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MINI REVIEW

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Oxidative stress in relation to chronic periodontal disease

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ABSTRACT

Chronic periodontal disease is a relatively common inflammatory disease which, untreated, can lead to premature tooth loss. Many factors, including oxidative stress, play a role in the etiology of this disease. Various markers of oxidative stress have been evaluated in saliva and sulcular fluid between patients with chronic periodontal disease and healthy people in many studies, with some current studies suggesting changes in both the local and systemic redox equilibrium of patients. Antioxidant therapy seems to have its place in the therapeutic options for patients with gingivitis and periodontal disease. There has been evidence of positive effects in treatment with antioxidants along with scaling and root planning.

In the future, we anticipate that the determination of the selected antioxidant markers could be helpful in the diagnosis of chronic periodontal disease or evaluating therapy.

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Introduction

Chronic periodontal disease is a relatively common inflammatory disease, resulting in the loss of supportive tissues of the teeth. The main cause of this disease is the presence of a microbial plaque containing a concentration of paropathogenic bacteria. These bacteria initially cause inflammatory changes in the gingiva. If treatment is not started in time, the changes caused by inflammatory conditions move into deeper structures and consequently lead to bone damage [1,2]. Particular symptoms of chronic periodontal disease are gingivitis, alveolar bone resorption, and the presence of periodontal chambers. In addition, there are other unconventional symptoms such as tooth movement and pain. Ultimately, this disease leads to premature tooth loss [2].

The body responds to the inflammatory changes occurring as a result of periodontal disease. In particular, polymorphonuclear cells release reactive forms of oxygen which react with the endogenous antioxidant system. However, if reactive oxygen species (ROS) overwhelm the capacity of the antioxidant system, oxidative stress occurs as a detrimental biological effect [3]. Periodontal diseases are the main cause of adult tooth loss due to ongoing infectious and inflammatory processes.

It is proven that oxidative stress is responsible for over 100 inflammatory diseases such as rheumatoid arthritis, diabetes, and many others, and also has adverse effects on ongoing pregnancy [4]. In addition, several previous studies describe a certain relationship between oxidative stress and chronic periodontal disease [3,5]. By treating inflammatory gingival disease, there was a decrease in the production of the pro-inflammatory cytokine IL-1 elevated in response to the presence of pathogens of periodontium and their products [6] or tooth extraction, which also led to a decrease in inflammatory markers (C-reactive protein, leucocyte count) in the blood [7]. The rate and course of periodontal disease is influenced not only by the genetic disposition of the individual but by many external factors (e.g., smoking, drug-induced disorders, stress, sanitation).

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Diagnosis and treatment of chronic periodontal disease

Clinical diagnosis of chronic periodontal disease is based on history and clinical examination along with additional screening. Anamnesis provides us with information about the overall health of the patient, which may also affect the condition of the periodontium. Information is also gathered on the patient's oral health, subjective and hygienic habits, which are important for determining the diagnosis as well as the treatment plan. It is also then necessary to assess the condition of the periodontal tissues using indices (most often Bleeding on Probing and Community Periodontal Index of Treatment Needs) to determine the mobility of teeth or periodontal suppuration. In addition, X-ray imaging of the alveolar bone and its possible resorption is required as a sign of periodontal disease [8,9].

In addition to the described basic methods of investigation, the literature also describes laboratory diagnostics and identifies certain biomarkers related to the phases of periodontal disease [10]. It has been found that by detecting biomarkers it is possible to detect periodontal disease before the onset of clinical manifestations and thus to diagnose it in its early stages [11]. Sulcular fluid and saliva have shown potential for the assessment of these markers, whose collection is simple for both the patient and the doctor. However, in clinical practice, their examination for the diagnosis of periodontal disease is not currently used [12,13].

A treatment plan is determined based on the established diagnosis. For chronic periodontal disease, the treatment is divided into three main phases. The first phase involves dental hygiene, the goal of which is to remove supra- and subgingival tartar and plaque as local irritants of periodontal disease. Thereafter, the patient should be instructed to maintain oral hygiene in order to keep the condition consistent [8,14]. Previous studies have shown a reduction in systemic oxidative stress after non-surgical treatment [15]. In addition, other factors have to be eliminated or modified including overhanging fillings, unsatisfactory prosthetic work, and extraction of teeth indicated for extraction among others [8,14]. Consequently, if a given condition necessitates it, pharmaceutical intervention may be indicated involving antibiotics (the most common being a combination of amoxicillin and metronidazole). Certain conditions also require surgical treatment, which aims to create appropriate conditions for oral hygiene and also the correction of the condition.

After stabilization in the previous phases of treatment, the third, supporting phase follows. Its goal is to maintain the periodontal tissues in the state achieved by the aforementioned procedure and to prevent further disease progression [8,16].

