ISSN 2706-6819 Vol.5, Issue 2: 83-87, DOI: 10.25236/IJFM.2023.050215

Relationship between Oxidative Stress and Several Common Oral Mucosal Diseases: A Review

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Abstract: *Free radicals include reactive oxygen species and reactive nitrogen, which are vital substances in the biological process of the body, which have a positive effect on the human body at normal concentrations. When the content of free radicals is too high, the body will activate the antioxidant system to defend against this damage in order to protect itself. The disorder of the balance between pro-oxidative and antioxidant reactions will lead to oxidative stress: excessive production of free radicals, and the body's antioxidant system cannot effectively resist this invasion, free radicals destroy the molecular tissues that make up DNA, proteins and lipids, followed by irreversible damage. Many studies at home and abroad have shown that patients with some oral mucosal diseases (recurrent aphthous ulcer, oral lichen planus, oral leukoplakia, oral submucosal fibrosis, burning mouth syndrome) often observe oxidative stress in oral tissue or saliva and blood, and explore many potential biomarkers. Through the study of the relationship between oxidative stress and oral mucosal diseases, it will be of guiding significance for the etiological exploration and treatment of oral mucosal diseases. This article reviews the latest research progress on the relationship between oxidative stress and several common oral mucosal diseases in recent years.*

Keywords: *oxidative stress, reactive oxygen species, free radical, recurrent aphthous ulcer, oral lichen planus, oral leukoplakia, oral submucosal fibrosis, burning mouth syndrome*

1. Introduction

When the free radicals produced by the body exceed the ability of the body's antioxidant system to repair damage, that is, the body's own antioxidant system is unable to balance free radicals, the state of the body is called oxidative stress [1] . The pathogenesis of many diseases is related to oxidative stress, and chronic inflammatory diseases and cancer are often discussed and studied. The oral cavity is a key part of oxidative stress, because physical, chemical stimulation and microbial infection often lead to tissue damage in this area. In recent years, more and more attention has been paid to the relationship between oxidative stress and the pathogenesis of some mucosal diseases. The purpose of this review is to report the latest research progress on oxidative stress in common oral mucosal diseases and the relationship between oxidative stress and oxidative stress.

2. Recurrent aphthous ulcer and oxidative stress

Recurrent aphthous ulcer (RAU) is very common in clinic. Scholars have done a lot of research on its etiology, but the specific etiology of RAU has not been completely determined. Now oxidative stress is gradually becoming a hot direction for scholars to discuss the etiology and pathogenesis of RAU[2].

Reactive oxygen species (ROS) are active molecules containing oxygen and are the most common free radicals. Another kind of free radical is active nitrogen (RNS), that is, active molecules containing nitrogen. ROS can be divided into oxygen center free radicals and oxygen center non-free radicals, and the components of RNS are peroxynitrite, nitric oxide and nitrogen dioxide[3]. Physiological concentration of ROS has positive biological effects. It occurs naturally and is necessary for life, but it can also cause oxidative stress and related pathological processes that are harmful to the body[4]. As a free radical, nitric oxide is an important endogenous vasodilator, which can react with superoxide to produce toxic peroxynitrite, which directly causes damage to the endothelium. It can destroy cell protein, DNA and lipid, and eventually lead to cell death, mitochondrial dysfunction, tissue damage and even

ISSN 2706-6819 Vol.5, Issue 2: 83-87, DOI: 10.25236/IJFM.2023.050215

organ failure[5].

It is reported that the imbalance between oxidation and antioxidation is one of the causes of tissue damage in patients with RAU[6]. Malondialdehyde (MDA), one of the stable end products of lipid peroxidation, represents the aggravation of lipid peroxidation. Excessive MDA has toxic side effects, which can change the amino acid chain, change the structure of cell membrane and impair the normal function of cells[7]. It is often used as an indicator to assess the level of oxidative stress.

Normal cells use both enzymatic and non-enzymatic antioxidants to protect themselves from oxidative stress, what we call antioxidant systems. Among them, enzymatic antioxidants include glutathione peroxidase, superoxide dismutase, etc., while ascorbic acid (vitamin C) and mercaptan are called components of the family of non-enzymatic antioxidants[8]. When ROS is excessive and antioxidants are insufficient, neutrophils gather and infiltrate and phagocytosis, protease secretion increases, and oxidation intermediates are produced in large quantities, which is the state of stress[9]. In one study, in order to study the inflammatory state and free radical metabolism in patients with RAU, the researchers measured the changes of antioxidant glutathione (GSH) and MDA, as well as the levels of cellular inflammatory factors such as tumor necrosis factor-α (TNF- α) and interleukin-2 (IL-2). They analyzed that MDA increased and GSH decreased in patients. The mechanism of cytokines has been pointed out to be abnormal: the increase of TNF- α and IL-2, IL-12 may lead to the increase of stress response to some extent. Although IL-10 can inhibit the release of cytokines to some extent, its low level can not inhibit inflammation, so it eventually leads to ulcers [10] . Another study found that MDA levels in saliva of RAU patients increased to a greater extent in the ulcerative stage than after the healing stage[11]. Zhang et al showed that compared with inactive patients and healthy controls, serum total antioxidant capacity (TAS) decreased and NO increased in patients with mild RAS in active stage, which were statistically significant[5]. Another recent study shows that many RAU patients have high levels of heavy metals (including lead, mercury, copper, etc.) in their saliva. The release of ROS may be due to the continuous accumulation of heavy metals, which leads to DNA damage and mucosal ulcer[12].

