

## Effect of Free Radicals and Antioxidants in Periodontal Disease

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### Abstract

All processes in the body are under a perfect balance, any disturbance of this balance will lead to a diseased state. In the oral cavity inflammatory periodontal diseases are the most prevalent; the main culprits in the pathogenesis of this condition are free radicals and reactive oxygen species. These are unstable molecules which easily affect the soft and highly permeable oral mucous membrane by creating 'oxidative stress'. Antioxidants stabilize the free radicals by donating one electron, thus body generally balances the harm of free radicals through antioxidants. Any disturbance in their equilibrium can prove detrimental. Oral cavity and systemic infections are linked, thus there is an increased risk of diabetes and other cardiovascular and metabolic disorders as a result of this disturbed equilibrium. Use of topical antioxidants should be encouraged by the dentists in management as well prophylaxis in patients of periodontal problems.

**Keywords:** Free Radicals; Oxidative Stress; Antioxidants.

### Introduction

In the human body the physiological processes are always in a perfect balance, the body is always in a state of attaining homeostasis (a constant and favorable internal environment). In recent times oxidative stress has been implicated in the etiology of several diseases and because of this stress the perfect balance between free radicals and antioxidants gets disturbed and favors the direction of the former.

Free radicals have assumed a dynamic importance in recent times, though generated as a part of normal physiology when the levels are disturbed it plays a role in the pathogenesis of metabolic and cardiovascular diseases- diabetes, psychological stress, ocular diseases, AIDS, in fetus, pulmonary disorders, autoimmune diseases, arthritis, ageing, cancer, male infertility[1]. A free radical is a toxic oxygen metabolite having one electron in the outermost shell which is not paired thus making it highly

reactive. The phrase reactive oxygen species (ROS) refers to free radicals and molecules which are highly reactive and derived from molecular oxygen like peroxides, hydroxides, superoxide. Free radicals are generated by oxidation process which is a part of normal metabolism but they are capable of initiating chain reaction which is responsible for making them a potential danger as they can damage cellular components and ultimately cause the cell to die. To antagonize the toxic effect of free radicals, antioxidants are present as the saviours. Antioxidants are substances which when present in lower concentrations then the oxidizable substrate inhibit or delays its oxidation. Antioxidant system of the body is very responsive and responds rapidly to the disturbance in redox balance of the body and neutralize 'oxidative stress' referring to the damage caused by free radicals [2].

In the oral cavity also the diseases relating to oxidative damage include periodontitis, oral cancer, oral lichen planus, dental caries, oral submucous fibrosis, peri-implantitis, burning mouth syndrome etc. All these periodontal problems are widely prevalent in Indian society; according to National Oral Health Survey and Fluoride Mapping (2002-2003), Dental Council of India, New Delhi, 2004 the periodontal prevalence was 57%, 67.7%, 89.6% and 79.9% in the age groups 12, 15, 35-44 and 65-74 years, respectively. Several theories have been proposed

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signifying the manner by which the ROS and free radical damage periodontium most accepted one suggests the role of polymorphonuclear cells (PMNs). [3].

#### *Free Radicals*

Oxygen is the primary essential constituent required for the survival of living beings, but its pricelessness comes along with its potential toxicity, often described as a double edged sword. Oxygen is the ultimate electron acceptor in the mitochondrial electron transport chain where flow of electrons is responsible for ATP production; the reduction of oxygen to water releases large amounts of energy that can give rise to free radicals or reactive oxygen species. The toxicity and reactance of these molecules may play a role in inflammatory and degenerative diseases.

Reactive oxygen species are not free radicals in the true sense but nevertheless are capable of generating free radicals in the intracellular and extracellular environment for example hydrogen peroxide, ozone, singlet oxygen, hypohalous acids.