Oxidative Stress and Chronic Periodontal Disease

As previously described, oxidative stress plays a role in the etiology of multiple inflammatory diseases, not uniquely chronic periodontal disease [3]. Neutrophils are blood cells in the first line of defense against bacterial infection and the main source of ROS. Neutrophils accumulation was observed in periodontal tissues, where other ROS originate in periodontal disease [17]. Only several types of bacterial species have been directly related to periodontitis as *Porphyromonas gingivalis* [18] and *Aggregatibacter actinomycetemcomitans* [19,20]. The hyperreactivity of neutrophils was also shown upon the stimulation of *Bacteroides forsythus* [21], *Prevotella intermedia* [20], *Peptostreptococcus micros* [22], and *Fusobacterium nucleatum* [23]. Recently, Vidya Hiranmayi et al. [24] have discussed novel pathogens (as *Cryptobacterium curtum*, *Dialister pneumosintes*, *Filifactor alocis*, *Mitsuokella dentalis*, *Slackia exigua*, *Selenomonas sputigena*, *Solobacterium moorei*, *Treponema lecithinolyticum*, and *Synergistes)* involved in onset and progression of periodontitis.

Neutrophils produce a superoxide radical ($O_2^{\cdot-}$) in the phagosome in a nicotinamide adenine dinucleotide phosphate-oxidase-catalyzed reaction during a respiratory burst [25]. Radicals may also be released into the extracellular space and subsequently converted to other active radical and non-radioactive forms (such as HOCl, H_2O_2, $^{\cdot}OH$) (Fig. 1). Peripheral blood analysis of patients with the periodontal disease showed higher ROS production compared to healthy individuals [26–28]. Several studies have shown that neutrophils produce greater amounts of ROS in patients with chronic periodontal disease than those with no chronic periodontal disease [29]. Subsequently, peripheral blood neutrophils of patients with chronic (CP) or aggressive periodontal disease (AgP) have been found to have a hyperactive neutrophil phenotype that is stimulated by the Fc-gamma receptor (FcgR) [26]. While treatment of periodontal disease led to a decrease in neutrophil stimulation via FcgR, it had no effect on unstimulated extracellular ROS

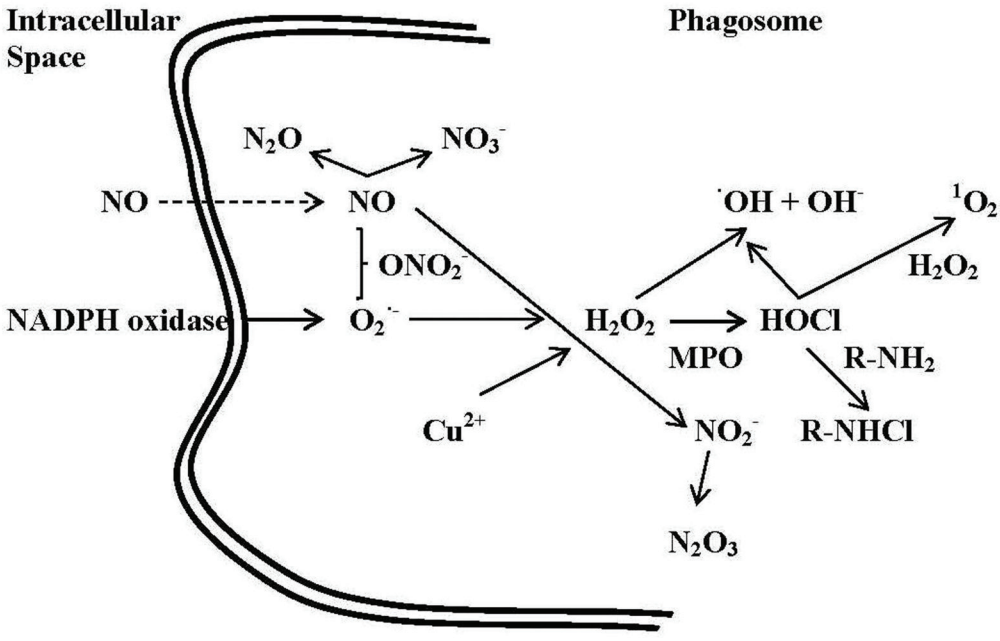

Figure 1. Reactive oxygen species formation in neutrophile phagosome. ($^1O_2$—singlet oxygen; H_2O_2—hydrogen peroxide; $HO^{\cdot}$—hydroxyl radical; HOCl—hypochloric acid; MPO—myeloperoxidase; N_2O—nitrogen oxide, N_2O_3—dinitrogen trioxide, $NO_2^{\cdot}$—nitrogen dioxide; NO_3^-—nitrate, $O_2^{\cdot}$—superoxide radical; OH^-—hydroxyl anion; ONO_2^-—peroxinitrite; R-NHCl—chloramine).

production, which is also higher in these patients than in healthy subjects [27]. Therefore, there is an assumption that increased production of ROS is not only the result of pathogen stimulation but also of genetic predisposition [30]. In CP patients, excessive production of $O_2^{\cdot-}$ from neutrophil hyperactivity was reduced only after non-surgical treatment [28]. Since the production of $O_2^{\cdot-}$ has a positive correlation with CRP concentration, one possible explanation is the influence of toll-like receptors via CRP, which in turn leads to increased formation of this radical [31].

