

OXIDATIVE STRESS - A POSSIBLE LINK BETWEEN SYSTEMIC AND ORAL DISEASES

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Abstract

Oxidative stress (OS) plays a major role in the pathogenesis of a wide range of systemic and oral diseases. The aim of this review is to provide an overview of the ways in which OS may be considered a possible link between systemic and oral diseases. There is increasing evidence linking some oral diseases, e.g. periodontal disease to systemic diseases, such as cardiovascular diseases, metabolic syndrome, and diabetes. Tooth loss has been associated with a higher risk to develop several types of cancer. Malign progression of tumors has been correlated with the development of OS. This article summarizes the roles of OS emphasized in relevant studies, including our department experience, focused on the relationship between systemic and oral diseases.

Rezumat

Stresul oxidativ este implicat în patogeneza a numeroase afecțiuni sistemice și orale. Scopul acestei lucrări este de a analiza modalitățile prin care stresul oxidativ poate fi un element biochimic de legătură între afecțiunile sistemice și cele orale. Numeroase studii au evidențiat interrelația afecțiunilor orale, de exemplu boala parodontală, cu afecțiuni sistemice precum sindromul metabolic, diabetul, afecțiunile cardiovasculare. Pierderea dinților a fost asociată cu creșterea riscului de apariție a proceselor neoplazice. Lucrarea sintetizează rezultatele a numeroase studii axate pe cercetarea unei posibile interrelații între afecțiunile sistemice și cele orale, inclusiv cercetările colectivului nostru.

Keywords: oxidative stress, periodontitis, metabolic syndrome, oral cancer.

Introduction

Reactive oxygen species (ROS) or oxygen free radicals are products of normal cellular metabolism. Oxidative stress (OS) can be defined as an imbalance between the production of highly reactive molecular species and antioxidant defense systems [1].

The most common free oxygen radicals include hidroxil ($\text{HO}^\bullet$), nitric oxide (NO) superoxide ($\text{O}_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and peroxynitrite ($\text{ONOO}^\bullet$).

Mitochondria are the main sites of oxygen metabolism and represent a source of ROS. The respiratory chain in mitochondria is an

important source of ROS, primarily $O_2^{\bullet-}$ and H_2O_2 . ROS can be generated by external environment, (the main sources are: heat, UV light, X and gamma radiations, therapeutic drugs), behavioural activities (smoking, chronic exercise). Other sources of ROS are the inflammatory reactions, especially chronic inflammation. Inflammation cells such as activated macrophages and neutrophils release various ROS (H_2O_2 , NO, $O_2^{\bullet-}$, $HO\bullet$ and $HOCl$). Polymorphonuclear leukocytes (PMN) have been demonstrated to produce a range of antimicrobial factors, including ROS [2, 3].

Increased generation of ROS may cause toxic effects by oxidative damage of proteins, lipids and DNA.

Lipids are targets for OS. The polyunsaturated fatty acids are major targets of ROS. Lipid peroxidation is one of the most explored areas of research. The major products of lipid peroxidation are malondialdehyde (MDA) and 4-hydroxyl-2-nonenal (HNE).

ROS can react with several amino acids, generating a wide range of products, from modified and less active enzymes to denatured, nonfunctioning proteins. An important structural modification of protein molecules is nitrosylation, the peroxynitrite being responsible for this modification. Tyrosine is an important amino acid involved in phosphorylation reactions and signal transduction pathways. Tyrosine nitration may not only compromise protein function, but may also have serious consequences in cellular regulation.

Enzymes, such as superoxide dismutase (SOD), have been identified as specific protein targets of nitrosylation.

Oxidative modifications can occur in DNA molecules. Both nuclear and mitochondrial DNA are known targets for ROS attack. The $HO\bullet$ can react with all components of DNA molecules, damaging both purine and pyrimidine bases and also the deoxyribose backbone. 8-hydroxy-deoxyguanosine (8-OH-dG) is the most studied DNA lesion marker [4, 5].

In the last few years, a rising number of research studies concerned OS as a new common link between systemic and oral diseases. Many of them are related to periodontal disease, by far the most common link being oral infections.

OS has been implicated in various pathological conditions involving cardiovascular diseases (CVD), cancer, neurological disorders, diabetes, ischemia/reperfusion, aging and now oral diseases. The oral cavity is a very complex and unique medium. Saliva is the first biological fluid that encounters inhaled cigarette smoke microorganisms, food, drugs. Saliva could constitute the first line of defense against OS.

There is increasing evidence linking periodontitis to systemic diseases such as metabolic syndrome (MetS), diabetes and, especially, CVD.

CVD and periodontitis

CVD including atherosclerosis and myocardial infarction are the major cause of death worldwide. More than 70 million North Americans have CVD, 7 million have coronary heart diseases and more than 5 million are suffering from stroke. Conventional risk factors known to accelerate the progression of CVD include diabetes mellitus, cigarette smoking, hypertension and dyslipidemia. These factors are associated with a marked increase of ROS production.

