Review Article

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Role of Antioxidants in Periodontal Health And Disease: A Review

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ABSTRACT

Background: Periodontitis is an increasing area of interest due to its global prevalence. This inflammatory condition results due to the loss of the critical balance between the virulence factors produced by microorganisms and the inflammatory host response. A number of efforts have been made in the past to address this condition and regain periodontal health. The primary etiological agent of this inflammatory disease is a polymicrobial complex, predominantly Gram negative anaerobic or facultative bacteria within the subgingival biofilm. These bacterial species initiate the production of various cytokines such as interleukin-8 and TNF-α, further causing an increase in number and activity of poly morphonucleocytes (PMN) along with these cytokines, PMNs also produce reactive oxygen species (ROS) superoxide via the respiratory burst mechanism as the part of the defence response to infection. ROS just like the interleukins have deleterious effects on tissue cells when produced in excess. To counter the harmful effects of ROS, human body has its own defence mechanisms to eliminate them as soon as they are formed. The aim of this review is to focus on the role of different free radicals, ROS, and antioxidants in the pathophysiology of periodontal tissue destruction.

Keywords: Antioxidants, Neutrophil, Reactive oxygen species, Vitamin C.

INTRODUCTION

Periodontitis is a ubiquitous chronic inflammatory disease affecting the supporting tissues of the teeth. It is one of the most common chronic diseases affecting humans. The disease is caused by infection induced by specific microorganisms or a group of microorganisms, which eventually causes progressive destruction of the periodontal ligament (PDL) and alveolar bone. The progression of this destructive disease appears to be dependent on abnormal host response to the biofilm organisms. The periodontitis phenotype is characterized by hyper-inflammation involving excess release of oxygen-free radicals by inflammatory cells, especially polymorphonuclear leucocytes (PMNLs).[1,2]

PMNLs are the first line of defense against any microbial invasion. In the event of amicrobial attack, there is a burst of O2 consumption (i.e., on-mitochondrial) at about 10 or 20 times that of resting consumption. This burst of oxygen consumption is the "respiratory burst" phenomenon, and the excessive uptake of oxygen in neutrophils and macrophages generates SO anion radicals, H2O2, hydroxyl radicals, and HOCl, all of which are capable of damaging either cell membranes or associated biomolecules. These are in fact the free radicals (FRs) or reactive oxygen species (ROS) capable of inducing tissue damage and cell destruction. Well-being of the organism depends on the activity of efficient defense mechanisms against oxidative damage induced by FRs/ROS. Antioxidants provide this defense and protection. They also counteract the destructive effects of ROS and help to maintain homeostasis in the body. It is believed that although the primary etiological agent of the disease is specific,

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predominantly Gram-negative anaerobic or facultative bacteria within the subgingival biofilm.[2,3]

The majority of periodontal tissue destruction is caused by an inappropriate host response to those micro-organisms and their products. Reactive oxygen species (ROS) form as a part of the physiological functions of all cells, and the significance of their role as mediators in cell signaling has become more evident.[4,5]ROS can harm different types of cells and tissues through protein damage, lipid peroxidation, and DNA damage. Excessive ROS production plays a role in the pathogenesis of various chronic inflammatory diseases, including periodontal disease [5]. Cells and tissues require antioxidants to prevent the tissue damage caused by overproduction of ROS.[6,7,23]

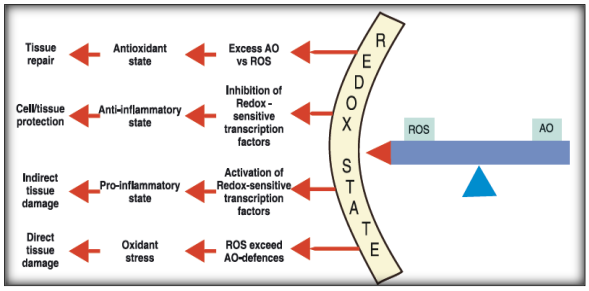

Fig 1: The biological effects of small and large shifts in the balance of activity between reactive oxygen species (ROS) and antioxidant (AO) species.