ROS are produced continuously during inflammation and can react with cells or be scavenged by the antioxidant system [32]. ROS are particles with high biological reactivity due to the presence of one or more unpaired electrons in the valence shell. Even those which are not radicals by nature are able to cause the oxidation of substrates. Oxidized substrates are potentially toxic to an organism. They are structurally modified, which also leads to a change in their functional properties [25].

Consequences of Oxidation by ROS and Oxidative Stress Markers in Saliva

As a result of the oxidation of lipids and fatty acids, other free radicals are formed. In addition, oxidative lipid products, especially 4-hydroxynonenal (HNE) and malondialdehyde (MDA), react with proteins and nucleic acids. The major agents responsible for DNA and protein oxidation are singlet oxygen and hydroxyl radicals. Protein radicals are most often produced by cleaving the bond with the more labile hydrogen atom at Cα. The hydroxyacid is formed from the alkoxyl radical and hydroperoxide is formed from peroxyl radical, while recombination of protein radicals results in protein oligomers. The primary products of free radical oxidation of carbohydrates following isomerization to 1-ene-1,2-diols are α-dicarbonyl compounds, with the original number of carbon atoms, which are further oxidized and degraded. The radicals are formed as intermediates, and the α-dicarbonyl compounds further react with proteins [33]. Excessive ROS production thus affects the functionality of cells by disrupting the function of nucleic acids, proteins and lipids, which can lead to cell death through induction of the apoptotic pathway.

Some studies have already focussed on detecting changes in oxidative stress markers as an indication of periodontal disease. These were end products of lipid oxidation by ROS such as MDA, thiobarbituric acid reactive substances (TBARS) (barbituric acid reactants formed as a by-product of lipid peroxidation), HNE and isoprostanes, protein

oxidation (protein carbonyl groups, advanced protein oxidation products (AOPP), advanced glycation end products (AGE), and DNA oxidation) and 8-hydroxydeoxyguanosine (8-OHdG) [29,34]. The analyses were mostly carried out on saliva, which appears to be a suitable material for monitoring the condition of periodontal disease due to non-invasive and repeatable sampling.

Baltacioğlu et al. [35] reported higher MDA values in saliva in a group of patients with chronic and aggressive periodontal disease compared with a healthy control group of individuals. However, differences between the group with chronic and aggressive periodontal disease were not observed. Wei et al. [36] have shown a more pronounced difference between MDA in sulcular fluid in patients with chronic periodontal disease and healthy individuals. In sera and saline, however, the MDA values in these two groups were almost the same. In contrast, Liu et al. [37] showed significant differences in serum MDA between a group of patients with chronic periodontal disease and a healthy control group. Isoprostane is another molecule arising from the action of ROS. It is a product formed by peroxidation of arachidonic acid. It is also measured in plasma as a reliable marker of oxidative stress [29].

ROS are also capable of protein damage. AOPPs are the result of this oxidative damage and also the most commonly used marker for its determination [29]. To date, there has been a dearth of studies showing the relationship between protein carbonyls and chronic periodontal disease. Baltacioğlu et al. [38] have reported higher levels of protein carbonyls in both the sulcular fluid and the serum of patients with chronic periodontal disease. Higher amounts of carbonyl proteins were observed in the group of patients with chronic periodontal disease [38].

Arunachalam et al. [39] observed higher levels of 8-OH-deoxyguanosine in the saliva of a group of patients with chronic periodontal disease. Subsequently, months after initiation of the treatment for chronic periodontal disease, this group experienced a marked decrease in serum 8-OH-deoxyguanosine levels. No changes in 8-OH-deoxyguanosine were detected in the group of patients without chronic periodontal disease after supra- and subgingival scaling.

Unique studies have also been carried out in this area in Slovakia. Within these, relationships have been shown between elevated TBARS concentrations in the saliva of patients and deteriorating status of the periodontium [40,41], especially in men [42] and children [43]. Increased concentrations of MDA have been reported in smokers regardless of the disease state [40]. AOPPs have also been detected in the saliva of children and adults but with no relation to periodontal status [41–43]. Concentrations of AGE and TBARS are higher in the morning and dental cleansing contributes to their decrease but increases AOPP concentrations [44].

