or hydrogen peroxide. Under certain circumstances, protective mechanisms can be inefficient at handling radicals/ROS, resulting in ‘oxidative stress’ (9). Several differentially localized and expressed enzyme systems contribute to ROS formation, including the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, nitric oxide (NO) synthases, cytochrome P450 monoxygenases, and xanthine oxidase (10). Some biomarkers are used to indicate oxidative stress like carbonyls for protein damage, 8-OHdG for DNA damage, and isoprostanes for lipid peroxidation.

This review focuses on the role of reactive oxygen species in the relationship between periodontitis and the development of cardiovascular diseases.

PERIODONTAL DISEASE AND ROS

Some evidence shows that oxidative stress is implicated in the pathogenesis of many systemic and oral diseases such as periodontal disease (11). Oxidative stress by-products, including lipid peroxidation, protein carbonyl levels and antibodies against ox-LDL (Ox-LDL), are significantly higher in individuals with periodontitis than in healthy controls, indicating excessive ROS production that probably results from local inflammatory responses (12,13,14,15,16,17,18). Additionally, reactive species and enzymes can be detected in the gingival crevicular fluid (GCF) of periodontal patients and used to differentiate oxidative stress in aggressive periodontitis and chronic periodontitis (CP) (19,20). GCF Malondialdehyde (MDA) levels were significantly higher in a generalized aggressive periodontitis (GAgP) group than in chronic periodontitis (CP) and control groups. Antioxidants such as superoxide dismutase (SOD), melatonin and glutathione have been investigated in human GCF. Patients with GAgP and CP present lower levels of SOD and melatonin than patients without periodontal disease (21,22).

Some studies have shown that biomarker levels of oxidative stress in periodontitis patients are different from those of periodontal healthy subjects (19,20). MDA, SOD and melatonin levels in the gingival crevicular fluid of patients with chronic periodontitis and generalized aggressive periodontitis were considered biomarkers for oxidative stress (21). They also demonstrated that GCF-MDA levels were significantly higher in a GAgP group than in CP and control groups, and were significantly higher in the CP group than in the control group. SOD and melatonin GCF levels were significantly higher in a control group than in GAgP and CP groups and were significantly lower in a GAgP group than in a CP group. Another study, found higher levels of SOD serum and glutatione in a healthy group than in other groups. Post-treatment levels of SOD were statistically higher than pre-treatment levels in a periodontitis and gingivitis group (22).

Interestingly, the reduction in inflammatory levels caused by periodontal disease treatment changes the redox state of the patients. Scaling and root planing (SRP) change the total antioxidant status (TAS) and SOD activity in the saliva of periodontally compromised patients. TAS was higher in the saliva of patients with severe chronic periodontitis than in healthy or gingivitis control patients before SRP. SOD activity in periodontitis patients was lower than in the control during the experiment period (23). Similar results were obtained for serum and GCF. Periodontal therapy decreased SOD and TAS levels and improved antioxidant profiles in both GCF and salivary compartments (24,25). It is important to note that periodontal therapy not only changes SOD concentration but also intereferes with SOD activity. Patients with chronic periodontitis had higher mean SOD activity than that of control subjects. After therapy, median SOD levels in serum and saliva approached the median SOD level in a control group, indicating that non-surgical periodontal therapy significantly improves clinical parameters and restores previously increased SOD levels to normal in chronic periodontitis patients (26,27). In conclusion, periodontal disease changes the redox status of the patient.

THE IMPORTANCE OF NADPH OXIDASE IN CVD DISEASE

Evidence showing the importance of vascular NADPH oxidase activity supports the relationship between ROS and CVD. Seven isoforms of NADPH oxidases are expressed in mammals: Nox1, Nox2, Nox3, Nox4, Nox5, Duox1 and Duox2. Four of these (Nox1, Nox2, Nox4 and Nox5) are most commonly expressed in vascular cells (10). Under physiologic conditions, vascular NADPH oxidases have a relatively low levels of constitutive activity. However, enzyme activity can be increased both acutely and chronically in response to stimuli such as inflammatory cytokines (28), growth factors (29), hyperlipidemia and high glucose (30), which disrupt vascular homeostasis and result in pathology. Genetic heredity studies reinforce the importance of vascular NADPH oxidase in the vascular homeostasis. NADPH oxidase subunits polymorphism was associated with increased arteriosclerosis. In particular, the -930(A/G) polymorphism in the p22 phox subunit could be related to hypertension, confirming the importance of NADPH oxidase (31). Genetic hereditary deficiency of NADPH

oxidases, particularly Nox2 (gp91phox), occurs in humans with chronic granulomatous disease (CGD). These patients have lower markers of vascular aging and oxidative stress (32). Significantly, these patients have lower levels of atherosclerosis burden, underscoring the possible role of vascular NADPH oxidase in atherosclerosis (33).

