Review Article

Oxidative Stress: A Link between Periodontal and Systemic Health

Dhanavendra Singh, Vivek Kumar Bains, Rajesh Jhingran, Ruchi Srivastava, Rohit Madan

ABSTRACT

Chronic periodontitis, characterized by inflammation and destruction of periodontal supporting tissues, is one of the most common oral diseases worldwide. In the pathogenesis of periodontitis, polymorphonuclear leukocytes (PMN) act as the primary mediators of the host response against proliferating periodontal pathogenic microorganisms. Activated PMN produce a large amount of reactive oxygen species (ROS) and result in destruction of periodontal tissues. Abundant evidence has shown that periodontal diseases were highly associated with several inflammation-related systemic diseases, such as cardiovascular disease, diabetes mellitus and chronic respiratory diseases. Reactive oxygen species (ROS) regulate cellular homeostasis and act as prime modulators of cellular dysfunction contributing to disease pathophysiology. Oxidative stress (OS) can be defined as an imbalance between the productions of highly reactive molecular species and antioxidant defense systems. Oxidative stress plays an important role in the pathogenesis of these diseases. It has also been hypothesized that oxidative stress arising from periodontal lesions may be an important cause of systemic inflammation. Scavenging or detoxification of excess ROS is achieved by an efficient antioxidative system comprising of the nonenzymic as well as enzymic antioxidants. In this review, we have summarized the current literature surrounding ROS and their role in metabolic and inflammatory regulation, focusing on ROS signal transduction and its relationship to disease progression.

Keywords: Antioxidants; oxidative stress; periodontitis; reactive oxygen species

INTRODUCTION

Free radicals and reactive oxygen species (ROS) are essential to many normal biologic processes. ROS include free radicals such as superoxide anion (O2 •−), hydroxyl radical (•OH), as well as non-radical molecules like hydrogen peroxide (H2O2), singlet oxygen (1O2), and so forth. Stepwise reduction of molecular oxygen (O2) by high-energy exposure or electron-transfer reactions leads to production of the highly reactive ROS.[1] At low concentrations, these free radicals stimulate the growth of fibroblasts and epithelial cells in culture, but at higher concentrations it may result in tissue injury. Excessive production of ROS oxidizes DNA, lipids and proteins, inducing tissue damage.[2] Reactive oxygen species (ROS) are key signaling molecules that play an important role in the progression of inflammatory disorders. In the last decade, studies have indicated that ROS, including superoxide and hydrogen peroxide, are crucial components that regulate the differentiation process of osteoclasts. Osteoclasts (OCs), cells specialized for bone resorption, utilize ROS as second messengers during receptor activator of NF-κB ligand (RANKL)-induced differentiation and activation.[3,4] When the level of ROS exceeds the defense mechanisms, a cell is said to be in a state of "oxidative stress." The term ''oxidative stress''

Department of Periodontology, Saraswati Dental College, Lucknow, Uttar Pradesh, India.
Address for Correspondence:
Dr. Ruchi Srivastava, Department of Periodontology, Saraswati Dental College, Lucknow (UP)-226016, India. +91 9793889594, drruchi117@gmail.com
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began to be used frequently in the 1970s, but its conceptual origins can be traced back to the 1950s to researchers pondering the toxic effects of ionizing radiation, free radicals, and the similar toxic effects of molecular oxygen, and the potential contribution of such processes to the phenomenon of aging.[5] It has been hypothesized that oxidative stress arising from periodontal lesions may be an important cause of systemic inflammation. Some but not all epidemiological studies have shown that biomarkers levels of oxidative stress in the peripheral blood of periodontitis patients were different from periodontal healthy subjects.[6]

Oxidative Stress has been linked with both onset of periodontal tissue destruction and systemic inflammation. Many studies have been done on oxidative stress between individuals suffering from severe periodontitis and control individuals.[7] Recent studies indicate that the increase in circulating oxidative stress following diabetes mellitus, cardiovascular diseases, obesity and inappropriate nutrition damages periodontal tissues.[8] Also oxidative stress markers have been evaluated according to diagnosis of periodontitis, and characterizing their changes after intervention trial of periodontal therapy (IPT).[9] Because of the multifunctional roles of ROS, it is necessary for the cells to control the level of ROS tightly to avoid any oxidative injury and not to eliminate them completely.

