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INVITED REVIEW

The role of oxidative stress in the interaction of periodontal disease with systemic diseases or conditions

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ABSTRACT

Periodontal diseases are among the most common chronic infectious and inflammatory diseases in the world. Bacteria in the dental biofilm trigger host response and the activated inflammatory system plays a major role in periodontal tissue destruction. Alterations in the oxidative stress-mediated inflammatory pathways could be one of the possible potential mechanisms in periodontal tissue breakdown.

Local or systemic infectious diseases, inflammatory diseases, such as periodontitis, obesity, type II diabetes, vascular diseases and other inflammatory conditions are associated with an increased risk of oxidative stress. A linear relationship between oxidative stress, periodontal disease and systemic disease is likely to exist.

The available literature clearly highlights the increased oxidative stress in periodontal disease that is associated with different systemic diseases and/or conditions. Further studies are needed to elucidate the role of oxidative balance in periodontal diseases and systemic disease interactions.

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INTRODUCTION

Periodontal tissues, known to be among the most common chronic infectious and inflammatory diseases in the world, consist of four components: gingiva, periodontal ligament, cementum and alveolar bone. The major causes of periodontal diseases are Gram-negative, anaerobic and microaerophilic bacteria that colonize the sub-gingival area, consequently leading to local as well as systemic elevations of pro-inflammatory prostaglandins and cytokines, and resulting in tissue destruction. Periodontitis is characterized by gingival inflammation, alveolar bone resorption and attachment loss [1]. Immune responses are activated upon stimulation by bacteria or their toxins present in the dental biofilm. However, the exact mechanisms of the molecular recognition and signaling transduction of host immune-inflammatory responses in periodontitis remain obscure [2].

Alterations in the oxidative stress-mediated inflammatory pathways could be one of the possible potential mechanisms in periodontal tissue breakdown (Figure 1). Oxidative stress represents an increase in the production of oxidants and/or a decrease in antioxidants, *i.e.* an oxidant/antioxidant imbalance. Oxygen is an essential element of aerobic life, but when partially reduced, it generates reactive oxygen species (ROS) [3. An unbalance between radical and non-radical ROS can damage periodontal tissues by a variety of mechanisms, including peroxidation of lipid membranes, protein inactivation, as well as stimulation of cytokine production [4, 5]. Large amounts of pro-oxidants are produced in the prolonged inflammatory responses, which occur in the context of gingivitis and periodontitis [6]. In periodontal diseases, ROS are produced during the inflammatory stimulation of the polymorphonuclear neutrophils (PMNL) and phagocytosis [7-9]. Mediators released by PMNLs also have adverse effects on periodontal tissue structures through the oxidative stress [10, 11. On the other hand, it have to be taken into consideration that oxidative processes contribute to progression of various diseases rather than acting as an etiological factor [12].

Oxidative damage to lipids, proteins, and nucleic acids can be detected in saliva. Established salivary markers of oxidative stress include thiobarbituric acid reactive substances (TBARS) as a marker of lipid peroxidation, 8-hydroxy-29-deoxyguanosine (8-OHdG) as a marker of oxidative damage of DNA, advanced oxidation protein products (AOPP) as a marker of protein oxidation and advanced glycation end products (AGE) as a marker of protein glycation and carbonyl stress that is tightly connected with oxidative stress [13-15, 16]. Despite their high biological variability the salivary concentrations of those markers can provide valuable information about oral health [17, 18].

Several studies have shown that periodontitis is associated with functionally activated PMNLs exhibiting increased ROS production. Patients with periodontal diseases have been reported to express higher oxidative stress, which is likely to be related with a hyper-inflammatory response [12, 19, 20]. Moreover, periodontal treatment has been reported to successfully reduce the levels of oxidative stress marker such as 8-OHdG [21]. Hydroxyl radical damage was elicited on DNA bases assessed by measuring 8-OHdG levels [22]. Several studies have indicated that increased 8-OHdG levels in body fluids, including saliva, constitute a reliable biomarker of oxidative stress [23-30]. Higher salivary and gingival crevicular fluid levels

