Review article

UDC: 616.311.2-002-074
611.311-002-092:577.1
doi:10.5633/amm.2016.0409

OXIDATIVE STRESS IN THE PATHOGENESIS OF PERIODONTAL DISEASE

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Periodontal disease is a chronic inflammatory disease caused by gram-negative bacteria, characterized by gingival inflammation and alveolar bone resorption. In the pathogenesis of periodontal disease free radicals and oxidative stress play a significant role. Free radicals are frequently formed as metabolic by-products and their overproduction leads to cell damage and the development of oxidative stress. Antioxidants are substances that reduce the effects of free radicals and represent a specific defense that protects the organism from their harmful effects.

Polymorphonuclear leukocytes (PMNL) are the main immune cells in oral tissue, protecting it from the damaging effects of bacteria. Interactions of leukocytes with bacteria initiate various defensive biochemical and physiological processes that lead to the destruction of the pathogen, but also leading to the respiratory burst in PMNL, with consequential production of free radicals and local tissues damage. Free radicals cause lipid peroxidation in a tissue, DNA and protein damage, enzyme oxidation, stimulation of pro-inflammatory cytokines.

Antioxidants play an important role in the protection of oral tissues from the damaging effects of free radicals. The group of enzymatic antioxidants includes superoxide dismutase, oral peroxidase, catalase and glutathione peroxidase; while nonenzymic antioxidants include uric acid, albumin, vitamin C and glutathione.

Free radicals play an important role in the pathogenesis of systemic diseases and diseases localized in the oral tissues as well. An imbalance between the production of free radicals and salivary antioxidants may trigger oxidative stress the onset of which is suggested as a basis for the development of periodontal disease. *Acta Medica Medianae 2016;55(4):66-72.*

Key words: *periodontal disease, free radicals, antioxidants, oxidative stress*

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Introduction

Because of the role they play in the pathogenesis of periodontal disease, more attention has been paid recently to oxidative stress and free radicals. In biological systems, free radicals are mainly the products of oxygen: superoxide anion radical (O_2), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), perhydroxyl radical (OOH), alkoxy radical (RO), peroxyl radical (ROO). Free radicals are frequently formed in the cells in physiological processes as metabolic by-products. An antioxidant is any substance present in low concentrations in comparison with a substrate, which is oxidized, and that significantly delays or prevents its oxidation. They represent a specific shield against possible harmful effects of free radicals. According to their nature and mode of action, they are divided into enzymatic and non-enzymatic antioxidants (1, 2).

Oxidative stress is a condition that occurs when a prooxidant (free radical) overcome the mechanisms of antioxidant protection of an organism. Due to their being highly reactive compounds, free radicals are able to cause rapid oxidative modification of cellular and extracellular biomolecules such as proteins, carbohydrates, lipids and DNA (2).

Periodontal disease is a chronic inflammatory disease caused by gram-negative bacteria, characterized by gingival inflammation and alveolar bone resorption (3). In the occurrence of periodontal disease, the following three types of bacteria are particularly relevant: Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, and Bacteroides forsythus. Destruction of the connective tissue extracellular matrix is a defense response mechanism to the antigens in oxidative stress. Numerous studies indicate that the activation of bacterial enzymes and host enzymes, including proteases, metalloproteinases and glycosidases, represents the principal mechanism in the destruction of periodontal tissue (4-6).

Role of free radicals in periodontal disease

Periodontitis is a periodontal disease occurring as the result of imbalance between bacterial colonization of the mouth and host immune defense. Polymorphonuclear leukocytes (PMNL) are the main immune cells of oral tissue which protect it from bacteria-induced damaging effects. Interaction between leukocytes and bacteria initiates various defensive biochemical and physiological processes that lead to the pathogen destruction and to local tissues damage. Induced by pathogens and due to increased oxygen consumption, a respiratory burst occurs in PMNL, leading to an increased release of free radicals acting bactericidally. However, due to oxidative modification of biomolecules, local tissues are being damaged as well (7, 8).