Therefore, the aim of this review is to summarize the relationship between periodontitis and systemic inflammation, and the effects of periodontal therapy on oxidative stress parameters. the way health care personnel retrieved and disseminated information in the past and will continue to do so.[3,4]

METHODOLOGY FOR SEARCH STRATEGY

A literature search Medline and PubMed databases were searched under the following key terms: “reactive oxygen species,” “oxygen radicals,” “free radicals,” “ antioxidants,” and “chronic periodontitis.” All keywords were restricted in title or abstract without the language limitation. Only highly relevant articles from manual and electronic databases were selected for the present review. The aim of this review is to highlight the role of ROS and antioxidant defence systems in the pathophysiology of periodontitis, and also to search for possible therapeutic modalities for future host-modulating therapies.

LITERATURE REVIEW

Concept of Free Radical Biology:

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process and they are well documented for playing a dual role as both deleterious and beneficial species. Though in normal physiological condition the generation of reactive species are tightly regulated by different enzymatic and non-enzymatic antioxidant, but overproduction of ROS results in oxidative stress, which is an important mediator of damage to cell structures, including lipids and membranes, proteins, and DNA.[10]

Free Radicals and Their Source :

Free radical is an atom (e.g., oxygen, nitrogen) or group of atoms or molecular species capable of independent existence that contains atleast one or more unpaired electrons in the outermost shell configuration. Free radicals are also known as reactive oxygen species (ROS) or reactive nitrogen species (RNS).[11]

Free Radicals are molecules with an unpaired electron.[12] This unpaired electron usually gives a considerable degree of reactivity to the free radical. Free radicals in biological systems were explored in 1956 by D. Harman who proposed the concept of free radicals playing a role in ageing. In 1977, Mittal and Murad provided evidence that the hydroxyl radical (•OH) stimulates activation of guanylate cyclase and formation of the “second messenger” cyclic guanosine monophosphate (cGMP).[13]

Due to the presence of a free electron, these molecules are highly reactive and they are important intermediates in natural processes

involved in cytotoxicity, control of vascular tone, and neurotransmission. Radiolysis is a powerful method to generate specific free radicals and measure their reactivity.[14]

As these species play a dual role as both toxic and beneficial compounds, a delicate balance between their two antagonistic effects is clearly an important aspect of life. At low or moderate levels, ROS and RNS exert beneficial effects on cellular responses and immune function. At high concentrations, they generate oxidative stress, a deleterious process that can damage all cell structures.[15]

Immune system: Immune system cells generate oxy-radicals and ROS in response to pathogens.[16]

Metabolic process: Free radicals can generate during metabolism of arachidonic acid, platelets, macrophages and smooth muscle cells. Lipid peroxidation an important source of free radicals and can formed from several sources like mitochondrial cytochrome oxidase, xanthine oxidases, and neutrophils. Mitochondria generate continuously and abundantly oxy-radicals and ROS as toxic waste through a number of metabolic processes, each of which can produce different free radicals.[17]

Inflammation: Inflammation releases cytokines and initiates neutrophils and macrophages to produce free radicals.[18]

Stress: Mental and body's stress can trigger the production of free radicals as a toxic by-product. Additionally, the hormones that mediate the stress reaction in the body like cortisol and catecholamine themselves degenerate into destructive free radicals.[18]

Pollution: The different type of pollutants like air pollutants (asbestos, benzene, carbon monoxide, chlorine, formaldehyde, ozone, and toluene), chemical solvents (cleaning products, glue, paints, paint thinners, perfumes, and pesticides), and water pollutants (chloroform and other trihalomethanes) are all potent generator of free radicals. Burning of organic matter during cooking, forest fires, and volcanic activities also can generate free radicals.[2]

Radiation: UV radiations, medical and dental x-rays, gamma rays, and microwave radiation can lead to free radical generation.[2]

Dietary factors: Additives, alcohol, coffee, foods from animal origin, foods that have been barbecued, broiled fried, grilled, or otherwise cooked at high, temperatures, foods that have been browned or burned, herbicides, hydrogenated vegetable oils, pesticides, sugar and processed foods containing high levels of lipid peroxides, and can produce free radicals.[17]

Toxins and drugs: Carbon tetrachloride, paraquat, benzo pyrene, aniline dyes, toluene and drugs like adriamycin, bleomycin, mitomycin C, nitrofurantoin, chlorpromazine etc. increases free radical productions.[18]