Free radicals:

An FR may be defined as an atomic or molecular species capable of independent existence with one or more unpaired electrons in its structure. These FRs at low concentrations are involved in performing various cell signaling functions but at higher concentrations, they react with certain cellular components such as DNA, proteins, lipids exerting an oxidative stress in the gingival tissues, PDL, and alveolar bone and mediate tissue damage. Hence, to maintain the biological balance, antioxidants come into play.[7,8,26]

Antioxidant defense and damage repair: (Fig.1)

Organisms use SOD, catalase and glutathione peroxidase to protect themselves against generation of reactive oxygen species. They also take great care to keep as much iron and copper ion as possible safely bound in storage or transport proteins. Thus, there is three times as much transferrin iron-binding capacity in plasma as iron needing to be transported, so that there is essentially no free iron ion in plasma. Iron bound to such proteins as transferrin cannot stimulate lipid peroxidation or -OH generation: the same is true of copper bound to the plasma proteins ceruloplasmin or albumin.

The value of this sequestration is shown by an inspection of the pathology suffered by patients with iron overload disease, in which free iron ions do circulate in the blood. The patients can suffer liver damage, diabetes, joint inflammation and hepatoma, among other problems.[9,10,21,24]

Pathophysiology of periodontal tissue destruction:

Periodontal disease can be caused by immune reaction between pathogenic bacteria and host. The sub-gingival dental plaque is the main etiological agent for the initiation of inflammatory changes in the periodontal tissue. Lipopolysaccharides (LPS) and DNA from these bacteria cause the activation of both activating protein-1 and nuclear factor-k pathways in the gingival fibroblast via CD14 and TLR-4 (toll like receptor) and production of inflammatory cytokines.

The cell component of bacteria and inflammatory cytokines causes recruitment and activation of hyper responsive PMNs and thus speeds up the production of ROS. On the other hand, activation of NF-k and AP-1 causes activation of osteoclasts and increases the concentration of MMP (matrix metalloproteinases), which ultimately results in tissue damage. Periodontal tissue destruction leads to over production of lipid peroxides, inflammatory mediator, And oxidized proteins. These products further activate macrophages, neutrophils, and fibroblasts to generate more ROS.[10,11,20,25]

Evidence of tissue destruction by ROS in periodontitis: (Fig.2)

The majority of tissue destruction in periodontitis is considered to be the

result of an aberrant inflammatory/immune response to microbial plaque adjacent to the gingival margin and to involve prolonged release of neutrophil enzymes and ROS. Thiobarbituric acid reactive substances and MDA have been investigated in chronic periodontitis. All the

published studies have suggested that patients with chronic periodontitis have higher levels of lipid peroxidation than periodontally healthy controls.[11,12,19]