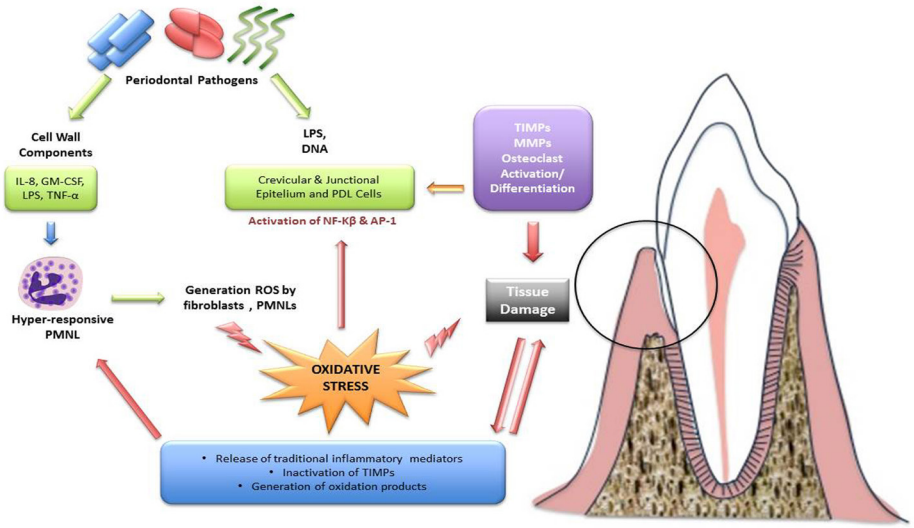

Figure 1. Possible oxidative stress-mediated inflammatory pathways related in periodontal tissue breakdown. LPS, lipopolysaccharide; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-8, interleukin-8; TNF-α, tumor necrosis factor-alpha; PDL, periodontal ligament; NF-κβ, nuclear factor-kappa B; ROS, reactive oxygen species; PMNL, polymorphonuclear leukocyte; TIMP, tissue inhibitor of metaloproteinases; MMP, Matrix metalloproteinase.

of 8-OHdG were detected in patients with advanced periodontal destruction, and they decreased after periodontal treatment [24-26, 31-34]. In this line, earlier studies have shown that salivary [26, 34 and gingival crevicular fluid [32] 8-OHdG levels correlate with clinical parameters of periodontal tissue destruction, particularly in chronic periodontitis [26]. Dede *et al* 32] collectively indicate that salivary levels of 8-OHdG are increased in patients with periodontitis compared with periodontal healthy individuals. Significant positive correlations have been reported between salivary levels of 8-OHdG and clinical periodontal status [26, 28, 29, whereas some other studies did not find significant correlations [24, 25].

The balance between ROS and the antioxidant defense systems is postulated as one of the mechanisms responsible for periodontal tissue breakdown [7. Salivary TBARS were higher in chronic periodontitis patients than in controls and it was speculated that lipid peroxidation in periodontitis might be caused by increased production of ROS in men and by decreased antioxidant status in women [35]. TBARS is a measure of ROS-induced lipid peroxidation [36], and chronic periodontitis patients are shown to exhibit higher levels of TBARS than periodontal healthy individuals [20, 37]. Periodontitis-affected gingival tissue displays significantly higher TBARS expression compared to healthy tissue; a finding that could implicate oxidative stress as a biomarker for the disease [20]. Accordingly, TBARS levels in plasma, erythrocytes or erythrocyte membranes were higher in patients with periodontitis than in healthy subjects [37].

The oxidative damage that characterizes oxidative stress has been linked to various inflammatory and neurodegenerative diseases, connective tissue diseases and aging processes, among other causes. Conditions in which oxidative stress has been implicated include periodontitis, obesity, type II diabetes mellitus (DM), vascular diseases and adverse pregnancy outcomes [38]. Recent studies indicate that this biochemical phenomenon can be found in the pathologic basis of chronic inflammatory processes, conditioning their evolutionary state [39, 40. The main target of ROS is polyunsaturated fatty acids (PUFA) in tissue lipids. Lipid oxidation leads to a number of secondary products; these by-products are mostly aldehydes that may aggravate oxidative damage [41]. Local or systemic infectious diseases, inflammatory diseases, such as rheumatoid arthritis, Sjogren's syndrome, Lupus Erythematosus and other inflammatory conditions are associated with an increased risk of oxidative stress [42, 43]. So, o linear relationship between oxidative stress, periodontal disease and systemic disease is likely to exist (Figure 2) [42, 43].

DIABETES MELLITUS AND PERIODONTAL DISEASES

Diabetes mellitus, a complex metabolic disorder characterized by prolonged hyperglycemia, has long been recognized as one of the leading causes of morbidity and mortality globally [44]. Diabetes mellitus is caused by a deficiency in insulin production or an impaired use of insulin. Patients with type II DM are 2.8 times more likely to have destructive periodontal disease [45] and 4.2 times more likely to have significant alveolar bone loss [46] compared to systemically healthy subjects. Periodontal disease was proposed to be the sixth complication of diabetes mellitus [47] with evidence showing a correlation between poor glycemic control and worse periodontal health [48-50].