Other factors: Automobile exhausts fumes, smoking of tobacco products, cause free radicals generation.[19]

Reactive Oxygen Species and Periodontitis:

Periodontitis is an inflammatory process, initiated by the plaque biofilm, that leads to loss of periodontal attachment to the root surface and adjacent alveolar bone and which ultimately results in tooth loss. Chronic periodontitis is initially caused by various hyperresponsive and destructive products of immune response stimulated by microbial plaque around the gingival margin. The inflammatory and immune responses to the bacteria and also viruses that colonize the periodontal and associated tissues, involve the systemic circulation and ultimately the peripheral systems of the body.[20] This creates a complex bi-directional series of host-microbial interactions involving cellular and humoral factors and networks of cytokines, chemokines, and growth factors. It is believed that while the primary etiological agent is specific, predominantly gram negative anaerobic or facultative bacteria within the subgingival biofilm, the majority of periodontal tissue destruction is caused by an inappropriate host response to those microorganisms and their products. More specifically, a loss of homeostatic balance between proteolytic enzymes (e.g. neutrophil elastase) and their inhibitors (e.g. a1-antitrypsin) and reactive oxygen species (ROS) and the antioxidant defense systems that protect and repair vital tissue, cell, and molecular components is believed to be responsible. When

periodontitis develops, ROS produced in the periodontal lesion diffuse into the blood stream, resulting in the oxidation of blood molecules (circulating oxidative stress). Such oxidation may be detrimental to systemic health.[21]

Antioxidant: Under normal physiological conditions, there is a balance between ROS and antioxidants. Oxidative stress happens only when the antioxidant defense system could not neutralize the elevated ROS production.[22] Antioxidants can be classified as two categories based on their mode of function.[23]

Classification of Antioxidants:

1. Enzymatic antioxidant

Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), and Glutathione reductase (GR).

2. Non-Enzymatic antioxidant

a. Metabolic antioxidant

Reduced glutathione, lipoid acid, L-arginine, coenzyme $Q_{10,}$ melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc.

b. Nutrient antioxidants

Vitamin E, vitamin C, carotenoids trace metals (selenium, manganese, zinc), flavonoid, omega-3 and omega-6 fatty acids, etc.

More recently, revealed that significant redox disturbances exist in neutrophils of patients with periodontitis, which are associated with deregulation of anti-inflammatory transcription factor Nrf2 pathway resulting in neutrophil hyperactivity/ hyper-reactivity.[24]

Multiple numbers of studies have shown association linking cigarette smoking and nicotine toxicity to glutathione depletion within periodontal tissues. Studies of betel nut chewing, and periodontitis have shown that arcea nut alkaloid, arecoline-induced thiol depletion in periodontal ligament fibroblasts may render them more susceptible to the effects of nicotine; glutathione protection negated nicotine toxicity; and that cigarette smoke decreased periodontal ligament fibroblast glutathione levels in a dose-dependent manner and stimulated stress-specific genes.[24]

Periodontal Inflammation: From Gingivitis to Systemic Disease:

Oral bacteria and gingival inflammation may influence systemic health through four potential pathways: bacteremia, systemic dissemination of locally produced inflammatory mediators, provocation of an autoimmune response, and aspiration or ingestion of oral contents into the gut or airway.[25]

Dental plaque stimulation of cytokine production in the periodontium may elevate levels of cytokines in the peripheral blood. Periodontal inflammation either contributes directly to the elevation of the concentration of these substances in peripheral blood or signals distant organs (e.g., the liver) to produce them. The liver could respond, through the acute-phase response by producing CRP, fibrinogen, etc. These proteins may have deleterious effects on other target organs (e.g., heart, brain) can induce vascular injury, atherogenesis, cardiovascular disease, and stroke. It is also possible that periodontopathic bacteria stimulate the periodontium to release proinflammatory cytokines that, when aspirated or swallowed, alter mucosal surfaces to promote adhesion of pathogenic bacteria that cause diseases such as pneumonia or gastric ulcers.[15] Finally, cytokines released from inflamed periodontal tissues may enter the respiratory tract in aspirated saliva, triggering the sequence of neutrophil recruitment, epithelial damage, and infection.[16]