The most adverse effect of free radicals is lipid peroxidation, which leads to the oxidation of polyunsaturated fatty acids in cell membranes. The final product of lipid peroxidation is malondialdehyde (MDA), a short-chain aldehyde, which is a biochemical marker of cell membrane oxidative damage (2).

Reactive oxygen species cause toxic tissue damage through DNA damage, lipid peroxidation, protein destruction (gingival proteoglycans and hyaluronic acid) (9), oxidation of important enzymes such as α1-antiprotease antitrypsin (10), stimulation of pro-inflammatory cytokines which are released by monocytes and macrophages (11).

DNA damage of periodontal tissues occurs as a result of DNA oxidative modification, which causes damage to the protein chains of nucleosome and base modification. Oxidative modification is most severe in the presence of metals with variable valence, due to formation of potent $OH^{\cdot}$ as the product of oxidation reaction. Addition of $OH^{\cdot}$ to guanine takes place very rapidly and formed 8-hydroxydeoxyguanosine (8-OHdG) is considered to be an indicator of oxidative DNA damage (12). Permanent oxidative DNA damage is the first step towards DNA mutation and aging (13).

Lipid peroxidation is the process of lipid oxidative damage. Cell membranes are targeted as the starting point of lipid peroxidation due to large amounts of lipids. The rupture of lysosomal membranes releases hydrolytic enzymes, leading altogether to vital cell disorders and eventually to apoptosis of the cell. Arachidonic acid metabolism through two basic enzymatic pathways (the cyclooxygenase and lipoxygenase pathways), leads to free radicals production. Host response to pathogens, which induce the formation of inflammatory molecules such as cytokines and prostanoids, is involved in the initiation and progression of periodontal disease. Numerous studies have shown that prostanoids, such as prostaglandin E2 (PGE2), have a role in the pathogenesis of periodontal diseases. Elevated levels of PGE2 were found in the gingival fluid of patients with periodontal disease. This marker is partly responsible for bone loss in periodontal disease. Obviously, prostaglandins are involved in the pathogenesis of this disease, which is supported by the data from some tests that non-steroidal inflammatory drugs are able to inhibit the disease progression (14). According to some recent studies, COX-2 plays a key role in the production of prostaglandins in periodontal disease, and a selective COX-2 inhibitor is equally effective as a non-steroidal anti-inflammatory drug in inhibiting the disease progression (15).

Protein degradation involves the activity of reactive oxygen species, leading to protein fragmentation and polymerization reaction, faster protease degradation of the modified protein, protein radical formation, protein complex formation of reactive oxygen species and formation of stable end-products of oxidatively modified proteins (carbonyl compounds) (16).

The enzyme α1-antitrypsin has a distinctive antiprotease activity. Biological role of this protein is the neutralization of lysosomal enzymes collagenase and elastase in phagocytosis. Due to their low molecular weight, these proteins can not pass through the capillary walls into the tissue fluid to bind proteolytic enzymes and to transfer them further in the circulation of α2-macroglobulin. Oxidation of α1-antitrypsin abolishes its inhibitory roles on proteases and proteolytic ferments action on chymotrypsin, renin, kallikrein, plasmin, urokinase, thrombin, elastase, and collagenase (1).

Cytokines are inflammatory mediators produced by non-lymphocytic cells such as macrophages, fibroblasts, and keratinocytes. Proinflammatory cytokines IL-1, IL-6, TNF-α and TNF-β play a central role in the destruction of periodontal tissues (17).

Activation of the transcription factor NF-kB reactive oxygen species is indirectly induced by the release of bacterial lipopolysaccharide, IL-1, and TNF-α. The cytokines IL-1 and TNF-α are capable of activating NF-kB via protein kinase C and other kinases, which phosphorylate the inhi-

bitor of NF-kB (I-kB), cytoplasmic part of the complex, by which they release free NF-kB. Free NF-kB diffuses from the cytoplasm and binds to the place of structural genes promoter and stimulates the transcription of mRNA for proinflammatory cytokines (18).