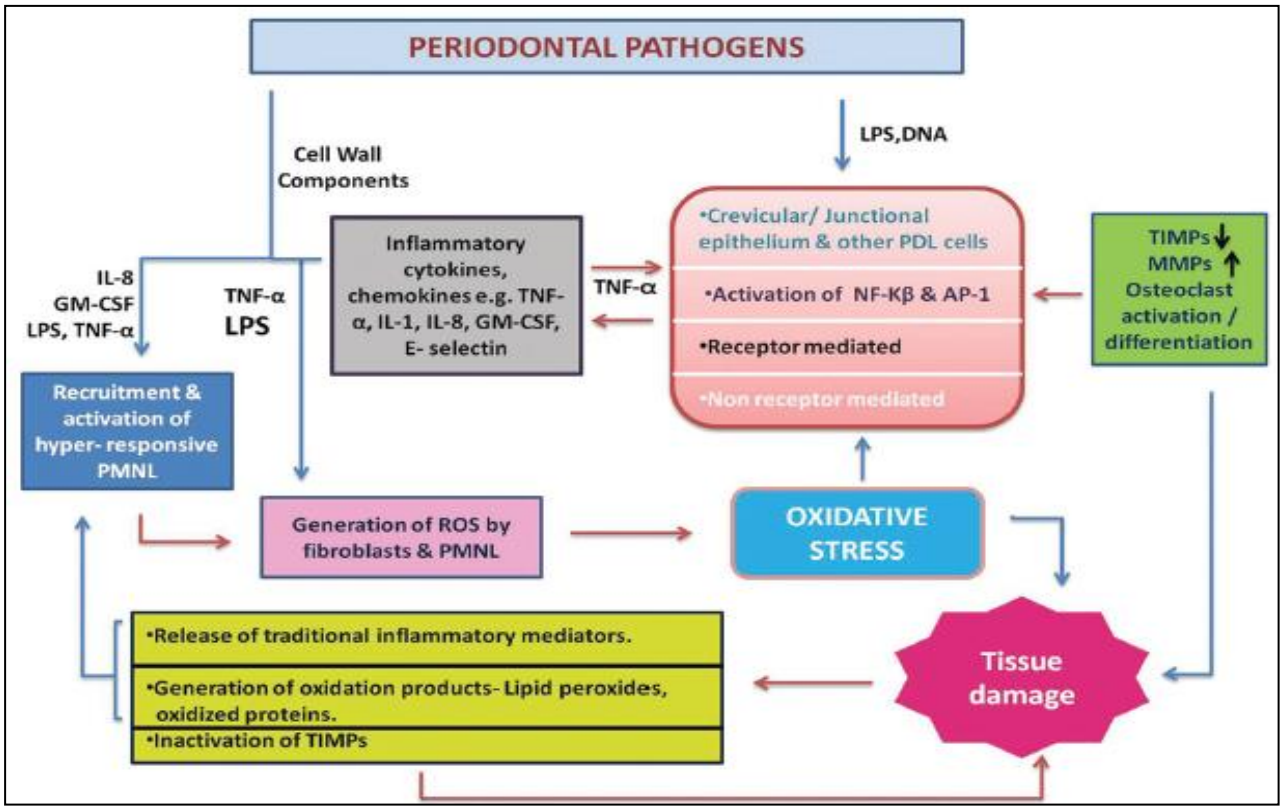

Fig 2: Simplified diagram illustrating a central role of ROS in generating chronic inflammation and tissue damage in response to periodontal pathogens. **MMP** – Matrix metalloproteinase; **TIMP** – Tissue inhibitor of matrix metalloproteinase; **NF-κβ** – Nuclear factor kappa beta; **AP-1** – Activating protein-1; **PDL** – Periodontal ligament; **TNF** – Tumor necrosis factor; **IL** – Interleukin; **GM-CSF** – Granulocyte–macrophage colony-stimulating factor; **LPS** – Lipopolysaccharide; **ROS** – Reactive oxygen species.

Table 1: Classification of Antioxidants:

Antioxidant classification	Example
a)Mode of action Preventive anti-oxidants	Anti oxidants enzymes: Superoxide dismutase enzymes (1, 2, and 3), catalase, glutathione peroxidase, DNA repair enzymes, e.g., poly (ADP-ribose) polymerase, others Metal ion sequestrators: Albumin, lactoferrin, transferrin, haptoglobin, ceruloplasmin, hemopexin, carotenoids, superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, uric acid, polyphenolic flavonoids
b) Scavenging (chain breaking) anti-oxidants	Ascorbate (Vitamin C), carotenoids (including retinol-Vitamin A), uric acid, α-tocopherol (Vitamin E), polyphenols (flavonoids), bilirubin, albumin, ubiquinone (reduced form), reducedglutathione and other thiols (free or protein bound)
c) Based on location	Intra-cellular Superoxide dismutase enzymes 1 and 2, catalase, glutathione peroxidase, DNA repair enzymes, e.g., poly (ADP-ribose) polymerase, others, reduced glutathione, ubiquinone (reduced form)
	Extra cellular Superoxide dismutase enzyme 3, selenium glutathione peroxidase, reduced glutathione, lactoferrin, transferrin, haptoglobin, ceruloplasmin, albumin, ascorbate, carotenoids, uric acid

	Membrane associated α-tocopherol

DNA – Deoxyribo nucleic acid; ADP – Adenosine diphosphate

Table 2: Studies investigating the relationship between antioxidants and periodontitis.