Sources of ROS production in CVD include xanthine oxidase, lipoxygenase, mitochondrial respiration, cytochrome P₄₅₀, cyclooxygenase, NAD(P)H oxidase. These sources contribute to ROS formation in all types of vasculature.

Many investigators constantly searched for new pathological mechanisms involved in the development of CVD lesions, especially those related to inflammation, obesity and infection. Inflammation is the initiating process of the atheroma formation. Chronic infections such as periodontitis might influence systemic and vascular inflammation processes.

In the last 20 years many clinical studies, mainly cross-sectional and case-control have shown positive associations between CVD and periodontitis [9, 10, 11].

Periodontal disease is an inflammatory response of the gingival and surrounding connective tissue to the bacterial plaque accumulation of the teeth. This condition is fundamental between the normal microbial biofilm on teeth and the host tissues. Neutrophils are the initial host defense against the periodontal pathogens. After stimulation by bacterial antigens, they produce O₂^{•-}, during phagocytosis and after being released into the phagosome is released into the extracellular environment.

ROS production stimulates the release of proinflammatory cytokine by monocytes and macrophages through activation of the transcription factor nuclear kB (NFkB). ROS can stimulate even osteoclast activation. C-reactive protein (CRP) is the most studied marker of atherosclerosis. CRP possesses a wide variety of functions, including pro-inflammatory properties, activation of complement factors, neutralization of invasive pathogens, stimulation of repair, and regeneration of a variety of tissues. CRP represents an emerging and reliable marker of acute phase response to infectious burdens and/or inflammation. It may also be an indicator of chronic infective processes possibly correlated with the risk of coronary

heart disease, and appears to be strongly associated with periodontal disease. Elevated levels of this protein have been observed in CVD patients and were consistently higher in periodontitis patients compared with controls. CRP levels were approximately one-third higher in patients with extensive pockets of disease in their gums than those with minimal disease after controlling for age, sex, cigarette use and diabetes mellitus.

A positive correlation between serum CRP, periodontal disease and CVD, may indicate that circulating inflammatory molecules contribute to the pathogenesis of both conditions. Salivary immunoglobulins IgA were positively correlated, while IgG was negatively associated with CVD [53]. The level of MDA is increased in plasma of patients with heart failure and for patients with chronic periodontitis.

Meta-analysis of 5 prospective cohort studies indicated that individuals with periodontal disease had a higher risk of developing coronary heart disease than the controls. The prevalence of this disease in the cross-sectional studies was significantly higher among individuals with periodontal disease than in those without it. This indicates that both the prevalence and incidence of coronary heart disease are significantly increased in periodontal diseases. Therefore, periodontitis may be a risk factor for CVD. Prospective studies are required to prove this assumption and evaluate risk factors with the treatment of periodontal disease.

Matrix metalloproteinases (MMPs) are locally increased in periodontal disease. MMP-9 is a possible link between periodontal disease and CVD [12, 13].

Metabolic syndrome and periodontitis

Metabolic syndrome (MetS) is a combination of obesity, hypertension, impaired glucose tolerance or diabetes, hyper-insulinemia and dyslipidemia [14]. These features are risk factors for atherosclerosis. MetS is considered to be a risk factor for coronary heart disease [15]. The origin of these metabolic disorders is a proinflammatory state derived from the excessive caloric intake. The inflammatory state leads to an increase in OS with the potential to impair several crucial biological mechanisms. Insulin resistance may be a common link between all the components of MetS.

A potential factor that can increase insulin resistance is the production of OS-enhancing ROS that can affect the periodontal tissues.

A relationship between MetS and OS in humans has been demonstrated by many studies. OS is significantly higher in MetS patients compared with non-obese normolipidemic subjects.

Some high density lipoprotein (HDL) subfractions are significantly lower in patients with MetS *versus* controls, and this can be correlated with

systemic OS and insulin resistance. Patients suffering from MetS present poor antioxidant status and significantly increased OS markers (serum lipid peroxide level), compared to those without MetS [16].

Advanced glycation end products (AGE) are important markers for OS and their endogenous secretory receptor (esRAGE) in plasma is significantly and inversely correlated with components of the MetS including body mass index (BMI), blood pressure, triglycerides, glycated hemoglobin (HbA1c), and an insulin resistance index.

The most important tissues implicated in the pathogenesis of MetS are muscle and adipose tissues [15, 16].

Adipocytes secrete a diversity of molecules, named adipocytokines, which can influence metabolic and immune functions. The most studied molecules are leptin and adiponectin. Resistin is another molecule weakly related to adipocytes in humans but very important in the inflammatory response and insulin resistance [17].

Leptin and periodontitis

It has been observed a decreasing leptin level in gingival crevicular fluid (GCF) and gingival tissue which was associated with deteriorated periodontal status. Smokers present reduced GCF leptin levels suggesting a protective role of leptin for the periodontium. GCF leptin levels are proportional to the body mass index (BMI). A significant negative correlation between GCF and serum leptin concentration has been observed in periodontitis [18].