Many reactive oxygen species have an extremely short half-life, but they cause significant tissue damage by creating the free radical chain reaction.

Exogenous sources of free oxygen radicals are smoking, ionizing radiation, heat, ultrasound, ozone, radiation, exhaust gases, infection, excessive exercise, trauma, drugs, while endogenous sources include the products of metabolic pathways, and immune and connective tissue cells (19, 20). The first endogenous sources are by-products of metabolic pathways in which superoxides are formed by way of electron release from the mitochondrial electron transport system. Cell metabolism involves oxygen consumption and its use in glycolysis, whereas pyruvate and adenosine triphosphate (ATP) are being produced within the mitochondria. Reactive oxygen species damage the mitochondrial DNA, which is considered an important process in certain chronic diseases and aging. Due to the proximity with created reactive oxygen species and due to the ability of histone proteins to bind radicals easily, mitochondrial DNA is much easier to damage compared to nuclear DNA (21). Another endogenous source is the functional generation from defense and connective tissue cells, such as phagocytes, fibroblasts, and osteoblasts. Chronic inflammatory conditions are accompanied by increased oxidative stress because of the role of phagocytes during the respiratory explosion and destruction of bacteria, which creates large amounts of reactive oxygen species. Respiratory explosion is characterized by increased oxygen consumption, peroxidase production, H_20_2 production and increased glucose metabolism. Along with superoxide and H_20_2, hydroxyl radical, singlet oxygen, hypochlorous acid, and chloramine radical anion are generated in phagocytes, being the reason why the respiratory burst exhibits toxic effects on the host tissue as well (22).

The most important matrix metalloproteinases (MMP) are neutrophil MMP-8 (collagenase-2) and MMP-9 (gelatinase-B). MMP-8 degrades interstitial collagen, while MMP-9 is a gelatinolytical enzyme which degrades extracellular matrix proteins, including collagen type IV, a basement membrane protein. Both matrix metalloproteinases are the enzymes of gingival fluids and saliva that degrade collagen, especially during the inflammatory processes in patients with gingivitis and periodontal disease. These enzymes stimulate fibroblasts and macrophages to produce a neutral metalloprotease procollagenase. Fibroblasts mainly produce MMP-1 (collagenase-1), MMP-13 (collagenase-13), MMP-2 (gelatinase-2), MMP-3 (stromelysin-1) and MMP-14. Collagenase-type MMP-1, which stimulates fibroblasts, was detected in the

