OPEN ACCESS
Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) |ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://scholarsmepub.com/sjm/

Review Article

Relation of Oxidative Stress on Oral Health and Disease - A Review

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DOI:10.21276/sjm.2019.4.8.23 | **Received:** 02.08.2019 | **Accepted:** 19.08.2019 | **Published:** 30.08.2019

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Abstract

The oxidative stress results because of the disturbance in systemic equilibrium of the oxidants and antioxidants. However, when there is increase in the generation of the free radicals such as reactive oxygen and nitrogen species (ROS and RNS respectively), then there is a shift in this systemic equilibrium. Various environmental and lifestyle factors such as pollutants, alcohol consumption, smoking, poor diet and other adverse habits contribute towards the oxidative stress. Oxidative stress can affect systemically (the whole body) as well as locally (in oral soft tissues).Various recent literatures have shown that the oxidative stress and inflammation are predisposing factors for various chronic illnesses, like atherosclerosis, rheumatoid arthritis, diabetes and periodontitis.

Keywords: Cancer, Free radicals, oral health, oxidative stress, potentially malignant diseases.

INTRODUCTION

In healthy individuals, the balance between the free radicals and antioxidants are maintained by the various metabolic processes [15]. When this equilibrium/balance between free radicals and antioxidants gets disturbed, there is an increased production of ROS and other free radicals. Thereby, when there is an excessive or over abundance of oxidants, it is called as oxidative stress. Oxidative stress causes cellular damage by protein deactivation, micro damage to the cell membrane, DNA damage by stimulation of various cell signaling molecules [1].

Some molecules like unsaturated lipid molecules are more susceptible for the attack of free radicals than other molecules in the cell membrane such as RNA, DNA and protein enzymes.

Oxidative Stress and Oral Tissues

The mucous membrane of oral cavity allow a rapid absorption of the substances across their surfaces; hence they are uniquely vulnerable to the free radical damage. The oral infections such as gingival and periodontal diseases can produce free radicals and cause oxidative stress which can further lead to breakdown of oral tissues.

Effects of ROS in Oral Diseases

Apthous ulcers- The pathogenesis of Recurrent Apthous Stomatitis (RAS) is multifactorial i.e., there is an important physiological interplay between the immune system, genetics and environmental factors [2, 9]. Many studies strongly suggested that there is a systemic imbalance in the ratio of oxidant to antioxidant in RAS patients, which favors the oxidative damage. Apthous ulcers are found to be stress associated, probably suggesting the correlation between increased stress, decreased peroxide and hence occurrence of the apthous ulcers. Moreover, it was found that the salivary peroxide levels were highest in the group that had no oral aphthae, while the peroxide levels dropped once the lesion was established.

Periodontal diseases- The products of some bacteria lead to altered PMN function modifying their response to second stimulus [3, 4]. For example, lipopolysaccharide extracted from Porphyromonas gingivalis was found to be responsible for neutrophils priming and for enhanced production of superoxides.

This condition is found within the periodontal pockets, which indicates that the periodontal tissue damage is a result of chronic or excess ROS production.[5, 6] The oxidation products which are produced locally by neutrophil ROS (e.g. oxidized low-density lipoprotein) could further increase the generation of neutrophil ROS. Due to the activation of the leukocytes in phagocytosis, there is release of reactive oxygen species (ROS), which causes the lipid peroxidation of the soft tissues of the periodontium. Reduced levels of specific antioxidants, such as CAT, SOD and GPX, were observed in the patients having periodontitis as compared with the healthy controls [7-9, 23].

Oral Lichen Planus -Many researchers have demonstrated that the increased lipid peroxidation in cell membrane can stimulate immune response and inflammatory processes. The main event in the pathogenesis of the lichen planus is the activation of cell-mediated immune response which results in keratinocyte apoptosis. Moreover, the recent studies have reported an increased lipid peroxidation and oxidative stress in the patients with lichen planus [10-12]. This suggests that the reactive oxygen species may have a role in the pathogenesis of lichen planus. However, there is insufficient data available in the literature regarding antioxidant defense status in the patients of lichen planus. The most important product of lipid peroxidation is Malondialdehyde (MDA) that can be used as a marker for measuring the oxidative stress [13, 14]. The serum levels of NO (Nitric Oxide) and MDA were higher in LP patients. It was observed that there is lower plasma GPX (Glutathione Peroxidase) activity in LP patients as compared to controls.