With appropriate intervention, this process can be reversed and the periodontium returned to a state of health. Unfortunately, periodontal disease goes untreated for many years and then, for the systemic host response to this insult to contribute to disease processes that result in cardiovascular disease and stroke, respiratory disease, and adverse pregnancy outcomes.[10] Oxidative stress seems to have a great role in the ethiopathogenesis of MetS. Metabolic syndrome (MetS) is characterized by multiple disorders. MetS was initially defined as Syndrome X, referring to the synergy of its components, such as hyperinsulinemia, hypertension, hypertri-glyceridemia, and visceral obesity. Subsequently, it was defined as insulin-resistance syndrome, since it is believed that insulin resistance was the

dominant factor predisposing the occurrence of other symptoms. Other peculiarities that seem to be associated with MetS include hepatic steatosis, inflamed adipose tissue, enhanced clotting factor activity, endothelial dysfunction, inflammation and obviously oxidative stress. A body mass index (BMI), a measure of percentage of body fat based on height and weight, greater than 25 increases the risk of MetS. Excess fat in the abdominal area is a greater risk factor for heart disease than excess fat in other parts of the body, such as on the hips. Therefore, so does abdominal obesity, *i.e.*, having an apple shape rather than a pear shape. Also, there is a greater likelihood of MetS if a family history of type-2 diabetes or a history of diabetes during pregnancy (gestational diabetes) is present. A diagnosis of fatty liver, gallstones, breathing problems during sleep, cardiovascular disease, or polycystic ovary syndrome (such metabolic problems affect a woman's hormones and reproductive system) also increases the risk of MetS.[26] The first goal of the clinical management of MetS is to reduce the major risks for CVD and type 2 diabetes by stopping smoking, stabilizing LDL and blood pressure parameters, maintaining glucose levels at the recommended values, reducing body weight (body mass index less than 25 kg/m^2) through an adapted diet, and doing moderate-intensity physical activity for at least 30 minutes on most days of the week.[27]

There is a physiological fine balance between oxidant activities and antioxidant defenses, but when this equilibrium is disrupted to the advantage of ROS, or to increased ROS activity or to want of antioxidant defenses, the result is oxidative stress. In this condition ROS operate by creating an adequate environment for phagocytic vacuole and enzymatic digestion, and by mediating cellular signaling. An amplified activity of ROS implies a large spectrum of molecular and cellular damage, such as lipoxidation. This results in covalent binding with proteins, which alters their structure and function. Some oxidized proteins are difficult to remove by cells and tend to accumulate with aging and in the presence of chronic diseases such as diabetes mellitus. Several studies have demonstrated a real correlation between oxidative stress and MetS. In fact, in patients suffering from MetS, systemic oxidative stress seems to be more elevated than in healthy controls, and antioxidant defense seems to be decreased, as demonstrated by the diminished rate of Vit C, α-tochopherol, and superoxide dismutase activity in serum, and by increased lipoxidation.[28]

Obesity is firmly related to oxidative stress–mediated endothelial damage.[29] An increased caloric excess not balanced by an elevated energy expense leads to an increase in the metabolism of Krebs cycle, generating a ROS excess. Some high-density lipoprotein cholesterol (HDL-C) subfractions present antioxidant activity that is diminished in people suffering from MetS, and this reduction is correlated with systemic oxidative stress and insulin resistance. Furthermore, obese adults with MetS have an increased plasmatic rate of oxidized low-protein lipoprotein cholesterol (LDL-C) compared with obese patients without this syndrome.[29] MetS allows a pro-oxidative state in periodontal tissue, altering antioxidant defense mechanisms. This adversely affects tissue response against bacterial plaque attack.

Insulin resistance is a condition in which the normal amount of insulin is insufficient to obtain an adequate response from muscular and adipose tissues and from hepatic cells, and this leads to a severe hyperglycemia with deleterious systemic effects, such as lower intracellular antioxidant defenses.[30]

Some studies have proposed tetracycline as useful in combating oxidative stress in periodontitis and metabolic disorders.[30,31] In fact, in addition to its antimicrobial effect, it shows antioxidant, anti-inflammatory, proanabolic, immunomodulatory, angiogenetic, and antiapoptotic effects. Decreased yields of oxidative stress were also obtained in the presence of minocycline, which demonstrates its potential role as an adjunctive therapeutic agent in an environment of oxidative stress, such as in periodontal disease and coexisting cardiometabolic pathologies.