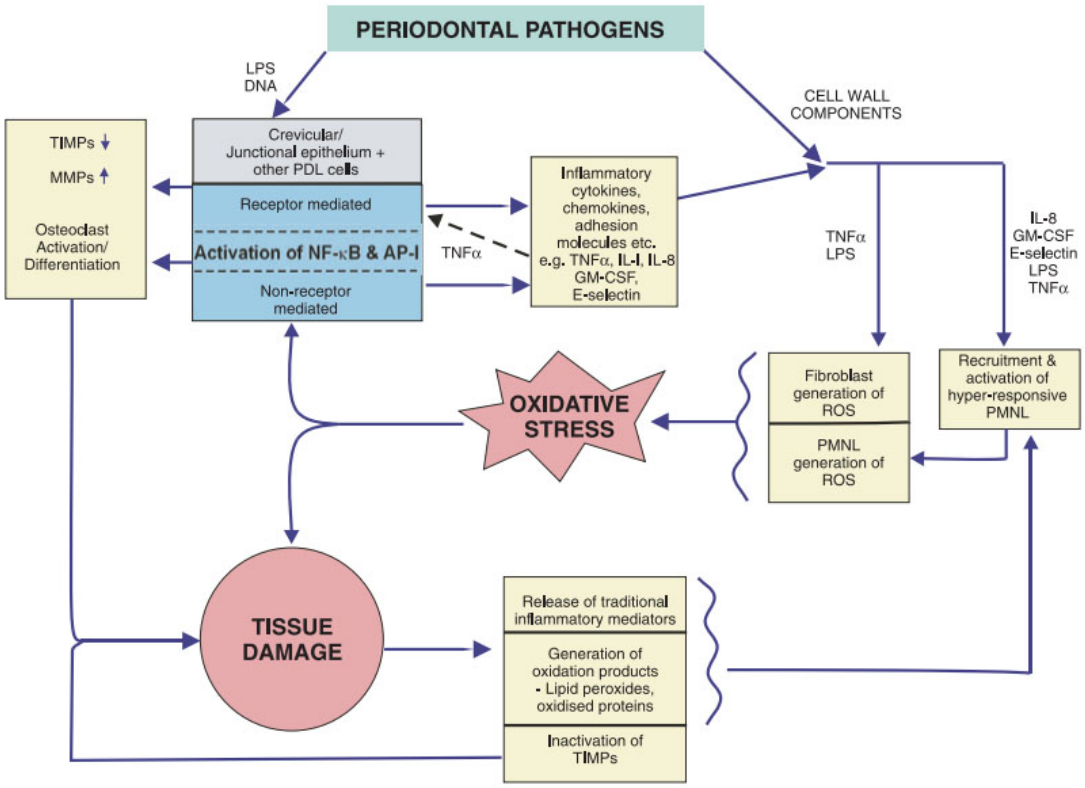

Figure 1. Oxidative stress in the pathogenesis of periodontal diseases(21)

gingival fluid of patients with periodontal disease (Figure 1) (15).

Role of antioxidants in periodontal disease

Antioxidants play an important role in the protection of oral tissues from the damaging effects of free radicals. They are found in the saliva, whose primary role is the maintenance oral homeostasis, or the preservation of a permanent biochemical oral tissue composition. There are enz-ymatic and non-enzymatic antioxidants in the saliva. Enzymatic antioxidants are superoxide dismutase, oral peroxidase, catalase and glutathione peroxidase, while non-enzymatic antioxidants include uric acid, albumin, vitamin C and glutathione (23, 24). The activity of superoxide dismutase (SOD) is increased in patients with recurrent aphthous stomatitis, and it is a host mechanism of adaptation to unfavorable conditions (2).

Approximately 80% of oral peroxidase is salivary peroxidase, while myeloperoxidase accounts for the remaining 20%. Salivary peroxidase is predominantly secreted by the parotid gland. The role of salivary peroxidase is the reduction of hydrogen peroxide (H_2O_2), a product of oral bacteria metabolism in the presence of thiocyanate ions (SCN-). Salivary peroxidase catalyzes the reaction of H_2O_2 and SCN-, which leads to the formation of thiocyanic acid and its salts, demonstrating an antibacterial effect. Myeloperoxidase is a haem-dependent enzyme that can be found in leukocytes and that forms an enzyme-substrate complex in the presence of H_2O_2. This complex oxidizes iodides and chlorides generating toxic products. Oxidation of chloride ions with the complex produces hypochlorus acid (HOCL). Hypochlorous acid has strong antioxidant characteristics and acts bactericidally (25-27).

Catalase is an enzyme present mostly in peroxisomes. They catalyse degradation of H_2O_2 to water and molecular oxygen. Enzyme activity increases with an increased production of H_2O_2, because they actively participate in tissue detoxification. Increased activity of catalase, as well as of superoxide dismutase, is observed in patients with recurrent aphthous stomatitis (2).