3. Oral lichen planus and oxidative stress

As a chronic inflammatory mucosal disease of unknown etiology, oral lichen planus (OLP), currently generally accepted risk factors include genetic susceptibility, immune factors, malnutrition and infection[13]. In addition to all the above factors, oxidative stress may constitute the pathogenic mechanism of OLP and its complications. The most important histological features of oral lichen planus include liquefaction of the basal cell layer accompanied by keratinocyte apoptosis and obvious subepithelial lymphocyte infiltration. Abnormal apoptosis is closely related to oral lichen planus. Studies have shown that the basic mechanism of cell signal transduction and transduction will be adversely affected by oxidative stress, leading to keratinocyte dysfunction and apoptosis[14]. It has been found that apoptosis occurs directly in keratinocytes due to oxidative stress, which changes the regulation of mitochondria, which depends on CD8+ lymphocytes, while CD8+ lymphocytes occur by affecting the activity of nuclear factor kappaB (NF-kB)[14]. A recent study conducted a comprehensive review of the relationship between micronutrients and OLP, showing decreased antioxidant levels and increased oxidant levels in patients with OLP[15] . Consistent with these findings, an increase in NO and MDA was found in patients with OLP, which is recommended as a biomarker for monitoring disease activity and treatment effectiveness in OLP[16] . Accordingly, studies have evaluated the role of antioxidants in the treatment of patients with oral lichen planus, with greater pain relief and improvement of clinical symptoms in patients treated with vitamin E than those who received placebo. These results suggest that the antioxidant vitamin E may be useful in the treatment of oral lichen planus[17] .

4. Oral leukoplakia and oxidative stress

Oral leukoplakia (OL) is a common potentially malignant oral disease [18]. Its diagnosis is usually exclusive, first based on medical history, and requires a combination of clinical symptoms and histopathology [19] .

Uric acid (UA), the end product of human purine metabolism, has been proved to be an important antioxidant, which can eliminate about 60% of free radicals in the human body. UA interacts with peroxynitrite to form a nitric oxide donor[20] . This process will dilate the blood vessels and reduce the oxidative damage caused by peroxynitrite. In the process of this game, uric acid is consumed and the level of oxidant in serum decreases, indicating that this is an active pathological process. The results of

ISSN 2706-6819 Vol.5, Issue 2: 83-87, DOI: 10.25236/IJFM.2023.050215

a study show that the average level of UA in blood of OL patients is lower than that of normal controls, which reflects the importance of oxidative stress in OL[21] . There is another view on the role of UA in oxidative stress, that is, UA has both oxidation and antioxidation [22] . The possible theoretical basis is that the antioxidation of UA is only shown in the hydrophilic environment of biological body fluids. In the hydrophobic environment formed by lipids, UA can react with other oxidants to form free radicals or directly oxidized lipids into oxidants[23] . Therefore, more clinical studies are needed on the role of UA in oxidative stress.

With regard to the role of oxidative stress in OL, it has been suggested that reactive oxygen species have been clearly regarded as the cause of precancerous progression, because cell damage is easy to accumulate, intracellular homeostasis may change, and autophagy may be impaired [24] . P62 is a cytoplasmic protein induced by oxidative stress and an adaptive protein involved in the formation of protein aggregates and autophagy induction and inhibition. Some studies have pointed out that the expression and accumulation of p62 in the nucleus can be used as a potential marker to predict the malignant transformation of oral leukoplakia: there is a correlation between oxidative stress and autophagy in OL lesions. Under basic conditions, Nrf2-Keap1 pathway plays a role as a key regulator of cellular defense mechanism against oxidative stress. P62 interacts with Nrf2 binding sites on Keap1. Overexpression or autophagy defects of p62 lead to competition between Nrf2 and p62 for Keap1, resulting in the stability of Nrf2 and transcriptional activation of antioxidant response elements including p62. This continuous response breaks the cycle, and p62 produces a positive feedback loop in the Keap1-Nrf2 pathway. This atypical mechanism of Nrf2 may explain p62 nuclear overexpression and p62 aggregation in OL under acute or persistent oxidative stress[25] .