Reznick *et al* [51] analyzed serum and salivary composition and oxidative stress markers in 20 patients with type I DM and 12 healthy control subjects. They reported that uric acid content and total antioxidant values in unstimulated whole saliva samples were increased in patients with diabetes mellitus compared to the healthy controls; however, the differences were significant only for total antioxidant status. Ben-Zvi *et al* [52] showed increased oxidative stress burden in serum and saliva of diabetes mellitus patients. Moreover, the redox state of the saliva from patients with diabetes

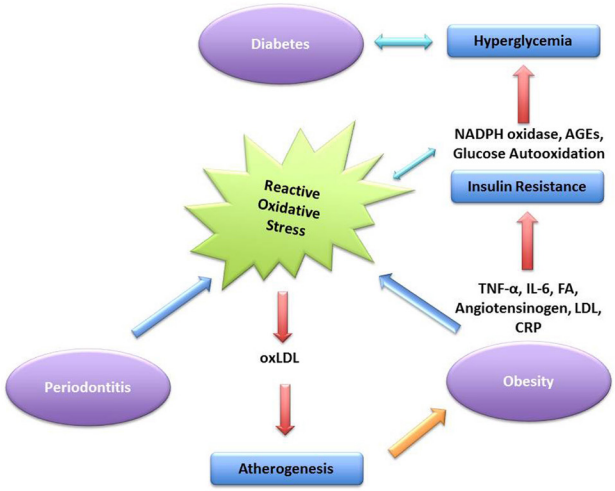

Figure 2. Relationship between oxidative stress, periodontal disease and systemic diseases. NADPH, nicotinamide adenine dinucleotide phosphate; AGE, advanced glycation end products TNF-α, tumor necrosis factor-alpha; IL-6, Interleukin-6; LDL, low density lipoprotein; CRP, C-reactive protein; oxLDL, oxidized low density lipoprotein.

mellitus differed from that of the normoglycemic control group [53]. Gumuş *et al* 54] evaluated sixteen patients with type I DM, 25 patients with type II DM and 24 systemically healthy patients and found that the mean salivary reduced-glutathione concentration was lower in patients with type I DM than in the other two groups. Oxidized glutathione levels in the patients with type I DM were significantly lower than those in the systemically healthy group. In both of the diabetic groups, salivary reduced-glutathione levels correlated positively with the probing depth, and total antioxidant capacity correlated with salivary flow rate.

Lipid peroxidation evaluated by malondialdehyde in plasma and gingival crevicular fluid was found to be increased in diabetes and may be related to modulation of inflammatory response. Significant correlations between lipid peroxidation markers and clinical periodontal parameters suggest a direct relationship between these two entities [55]. Several studies have shown the relationship between diabetes and periodontal disease [56-60] and correlations between glycated hemoglobin (HbA1c), and periodontal parameters [61-65]. Moreover, there exist increasing evidence of the deleterious effects of AGEs on the pathogenesis [66] and progression of periodontitis [67]; this effect could be mediated through the highly expressed receptors for AGE (RAGE) in periodontal tissues [68].

Metabolic syndrome encompasses risk factors, including insulin resistance, abdominal obesity, atherogenic dyslipidemia, essential hypertension and hyperglycemia, which contribute development of atherosclerosis, cardiovascular disease and diabetes 69]. Metabolic syndrome is related with poor anti-oxidant status and increased oxidative stress [70, 71]. Moreover, adults with metabolic syndrome have tendency for higher plasma concentrations of oxidized-low density lipoprotein (ox-LDL)-cholesterol and urinary 8-iso-prostaglandin compared with individuals without metabolic syndrome [72]. On the contrary, there are also studies reporting similar levels of oxidative stress markers in patients with metabolic syndrome and systemically healthy controls [73]. AGEs show negative correlation with parameters of metabolic syndrome such as body mass index (BMI), blood pressure, triglyceride, HbA1c and an insulin resistance index 74].

Free radicals associated with increased oxidative stress may trigger local and/or systemic inflammation and create risk for development of metabolic syndrome [75-77]. Pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α, are activated via activation of nuclear factor-kappa B (NFκB) because of ROS activity in patients with periodontitis [7]. Periodontitis is related with chronic systemic inflammation and oxidative stress [78, 79] and nonsurgical periodontal treatment helps to decrease oxidative stress markers and control the inflammatory status in patients with metabolic syndrome [80. Borges and coworkers found that the prevalence of metabolic syndrome was higher among individuals with advanced periodontitis (66.7%) than in periodontal healthy individuals (48.8%) [20]. Periodontitis has been found to be directly related with metabolic syndrome in terms of larger waist circumference, decreased high density lipoprotein (HD)-cholesterol and higher fasting glucose levels, which are associated with probing depths [81, 82].