Antioxidants

Under normal physiological conditions, the balance between the formation of ROS and their removal through endogenous antioxidants is maintained. Enzymatic and non-enzymatic antioxidants are effective in removing these radicals, helping to amplify the immune response or suppress it, control their production, and function as mediators and sensors (Fig. 2). Some studies on antioxidant enzyme activities in patients with periodontal disease have been shown decreased activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and catalase (CAT) [45–47]. Others have seen their increase in plasma, erythrocytes, and gum tissues together with decreased activity of non-enzymatic antioxidants [48].

SOD is an enzyme that protects against free oxygen radicals by converting superoxide to O_2 and H_2O_2 [49]. In a study by Biju et al. [50], a difference was shown in serum SOD values between a group of patients with periodontal disease, gingivitis, and healthy individuals. In the healthy group, serum SOD values were highest, gradually lower in gingivitis patients and lowest in patients with chronic periodontal disease. However, after

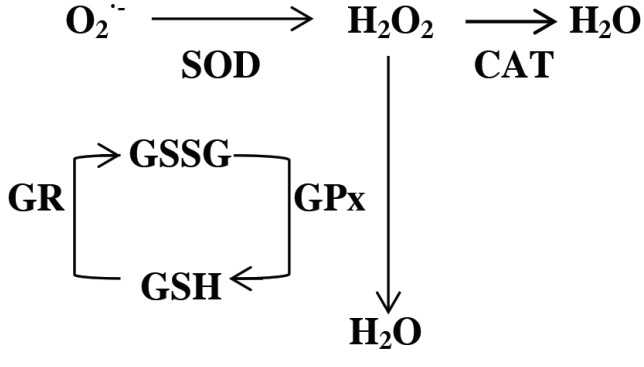

Figure 2. Endogenous enzymatic and nonenzymatic antioxidants involved in antioxidant response to respiratory burst. (CAT—catalase; GPx—glutathione peroxidase; GR—glutathione reductase; GSH—reduced glutathione; GSSG—glutathione disulphide; H_2O_2—hydrogen peroxide; $O_2^{\cdot-}$—superoxide radical).

treatment, there was an increase in serum SOD in the gingivitis and CP group. The meta-analysis of six studies has shown an interesting finding that there is no difference between SOD in circulating activity between patients with periodontal disease and healthy individuals, but there is a clear decrease in non-enzymatic antioxidants in patients [51].

Catalase is another enzyme that protects cells from ROS [52]. It is responsible for catalyzing the reaction that converts two molecules of hydrogen peroxide into two molecules of water and oxygen [53]. The reaction is self-induced but is accelerated several times in the presence of the enzyme.

Glutathione peroxidase also provides protection against oxidative stress. It is an enzyme that catalyzes the reduction of hydrogen peroxide with glutathione as a reducing agent [54,55]. Almerich-Silla et al. [56] compared glutathione peroxidase values in saliva. As in previous studies, groups of healthy individuals, patients with gingivitis, and subsequently CP were evaluated. In the CP group, the highest values of glutathione peroxidase were observed compared to the healthy group and the patients with gingivitis.

Total antioxidant capacity (TAC) is one of the parameters used in the context of oxidative stress. It expresses the activity of non-enzymatic antioxidants and provides an indication of the balance between oxidants and antioxidants. In fact, insufficient TAC is associated with tissue destruction during periodontal disease [57]. Baser et al. [57] have compared serum and saliva TAC values in patients with CP and AgP and in healthy individuals. The results have shown significantly lower TAC values for AgP and also lower TAC values in patients with CP compared to the healthy group. Bansal et al. [3] have published similar results, although they observed higher TAC levels in the healthy control group than the group with CP. After initial treatment, there was a certain increase in TAC levels. TAC may be used as a marker for determining periodontal damage [3].

Conclusion

From this brief overview, there are clear links between oxidative stress markers and periodontal disease. They may have limited use as a diagnostic tool but can be used to monitor the status and course of the disease. In the field of monitoring enzymatic and non-enzymatic antioxidants, it is necessary to clarify the connection between their activities and the disease. The endogenous antioxidant system is an effective defense of the body against oxidative stress. Its response is, therefore, an intrinsic part of an organism, reflecting the ability of an individual to respond to increased formation of ROS after stimulation of neutrophils during inflammation. Previous studies have produced controversial results with respect to enzyme activities, but have consistently confirmed a decrease in the concentration of non-enzymatic antioxidants. While CP is a multifactorial disease, several studies have confirmed the place of oxidative stress markers in relation to periodontal disease and their use at the time of diagnosis or treatment.

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