Thymoquinone has also demonstrated a variety of pharmacologic properties, including antihistaminic, antibacterial, antihypertensive, hypoglycemic, anti-inflammatory, and antioxidative activities. Through its anti-

inflammatory and antioxidant properties, thymoquinone seems to play an important role in preventing periodontal diseases.[32] Also, S-nitrosoglutathione is a nitric oxide donor that seems to exert antioxidant, anti-inflammatory, and microbicidal actions, and has been demonstrated as a potential drug for the topical treatment of periodontitis. Finally, because of its anti-inflammatory effects, a novel α-iso-cubebenol isolated from the dried fruit of S. chinensis is considered a novel therapeutic agent to ameliorate periodontitis.

Ischemic stroke is also a leading cause of death and long-term disability and patients who exhibit metabolic risk factors including diabetes mellitus, obesity, and dyslipidemia are at a greater risk of experiencing stroke-related events. Within minutes of hypoxia and glucose deprivation, a complex cascade of molecular events ensues, involving depolarization of neurons, increased Ca2+ influx, ATP depletion, and release of the excitatory neurotransmitter glutamate. Activation of glutamate receptors leads to a further increase in intracellular Ca2+, activation of NOS and NOX signaling, mitochondrial dysfunction, and neuronal death. Although hypoxia and glucose deprivation play a major role in the neurodegeneration induced by stroke, a role for ROS is very clear. Indeed, several clinical studies have shown a correlation between elevated oxidative stress and brain ischemia and decreasing oxidative stress may be protective against stroke-induced complications.[13] Moreover, specific pathways, such as the glycation and glyoxidation of proteins to produce advanced glycation endproducts (and increased receptor for advanced glycation end product expression), are dependent on oxidative mechanisms and are highly prevalent in type 2 diabetes and smokers, the two major risk factors for periodontitis. Such oxidation products increase neutrophil adhesion, chemotaxis and priming and in hyper-active/reactive neutrophils, may have damaging effects of periodontal bacteria-mediated increases in ROS and oxidative stress, providing one explanation for the increased risk of periodontitis in type 2 diabetes and smokers. Periodontal diseases seem related to pathologies and conditions characterized by high oxidative stress and by the presence of advanced glycation end-products (AGE), such as diabetes and physiologic aging. AGEs are able to favor chemotaxis and the production of proinflammatory mediators, to inhibit fibroblasts and osteoblasts, and to accelerate periodontal damage directly or binding their receptors for AGEs (RAGE).[25] Periodontitis is strictly correlated to hyperglycemia; in fact, it is also considered the sixth complication of diabetes mellitus, predialysis and hemodialysis in chronic kidney diseases are also associated with a higher prevalence of severe periodontitis compared with healthy individuals. Chronic kidney failure is a clinical syndrome due to the slow, progressive, and irreversible loss of the glomerular filtration rate, and may be associated with several oral manifestations, such as xerostomia, uremic stomatitis, and periodontitis, diagnosed as clinical attachment loss. Recent studies have shown an association between high levels of CRP and IL-6 and periodontitis, an association that decreases after periodontal treatment. Due to this association with the systemic inflammatory response, chronic periodontitis has recently been included as a nontraditional risk factor for chronic kidney failure. In synthesis, metabolic alterations related to MetS component diseases cause an augmented response to bacterial plaque, which favors periodontitis insurgence. Hence, it has been pointed in many studies that how periodontal treatment can reduce inflammatory mediators related to endothelial and cardio-circulatory dysfunctions.[33]

CONCLUSION

Reactive oxygen species (ROS) are known to determine oxide-reducing balance alteration, oxidative stress, and carcinogenicity. Many diseases, including cancer and other pathologies associated, like arteriosclerosis and cataracts, are related to mitochondrial dysfunctions provoked by reactive oxygen species. Reactive oxygen species (ROS) play a role in a number of degenerative conditions including osteoporosis. An increased understanding of specific sources of ROS production and an appreciation for how ROS influence cellular metabolism may help guide us in the effort to treat various systemic diseases.

In addition, improvement of periodontitis by adjunctive use of anti-oxidants with various surgical and non-surgical periodontal therapies could reduce the occurrence of circulating oxidative stress. Also in such cases, therapeutic approaches to systemic oxidative stress might be necessary to improve periodontal health.

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