A free radical is either an atomic or a molecular species with a single unpaired electron in its structure, it can be negative or positive in charge or neutral electrically. There are three possible means of free radical production [4]:-

- Homolytic cleavage of a covalent bond of a normal molecule, resulting in each fragment retaining one of the paired electron, a high energy input is required for this operation.  $A:B \Rightarrow aA \cdot + B \cdot$  (electrically neutral free radical)
- A normal molecule may undergo loss of a single electron.  $A+B:\Rightarrow A \cdot + B \cdot$  (+ or - charged free radicals)
- 'Electron transfer' or addition of single electron to a normal molecule, a common occurrence in the biological system.  $A+e \cdot \Rightarrow A \cdot$  (- charged free radical)

Free radicals and Reactive oxygen species are a product of the normally occurring metabolic processes of the human body or from sources external to the body such as ozone cigarette smoking, air pollutants, X-rays and chemicals from industries to name a few [5]. The formation of free radical occurs continuously as an outcome of enzymatic as well as non enzymatic reactions of the body. Enzymatic reactions also act as a free radical source and include those involved in respiratory chain, cytochrome P-450 system, phagocytosis and in prostaglandin synthesis. Non enzymatic reactions of oxygen with organic compounds also yield free radicals as well

as ionizing reactions [6].

Some endogenous sources resulting in the formation of free radicals include inflammation, electron leakage from mitochondrial transport systems forming superoxide peroxisomes, phagocytosis, arachidonate pathways, exercise, ischemia/reperfusion injury, Xanthine Oxidase. Other exogenous sources include cigarette smoke, radiation, environmental pollutants, certain drugs, pesticides, industrial solvents, heat trauma, therapeutic drugs [7].

#### *Pathogenesis of Free Radicals and Reactive Oxygen Species*

Owing to their highly reactive nature free radicals can modify rapidly small biomolecules (vitamins, carbohydrates, minerals), macromolecules (proteins, fats) or supramolecules (circulating lipoproteins, cell membrane). The extent and type of damage they cause will vary according to their site of generation.

There are 5 ways by which free radicals and reactive oxygen species generally cause damage to the human body these include [8]:

- Lipid peroxidation (through activation of cyclooxygenases and lipoxygenases)
- DNA damage (through strand break and base hydroxylation)
- Protein damage which includes proteoglycans and gingival hyaluronic acid.
- Oxidation of important enzymes such as anti proteases like alpha-1-antitrypsin.
- Stimulation of pro-inflammatory cytokine release by macrophages and monocytes.

The oral cavity is highly susceptible to damage from free radicals because various substances are rapidly absorbed by the oral which then contribute in generating free radicals and initiating oxidative stress such as peroxide in the whitening agents, nicotine, alcohol and the conventional dental materials also. Periodontal infection may also be a major player in oxidative stress. Periodontal disease is a chronic inflammation of the tooth's connective tissue progressing to bone damage; one of the causes maybe attributed to impaired immune system. Periodontal disease has also been linked to heart diseases, diabetes, stroke, pre-term births and infections of respiratory tract.

Periodontal diseases are generally caused by an immune reaction between host and the pathogenic bacteria. The primary etiological agent for initiation of inflammatory changes in the periodontal tissue is

the sub-gingival dental plaque; specifically the gram negative anaerobic bacteria or facultative anaerobes within this biofilm. The bacterial antigen invigorates the neutrophils to produce  $O_2^-$  via the 'respiratory burst' pathway of metabolism catalyzed by the enzyme NADPH Oxidase during phagocytosis. These bacterial species also stimulate the release of various cytokines including interleukin-8 and TNF- $\alpha$ , which further lead to an increase in number and activity of neutrophils along with these cytokines. The bacterial cell component and inflammatory cytokines causes increased recruitment and activation of hyper active PMNs and thus accelerating the production of ROS and free radicals.

On the other hand, during acute inflammation the macrophages of the vascular endothelium produce NO free radical by nitric oxide synthase. Recent research in this area has also shown how superoxide and hydrogen peroxide also play a role in activating the osteoclasts and thus leading to increased levels of matrix metalloproteins (MMP) which cause tissue damage. Periodontal tissue destruction leads to excess production of lipid peroxides, inflammatory mediators, and oxidized proteins. These products on the other hand cause further activation of fibroblasts, macrophages and neutrophils to generate more of the reactive oxygen species. To sum up in short, we can say that a vicious circle is formed in the presence of ROS, periodontal pathogens and tissue destruction [9, 10].

### Antioxidants

Antioxidants are substances antagonistic to free radical action; these substances when present in a concentration lower than those of oxidizable substrate will inhibit or delay the oxidation of that substrate. Antioxidant defense system is dynamic and prompt in action against slight disturbance in the redox balance of the body. Antioxidants can be up-regulated and neutralize the free radical formation in oxidative stress conditions.