5. Oral submucosal fibrosis and oxidative stress

Oral submucous fibrosis (OSMF) is a precancerous condition. The disease is accompanied by subepithelial inflammation, followed by deterioration or even disappearance of lamina propria fiber elasticity and epithelial atrophy, resulting in hardening and inelasticity of the oral mucosa. Patients with limited mouth opening may even suffer from trigeminal neuralgia and the pain caused by inability to eat [26] .

In recent years, some progress has been made in the study of the mechanism of oxidative stress on OSMF. 8-isoprostaglandin is a metabolite of lipid peroxidation and a sensitive and specific marker of oxidative stress[27]. The mean value of plasma 8-isoprostaglandin increased gradually from control group to OSMF group and then to oral squamous cell carcinoma group. This reflects that the basic level of cell oxidation due to aerobic metabolism in the test group has changed significantly compared with normal individuals. The significant increase of 8-isoprostaglandin in saliva of patients with oral squamous cell carcinoma may be due to the harmful interaction between saliva and toxic metabolites, which leads to the rapid destruction of biological macromolecules. The reaction between redox active metals and low active free radicals in saliva is the cause of fatal synergistic effect [28].

More and more epidemiological and in vitro experimental studies have shown that betel nut chewing is the main pathogenic factor of OSMF[29]. The relationship between arecoline and oxidative stress has been studied by scholars. Arecoline is a kind of arecoline alkaloid. A study showed that arecoline nitrogen oxide (ARNO), an oxidative metabolite of arecoline, has stronger cytotoxicity, mutagenicity and cleavage in vitro than its parent compound arecoline. The increased toxicity of ARNO can be explained by the production of ROS induced by metabolism mediated by mitochondrial targeted cytochrome P450. In addition, the polyphenols in the saliva of betel nut chewers and the ROS produced during the self-oxidation of betel nut also play an important role in the occurrence and promotion of oral cancer[30]. Another study showed that saliva SOD levels in patients with OSMF decreased significantly, which to some extent reflected the decline of antioxidant capacity in patients with OSMF. Researchers found that mouth opening in OSMF patients decreased with the decrease of SOD levels[31].

In order to consider the pathogenesis of oxidative stress, many scholars have made studies on the use of antioxidant therapy in patients with OSMF. For example, some scholars have found that curcumin, a natural product with antioxidant effect, has a positive effect on OSMF, especially on mouth opening[32]. Lycopene is a prominent carotenoid whose unique characteristic is to combine with chemicals that react with oxygen. Therefore, it is a very effective biological antioxidant [33] . After three years of follow-up of OSMF patients using lycopene, G.Arakeri et al concluded that lycopene as an antioxidant is effective in improving the clinical symptoms of OSMF patients[34].

ISSN 2706-6819 Vol.5, Issue 2: 83-87, DOI: 10.25236/IJFM.2023.050215

6. Burning mouth syndrome and oxidative stress

Burning mouth syndrome (BMS) is defined as a sensation of burning or discomfort in the mouth for more than two hours a day for three months without clinical lesions. The prevalence rate ranges from 1% to 3.7% in the general population, and is more common in postmenopausal women[35]. The etiology of BMS is unknown worldwide. It is generally believed that the etiology of BMS is multifactorial and may involve complex interactions among local, systemic and psychological factors. In recent years, the relationship between BMS and oxidative stress has been paid more and more attention: Kang et al found that stress-related hormone changes in postmenopausal BMS patients may affect the expression of MUC1 and burning sensation[36]. The report shows that the changes of ROS in saliva of patients with BMS[37], and the changes of UA in saliva and iron reduction activity (FRAP) in plasma of patients with BMS support the contribution of oxidative stress to the pathogenesis of BMS[38].

7. Conclusion

As the etiology of oral mucosal disease is mostly complex, treatment is still difficult, to find its pathogenesis is of great help and significance to guide clinical treatment and alleviate the condition of patients. In this review, the relationship between several common oral mucosal diseases and oxidative stress is briefly described. a large number of and in-depth studies in this direction will help to clearly understand the relationship between oxidative stress and oral mucosal diseases. to find out whether oxidative stress directly leads to oral mucosal diseases or whether it is a susceptible factor for these diseases. It has important guiding significance for the study of etiology and related mechanisms of these diseases, and can find therapeutic targets for clinic from a new perspective. In addition, various oxidative stress products may be useful biomarkers, and the detection of these biomarkers can reflect the disease status, and can also be used as a tool to evaluate the disease progression of these common oral mucosal diseases during follow-up. And as a supplementary measure of clinical surveillance.

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