Leukoplakia-Tobacco smoking and chewing causes imbalance in the oxidant and antioxidant equilibrium and results in oxidative stress [15]. This goes hand in hand with increased lipid peroxidation, damage to micro and macro molecules of the cells, oxidative DNA damage and disturbed antioxidant defense mechanism which can induce the malignant process [16]. The disturbance in the pH and heat generated during smoking affects the formation as well as stabilization of free radicals. Tobacco products increase the production of ROS and free radicals production, which have a significant role in the multistep pathogenesis of carcinogenesis. These reactive species initiate the mutagenic events by causing oxidative damage to DNA that ultimately leads to the degeneration of cellular components. Thereby, the free radicals and ROS stimulate the malignant transformation as well as leads to its progression. These reactive species and free radicals primarily cause the peroxidation of polyunsaturated fatty acids (PUFAs) in the membrane lipids [17]. The levels of serum Malondialdehyde (MDA) in the patients of oral leukoplakia were higher than in the controls [18]. The serum MDA levels in the oral cancer patients were highest as compared with the controls and patients having oral leukoplakia [19]. However, when the mean values between the well differentiated ad the moderately differentiated oral squamous cell carcinoma (OSCC) were compared, not much difference was observed.

Oral Submucous fibrosis-Nair *et al.*, first demonstrated that the catechu and the aqueous extracts of areca nut were capable of producing the hydrogen peroxide and the superoxide anion at pH > 9.5. Iron (Fe2+, Fe3+) and copper (Cu2+) enhanced the areca nut induced production of ROS but inhibited by Mn2+ [20, 21]. The ROS production is favored by the presence of Ca (OH) 2 in slaked lime because it leads to alkaline conditions in the oral cavity. Moreover, the continuous and chronic local irritation due to the fine particulate nature of gutka, panmasala or areca nut induces injury-related chronic inflammation, cytokine production and oxidative stress which leads to the cell proliferation, apoptosis or cell senescence, miscoding DNA adduct; and thus inhibit DNA repair activity [22].

Carcinoma- Reactive oxygen species play a crucial role in the pathogenesis of many head and neck cancers. Alcohol, tobacco and betel nut/areca quid chewing have all been shown increase the DNA damage due to increase in the generation of ROS which contribute in the oral carcinogenesis [20-22]. The disturbances in the antioxidant defense mechanism associated with the increased oxidative and nitrosative have been suggested in the pathogenesis of several diseases, most notably the oral cancer. Tobacco smoke which is a well studied and one of the most significant risk factors in multiple types of head and neck cancer produces both the reactive nitrogen and oxygen species, via the generation of superoxide, NO and hydrogen peroxide. [23] Areca nut/betel nut quid chewing is the other most well studied risk factor for causing the oral cancers and it also has been shown to increase the hydroxyl radical formation which leads to the oxidative DNA damage. Moreover, several viruses like Epstein–Barr virus (EBV) in nasopharyngeal carcinoma (NPC) and human papilloma virus (HPV) in oral squamous cell carcinomas are also involved in the head and neck cancers and the mechanism of the pathogenesis in both of them are based on generation of reactive oxygen species [24].

Radiation therapy-apart from the pharmacologic manipulation of reactive oxygen species, the radiation therapy for the head and neck squamous cell carcinomas can also be altered by the interference in the redox pathways [25].

CONCLUSION

Although the reactive oxygen species are required for the normal cellular processes, at the same time, they are also involved in variety of disease processes in creating the chronic oxidative stress, including the carcinogenesis. Reactive oxygen species

play a vital role in the head and neck cancers not only through the general mechanisms of the protein modulation and the DNA damage but also by inducing various risk factors. Since these reactive species have widespread effects, ROS and the redox pathways represent attractive targets for the various research purposes. According to several literature and the studies, the initial results regarding these reactive species are very promising and also they have the potential to be widely applicable not only in oncology, but also in the mechanism of several other pathologies these ubiquitous molecules promote.

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