Sr.no	Analyzed markers	Biological Samples	Participants	Results	References
1.	SOD; CAT; GPx; glutathione reductase; vitamin C; vitamin E	Plasma; erythrocytes; erythrocyte membranes; gingival tissues	25 CP; 25 controls	#SOD, #CAT, #GPx and glutathione reductase of all types of samples in CP; vitamin C and vitamin E of all types of samples in CP (except for reduced glutathione in the gingival tissues).	**Panjamurthy et al., 2005** [17]
2.	SOD; CAT; glutathione; total thiol	Gingival tissue; blood	35 CP (20 smokers, 10 non-smokers)	"CAT and "total thiol of all types of samples in smokers; #glutathione of gingival tissue in smokers; #SOD of all types of samples in smokers	**Garg et al., 2006**[18]
3.	Urate; vitamin A; vitamin C; vitamin E; thiols; bilirubin; cholesterol; thiglycerides; albumin	Serum	256 participants	Vitamin A ($p < 0.0001$), urate ($p < 0.0001$) and thiols ($p < 0.01$) are influenced by gender.	Maxwell et al., 2006[19]
4.	SOD	Gingival tissue	34 CP (17 with type 2 diabetics, 17 systemically healthy); 35 controls (18 with type 2 diabetics, 17 systemically healthy)	#SOD in CP than controls ($p < 0.05$); "SOD in participants with diabetics than systemically healthy participants	Akalin et al., 2008
5.	SOD; GPx	Saliva	30 CP; 30 controls	#SOD and #GPx in CP ($p < 0.05$); SOD and GPx negatively correlates with MDA and 8-OHdG ($p < 0.001$)	Canakci et al., 2009
6.	SOD	GCF; saliva	60 smokers; 10 non-smokers	#SOD of all types of samples in smokers than controls, and correlates with the extent of smoking	Agnihotri et al., 2009[20]
7.	SOD	GCF; saliva	60 CP (33 pregnant, 27 non-pregnant); 18 gingivitis (pregnant); 46 controls (21 pregnant, 25 non-	"clinical parameters and #SOD in pregnancy, especially for the last phase of pregnancy	Akalin et al., 2009[16]

			pregnant		
8.	SOD; CAT; GPx	Serum; gingival tissue	49 CP (23 smokers, 23 former smokers, 20 non-smokers); 20 controls (non-smokers)	#SOD, #CAT, and #GPx of gingival tissuein CP than controls ($p < 0.01$); #SOD, #CAT, and #GPx of gingival tissue in CP (non-smokers) than CP (smokers and	Tonguc et al., 2011[21]
				former smokers) ($p < 0.01$).	
9.	SOD; CAT; glutathione reductase	Saliva	30 CP; 30 controls	#SOD, #CAT, and #glutathione reductase in CP; SOD, CAT, and glutathione negatively correlates with clinical parameters.	Trivedi et al, 2015 [22]

SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GCF, gingival crevicular fluid; CP, chronic periodontitis.

CONCLUSION

Periodontitis is an increasing area of interest due to its global prevalence. This inflammatory condition results due to the loss of the critical balance between the virulence factors produced by microorganisms and the inflammatory host response. A number of efforts have been made in the past to address this condition and regain periodontal health. ROS just like the interleukins have deleterious effects on tissue cells when produced in excess. To counter the harmful effects of ROS, human body has its own defence mechanisms to eliminate them as soon as they are formed.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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