Uric acid has an important role in the total blood plasma antioxidant capacity. Uric acid is suggested to be present in the saliva in the form of urates, uric acid salts, being transported by passive diffusion from the circulation into the saliva. Uric acid is considered a major antioxidant of saliva, because it takes part in about 70% of the total salivary antioxidant capacity. Its significant role in reducing and neutralizing free radicals should be mentioned, as well as in the formation of complexes with metal ions of variable valence, because it reduces the oxidation potential by preventing the entry of iron in the Fenton reaction and the production of highly reactive hydroxyl radicals. Urates can directly remove singlet oxygen, hydroxyl anion and peroxyl radicals. Urates also bind transition metals that can be responsible for lipid peroxidation. Several studies have shown that this antioxidant is found in lower concentrations in the saliva of patients with periodontal disease compared to the healthy patients. This is explained by the fact that uric acid in periodontal disease is largely spent to neutralize free radicals, the concentration of which is significantly increased in these pathological conditions (2).

Albumin is a plasma protein that is synthesized in the liver and that reaches saliva by blood filtration. In terms of increased vascular permeability that occurs in the process of tissue damage, extravasation of albumin, transferrin and ceruloplasmin can contribute to a better antioxidant protection at the place of local inflammatory reaction. Recent studies have shown that the infusion of albumin in patients with oxidative damage have beneficial effects that can be attributed to strong antioxidant capacity of human serum albumin (HSA). The antioxidant characteristics are related to: 1. the native form of albumin; 2. chemically modified form of HSA; 3. commercial human serum albumin (28).

1. Native form of albumin containing 6 methionine and 35 cysteine residues that participate in the formation of 17 disulfide bonds. In a cysteine molecule, Cys-34 is the only free residue. Antioxidant activity of HSA results from its structure, which is reflected in the existence of multiple binding sites for the ligand and the possibilities for free radical neutralization.

2. Human serum albumin binds various molecules, including fatty acids, drugs, hormones and metal ions. Due to that, free metal ions with transitional valence, mainly iron and copper, participate in the propagation of free radical reactions, formation of a metal-albumin complex represents a kind of antioxidant protection. Albumin has a high affinity to bilirubin which binds to Lys-240 which directly inhibits lipid peroxidation

In physiological conditions, a third of the albumin pathway is made of disulfides combined with cysteine, homocysteine or glutathione, and the other two thirds of HSA is in a reduced form with a free thiol in the Cys-34 residue, known as mercaptalbumin. Its antiradical activity is attributed to the Cys-34 residue, since it has the capacity to neutralize hydrogen peroxide, peroxynitrite, superoxide anion or hypochlorous acid. Albumin exposed to oxidative stress and nitrosative stress is converted into sulfenic acid (HSA-SOH) or nitroso-albumin (HSA-S-NO). These intermediates can be reduced under the impact of glutathione or free cysteine into mercaptalbumin. Human serum albumin is considered to be the major extracellular molecule responsible for the maintenance of redox conditions in the plasma (Figure 2) (28).

Glutathione is a tripeptide present in cells in reduced and oxidized forms. A sufficient quantity of glutathione is required for normal cell functio-

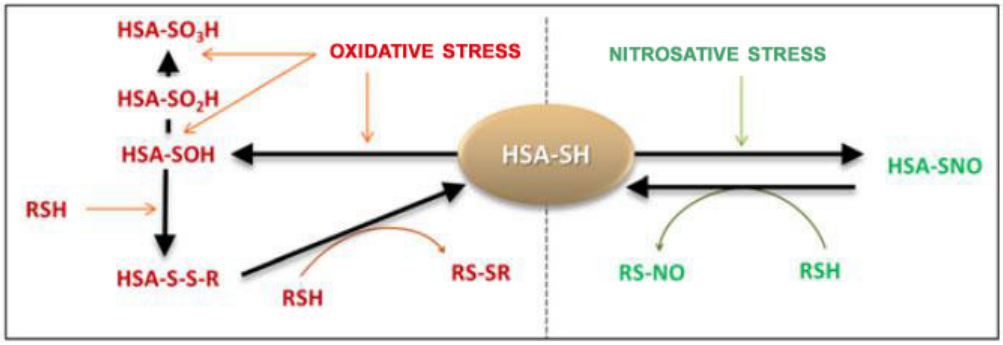

Figure 2. Albumin under the effect of oxidative and nitrosative stress(28)

ning, as well as for the glutathione peroxidase activity. This enzyme oxidizes glutathione, leading to the H_2O_2 degradation. Studies have shown that smoking is one of the causes of reduction of glutathione concentration in the saliva, which has the effect of reducing the total antioxidant capacity of the saliva (1, 2).