The antioxidant defence system of the body is dynamic to cope with oxidative stress caused by free radical formation under normal conditions and maintain the redox balance; however any disturbance in this balance due to either over production of free radicals or fall in antioxidants levels will lead to deleterious effect on the body [11].

The different mechanisms by which anti-oxidants may offer protection against free radicals damage include [12]:

- Preventing the formation of free radicals
- Scavenging of the reactive metabolites and

converting them to less reactive stable molecules.

- Eases the process of repair of the damage caused by free radicals
- Facilitate the functioning of other antioxidants by providing a favorable environment. Many studies have proved the association of oxidative stress with periodontal disease, a recent study titled 'Oxidative stress, systemic inflammation and severe periodontitis' explored this relationship. They made a comparison between oxidative stress and blood antioxidant level and measured IL-6, C-Reactive protein, total HDL, LDL cholesterol and triglyceride levels in individuals with severe periodontitis and compared them against control patients with no signs or history of periodontitis. Results revealed that individuals with severe periodontitis had higher oxidative stress levels and lower antioxidant potential compared to the healthy control; independent of parameters like age, gender, smoking habits, ethnicity [13].

Antioxidants can be classified in a number of ways including mode of function, location of action, structural dependence, solubility and source (Table 1). Some important antioxidants include: Vitamin C, adenosine Vitamin E, NADPH, Vitamin A, Polyphenols, flavonoids, Beta Carotene, Nitric Oxide synthase etc [2].

**Table 1:** Antioxidants classification based on their origin

Endogenous antioxidants (synthesized by the body)	Catalase, glutathione peroxidase, glutathione-S transferase, ceruloplasmin, transferrin, ferritin, proteases.
Exogenous antioxidants (obtained through diet)	Carotenoids, ascorbic acid, flavanoids, folic acid, cysteine
Synthetic antioxidants	N-acetyl cysteine, tetracycline, penicillinamine

### Implications of Free Radicals and Antioxidants in Periodontal Management

A large proportion of the world population suffers from periodontal disease especially periodontitis. Scaling, surgical intervention and antibiotic use to control infections are routine treatments. However in today's time alternative treatments are available and dental professionals are trying other innovative ways to combat these problems.

Since inflammation accompanies all periodontal diseases and main malady associated with it is oxidative stress hence the role of antioxidants to deal with this clinical scenario has enhanced. They

stabilize these unstable molecules thus prevent further progression of the disease as well as act as a prophylactic agent. Inflammation of the oral tissues can be a contributing factor in various chronic systemic illnesses like Alzheimer's, osteoporosis, Parkinson's disease, osteoarthritis and other cardiovascular problems [14]. Thus proper management of these patients is imperative. There are a plethora of antioxidants-including enzymes, minerals, vitamins and other compounds [15]. Antioxidants are produced within the body and some can be supplied to the body through diet such as vitamin A through consumption of carrots, green leafy vegetables, even pharmacological supplements of such vitamins acting as antioxidants are available [15]. A healthy, varied diet rich in fruits and vegetables, whole grains, and nuts is an excellent source of antioxidants.

Antioxidants may be supplied by other external means as well in the form of pastes, lozenges, gums and gels. These topically applied antioxidants are being increasingly used by dentists in the management of periodontal problems as well as malignant conditions like oral leukoplakia and oral cancers. These are a combination of a wide variety of antioxidants like-phloretin, feluric acid, silymarin, hesperetin, tetracurcuminoid. Clinically the efficiency of oral antioxidants has been proved in a study conducted among 100 dental patients, six weeks use of these antioxidants showed great improvement in the gingival color and form and a decreased probe depth, although research is ongoing in proving the efficacy of oral topical antioxidants [16].

## Conclusion

Periodontal disease is a common disorder affecting the globe, it causes slow destruction of periodontium and the effects caused are generally irreversible [17]. Free radicals and antioxidants play a vital role in the pathogenesis of periodontal diseases. The increased production of free radicals leads to oxidative stress and damage; antioxidants on the other hand scavenge these free radicals and act as 'life saving agents'. Oral cavity lesions have a profound impact on the other body systems, this is an interdependent existence; thus consumption of antioxidants in diet should be encouraged for general well being.

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