PERIODONTAL DISEASE AND ATHEROGENESIS

Infectious agents, including periodontal bacteria, have been implicated in the a etiology of various vascular conditions via multiple mechanisms, including direct microbial invasion of endothelial cells, that leads to entry of bacteria or their products into the blood stream (34). Following injury, endothelial cells initiate a series of pro-inflammatory signals such as the release of chemokines, increased expression of cell adhesion molecules that promote attachment and transmigration of leucocytes into the vascular intima (35, 36).

Activated leucocytes that have migrated into the subendothelial space continue the inflammatory cycle through production of additional pro-inflammatory cytokines, reactive oxygen species (ROS) and the release of tissue proteinases that degrade the surrounding extracellular matrix (34).

Links between periodontitis and atherosclerosis would be predicted based on inflammatory mechanisms initiated by bacteria associated with periodontal lesions, locally or systemically, that then influence the initiation or propagation of the atherosclerotic lesion (37). It has been hypothesized that oxidative stress arising from periodontal lesions may be an important cause of systemic inflammation. Abundant evidence has shown that oxidative stress caused by periodontal disease is strongly associated with several inflammation-related systemic diseases such as cardiovascular disease, type-2 diabetes and chronic inflammatory lung disease (10, 38, 39, 40, 41, 42). At physiological levels, reactive oxygen species act as signaling molecules that regulate a wide range of processes in the cardiovascular system and contribute to the maintenance of cardiovascular homeostasis. In contrast, excessive and sustained increases in ROS generation play a pivotal role in the initiation, progression and clinical consequences of CVD. As previously shown, periodontal disease is associated with increases in oxidative stress biomarkers (43,44). Bacterial pathogens, antigens, endotoxins, and/or inflammatory cytokines from periodontal lesions in the oral cavity

have been proposed as mechanisms that increase ROS production, atherogenesis and thromboembolic events and thereby increase CVD risk (45,46,43). An intrinsic mechanism can explain the role of ROS in atherogenesis.

Specifically, low-density lipoprotein cholesterol (LDL) is slightly oxidized to modified LDL, which in turn stimulates smooth muscle cells and endothelial cells to produce monocyte chemoattractant protein-1 (MCP-1). Similarly, ROS increases the expression of ICAM-1 and VCAM-1 cell adhesion molecules and endothelial leukocyte adhesion molecules in endothelial cells (47,48). Further oxidation of LDL (OX-LDL) and MCP-1 promotes monocyte migration to subendothelial areas. Thus, monocytes differentiate into macrophages due to stimulus from the macrophage colony stimulating factor (M-CSF) released by endothelial cells. Macrophages generate enormous growth factors that lead to the proliferation of smooth muscle cells and synthesis of connective tissue that thickens vessel walls and results in the development and progression of atherosclerosis. In fact, excessive ROS production causes endothelial and smooth muscle dysfunction, which in turn leads to the progression of atherosclerosis (49,50).

NO and H2O2 produce contractions in aortic rings isolated from rats (51,52). ROS can also induce the formation of endothelin-1, a vasoconstrictor. Endotlhelin-1, in turn, can control ROS production as a feedback mechanism (53,54). ROS also participates in the mechanisms of smooth muscle contractions by increasing intracellular calcium and inducing muscle contractions. Supporting this assertion, superoxide anions (55,56), H2O2 (55,57) and OH increase intracellular Ca2+ in cultured vascular endothelial cells. These species can induce vascular contraction directly via endothelin-1 or by reducing the bioavailability of nitric oxide, a vasodilator (58,59). ROS would reduce the production of the vasodilator prostacyclin by damaging the endothelial and reducing the capacity of the cells to convert arachidonic acid to prostacyclin (60).

PERIODONTAL DISEASE AND HYPERTENSION

Hypertension plays a key role in the development of CVD events such as cardiac and renal failure, stroke and myocardial infarction (61). It is believed that chronic inflammation associated with periodontitis could have hemodynamic influences and therefore impact hypertension pathogenesis and progression (62), through increased

endothelial dysfunction and arterial stiffness. Hypertensive patients produce significantly more plasma H2O2 than do normotensive subjects. In fact, ROS production increases in the vascular smooth muscle cells of resistance arteries in hypertensive patients, which is associated with upregulation of vascular NADPH oxidase (63,64). Additionally, normotensive subjects with family histories of hypertension naturally produce more H2O2, suggesting that some genetic disorders could lead to elevated H2O2 production (65,66). Interestingly, oxygen free radical levels are heritable, implying possible genetic disorders (67).

Studies have shown that periodontal therapy in patients with severe periodontitis and hypertension had a positive effect on endothelial function (68). It was also demonstrated that periodontal treatment improved endothelial function and reduced markers of atherosclerosis in patients with CVD and /or diabetes (68,69,70).

Single session of intensive periodontal treatment triggered a substantial increases in oxidative stress (assessed by circulating ROS) followed by a progressive reduction up to one month after therapy (71).

CONCLUDING REMARKS

Current epidemiological data show associations between cardiovascular disease and periodontitis. These associations would be predicted based on inflammatory mechanisms initiated by bacteria associated with periodontal lesions, locally or systemically, including reactive oxygen species produced during chronic periodontal inflammation that induce vascular changes causing atherogenesis and hypertension.

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