Adiponectin and periodontitis

Under normal conditions, adiponectin levels remain relatively constant but are decreased in obesity, insulin resistance and diabetes, CVD with increasing severity. Low adiponectin levels have been able to predict the development of insulin resistance and type 2 diabetes. Therefore, adiponectin may present a key role in the development of MetS [19, 20].

Diabetes and periodontitis

Diabetes, a globally important chronic disease, considered to be epidemic by the World Health Organization (WHO), is an established risk factor for periodontitis. Periodontal disease has been recognized as the “sixth complication of both types of diabetes”. Many biochemical pathways strictly associated with hyperglycemia such as glucose auto-oxidation, polyol pathway, prostanoid synthesis and protein glycation can increase the production of ROS. Furthermore, exposure of endothelial cells to high glucose levels leads to the production of $O_2^{\cdot-}$ [21].

The interaction between mononuclear phagocytes and AGE induces the up-regulation of cytokines expression and the induction of OS. The periodontal infection amplifies the magnitude of the macrophage response to AGE, leading to cytokine production and OS. This may explain the higher prevalence and severity of periodontitis in diabetic patients. Approximately 65% of the US population has periodontal disease and this prevalence increases to 90% in patients with diabetes. Many studies revealed a decreased SOD activity, in gingival tissue from periodontitis patients without diabetes compared to periodontitis and diabetic patients. This may represent a compensating mechanism derived from hyperglycaemia. Periodontitis and diabetic patients present a decreased activity of one pro-oxidant enzymes, myeloperoxidase, in GCF compared to those without diabetes.

Salivary aspartate aminotransferase (AST) activity was significantly increased in patients with diabetes and periodontal disease, and alanine aminotransferase (ALT) activity was not significantly modified in saliva from patients with periodontitis but increased in the case of diabetic patients [22, 23].

Periodontal disease and cancer

Severe forms of periodontitis can influence the progression of systemic diseases, including carcinogenesis. Malignant progression of tumors has been shown to be associated with the development of OS. Between OS and cancer there is a complex relationship.

The associations between periodontal disease and carcinogenesis have been recently reported, underpinned by inflammatory mechanisms common to both entities. Many studies have revealed an association between periodontal status and lung cancer. The study included individuals with gingivitis and periodontitis who can present a greater risk of fatal malignant neoplastic change in the bronchus and lung than those with a healthy periodontium over a 10 year period. The patients who never smoked, didn't present any association between periodontitis and lung cancer. There are some indications of association between periodontal disease and prostate, breast and pancreatic cancers.

Smoking leads to OS and triggers a series of events that could contribute to cell transformation [24, 25].

The common causes of tooth loss in adults are the chronic and aggressive forms of periodontitis. There are increasing evidences that chronic inflammatory periodontitis is a risk factor for premature death from several causes.

A recent study investigated young persons aged between 30 and 40 years old with periodontal disease and missing molars. These persons presented an increased risk of death from neoplasms, circulatory and digestive disorders.

A study realized by Michaud and co-workers demonstrated a significant association between periodontal disease and hematological, renal and pancreatic cancer, reported in never-smokers. An association between periodontal disease and pancreatic cancer was reported in male health professionals. Periodontal disease could influence pancreatic carcinogenesis, through increased generation of carcinogens, namely nitrosamines. Individuals with periodontal disease and poor oral hygiene present elevated levels of oral bacteria and have much higher nitrosamine levels in their oral cavity [26, 27].

Conclusions

The studies reviewed could explain one of the factors that constitute the bidirectional systemic disease-oral disease link, OS. According to the presented data we propose a possible mechanism that can explain this relationship (Figure 1). Elevated OS caused by diabetes mellitus, CVD (cardiovascular, MetS (metabolic syndrome), smoking and an inappropriate nutrition are essential for periodontal health. OS is involved in the progression of systemic and oral diseases. The decrease of systemic and oral OS may be important in improving oral health. These data could explain recent advances for understanding the oral cavity and its impact on systemic diseases, the necessity of including oral health as part of routine health care for the population, and last but not least, can serve as a reason for medical and dental care professionals to collaborate and coordinate.

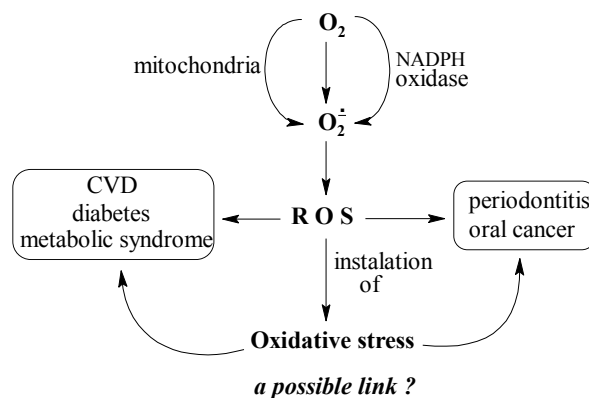


Figure 1

Oxidative stress- a possible link between systemic and oral diseases
(NADPH= nicotinamide adenine dinucleotide phosphate, CVD= cardiovascular diseases,
ROS= reactive oxygen species)

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