One of the most important markers of oxidative DNA damage is 8-OHdG. The concentration of 8-OHdG in the saliva of patients with periodontal disease is higher than in the saliva of healthy patients, but it significantly decreases after treatment (29).

Several studies showed a significant decrease in the total saliva antioxidant capacity in patients compared to the groups of healthy subjects. This proves that periodontitis is associated with oxidative stress and this can be one of the causes or driving forces of a more dynamic increase of oxidative stress. Furthermore, smoking increases the production of free radicals and is a significant factor of further tissue damage in periodontal disease (30).

The obtained results suggest that oxidative stress and free radicals play an important role in the pathogenesis of not only system diseases, but also the diseases localized in the oral cavity, such as periodontal disease. Saliva and its antioxidants are of utmost importance in oral tissue defense against the damaging effects of free radicals. An imbalance between free radicals production and salivary antioxidants could result in oxidative stress, which can be the basis for the development of periodontal disease.

Acknowledgements

This paper was supported by the grant from the Serbian Ministry of Education and Science, No. 41018.

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Revijalni rad

UDC: 616.311.2-002-074

611.311-002-092:577.1
doi:10.5633/amm.2016.0409

OKSIDATIVNI STRES U PATOGENEZI PARODONTOPATIJE

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Parodontopatija predstavlja hronično inflamatorno oboljenje izazvano gram negativnim bakterijama koje karakterišu upalni procesi na gingivi i alveolarna resorpcija kostiju. U patogenezi parodontopatije značajnu ulogu imaju slobodni radikali i oksidativni stres. Slobodni radikali učestalo se stvaraju kao nusprodukti metabolizma, a njihovo prekomerno stvaranje dovodi do oštećenja ćelija i nastanka oksidativnog stresa. Antioksidansi su supstance koje umanjuju delovanje slobodnih radikala i predstavljaju specifičnu odbranu koja štiti organizam od njihovog štetnog uticaja.

Polimorfonuklearni leukociti (PMNL) predstavljaju glavne odbrambene ćelije tkiva usne duplje koje je štite od destruktivnog delovanja bakterija. Interakcijom leukocita i bakterija pokreću se različiti odbrambeni biohemijski i fiziološki procesi koji dovode do uništenja patogena, ali istovremeno dolazi i do respiratorne eksplozije u PMNL koji dovode do produkcije slobodnih radikala i oštećenja lokalnog tkiva. Slobodni radikali izazivaju lipidnu peroksidaciju tkiva, DNK i proteinska oštećenja, oksidaciju enzima, stimulaciju proinflamatornih citokina.

Antioksidansi imaju značajnu ulogu u zaštiti oralnog tkiva od štetnog delovanja slobodnih radikala. U enzimske antioksidanse ubrajamo superoksid dizmutazu, oralnu peroksidazu, katalazu i glutation peroksidazu, dok u neenzimske mokraćnu kiselinu, albumin, vitamin C i glutation.

Slobodni radikali imaju važnu ulogu u patogenezi ne samo sistemskih, nego i oboljenja lokalizovanih u oralnoj sredini. U slučaju disbalansa između produkcije slobodnih radikala i salivarnih antioksidanasa, može doći do oksidativnog stresa koji predstavlja osnovu za nastanak parodontopatije. *Acta Medica Medianae 2016;55(4):66-72.*

Ključne reči: *parodontopatija, slobodni radikali, antioksidansi, oksidativni stres*