PREGNANCY AND PERIODONTAL DISEASES

Pregnancy is a physiological condition with affected lipid profile parameters [83] and increased oxidative stress [84]. Increased ROS production beyond the mother's antioxidant potential leads to oxidative stress, which can affect the health of both the mother and fetus, leading to adverse pregnancy outcomes [84]. Therefore, periodontal disease could contribute to increased local and systemic burden of ROS in mothers. It has also been shown that weight gain during pregnancy is associated with an increase in TBARS [85]. Gumus *et al* 86] demonstrated lower salivary post-partum TBARS levels compared to pregnant women. When considering the periodontal health status, no association was found between clinical measurements and TBARS salivary levels in pregnant and postpartum women. Moreover, non-pregnant women exhibited lower levels of 8-OHdG than pregnant or postpartum women [86]. This finding suggests that pregnancy as well as delivery increase ROS in the oral environment, as determined by higher salivary levels of 8-OHdG. In another study where urine 8-OHdG was measured once during 24-26 weeks of gestation, its concentrations were higher in women, who delivered a low birth-weight infant, although there was no association with preterm birth [87]. In pre-eclamptic women, gingival crevicular fluid and serum glutathione peroxidase (GPx) activities were lower in the presence of periodontal disease [88]. Gumus *et al* 86] found also that GPx activity in saliva was low during pregnancy, whereas increased again after delivery. The increase in the antioxidant levels immediately after birth may be a compensatory mechanism, particularly after a long period of exposure to increased ROS during pregnancy.

There was no association between periodontal disease status and salivary GPx levels in pregnant women. However, there was a positive correlation with probing depth, bleeding on probing and total bacterial counts in postpartum and non-pregnant women [86].

CARDIOVASCULAR DISEASES AND PERIODONTAL DISEASES

Cardiovascular diseases are among the major global health problems with an increasing incidence in the developing countries. Atherogenesis and endothelial dysfunction are the determining factors in the onset and progression of cardiovascular diseases. There are other confounding factors such as hypercholesterolemia, oxidative stress, diabetes, cigarette smoking and infection that can increase expression of adhesion molecules and cause endothelial dysfunction. Cross-sectional studies and systematic reviews have shown an association between the higher risk for cardiovascular diseases and risk for periodontitis [89-92]. D'Aiuto and coworkers reported that periodontal therapy decreases systemic inflammation and improves endothelial function [93]. In an experimental study in rats, hydrogen-rich water intake has been suggested to decrease serum ox-LDL levels and aortic oxidative stress and thereby prevent lipid deposition induced by periodontitis in the rat aorta [94].

In another experimental study in rats, cardiac effects of ligature-induced periodontitis in both normotensive and nitric oxide-deficient hypertensive rats have been investigated. Periodontitis-induced alveolar bone loss was significantly diminished in the nitric oxide-deficient hypertensive rats. Nitric oxide is an important mediator of alveolar bone loss and it also contributes to cardiac effects of periodontitis [95]. Periodontitis is a likely factor in the etiology of cardiovascular diseases and a bidirectional interaction seems also to be possible [90, 94, 96-99]. Lipid peroxidation is also involved in the pathogenesis of cardiovascular diseases and it may be the key factor that explains relationship between atherosclerosis and periodontitis [100-103].

OBESITY AND PERIODONTAL DISEASES

A person is defined as obese if the BMI is higher than 30 kg/m^2. Obesity has been shown to be associated with several chronic diseases including periodontal diseases [104]. Increased levels of pro-inflammatory cytokines in obesity lead to increased oxidative stress by overproduction of reactive oxygen and nitrogen species by macrophages and monocytes [105]. Thus, oxidative stress may be responsible for the possible interaction between obesity and periodontal disease [8]. Lower total antioxidant capacity and higher oxidative stress index values have been reported in gingival crevicular fluid and serum of obese women [106]. Moreover, gingival crevicular fluid total antioxidant capacity values showed a negative correlation with body mass index, whereas gingival crevicular fluid oxidative stress index was positively correlated with fasting insulin and LDL-cholesterol levels. Clinical periodontal indices showed significant correlations with BMI, insulin and lipid levels, and also with oxidative status markers [106]. Perlstein and Bissada [107] speculated that obese rats had a more pronounced inflammatory response to plaque accumulation and higher alveolar bone resorption than non-obese rats. Another experimental study in rats concluded that the combination of these two diseases caused an increase in the expression of pro-inflammatory mediators from hepatocytes and adipose tissue [108]. Pro-inflammatory cytokines and the oxidative stress can be the possible link between obesity and periodontal diseases [109-112].

CONCLUDING REMARKS

The available literature clearly highlights the increased oxidative stress in periodontal diseases that is associated with different systemic diseases and/or conditions. Yet, the differences in sample sizes, sampling and processing methods and study protocols, sensitivity/specificity of the immunoassays used as well as possible individual variations between the study populations may play a modifying role on the oxidative stress-related biomarker levels obtained in different studies. Moreover, oxidative stress-related biomarkers could be differentially regulated during disease remission/exacerbation periods. Further studies are needed to better understand the role of oxidative balance in periodontal diseases and systemic disease interactions.

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