Asian Journal of Medical Research Review Article

Role of Antioxidants in Periodontal Disease and Its Therapy

Amit Bhardwaj[1], Shalu Verma Bhardwaj[1]

[1]SGT Dental College, Gurgaon, Haryana; Private dental practitioner, Gurgaon,India.

Abstract

Periodontal disease is a chronic adult condition. Bacteria implicated in the etiology of this disease causes destruction of connective tissue and bone. As a result of stimulation by bacterial antigen polymorphic neutrophils (PMN) produces free radicals via respiratory burst as a part of host response to infection. Patients with periodontal disease display increased PMN number and activity. This proliferation results in high degree of free radical release culminating in heightened oxidative damage to gingival tissues, periodontal ligament and alveolar bone. Damage mediated by free radicals can be mitigated by "ANTIOXIDANT DEFENSE SYSTEM ". Physiological alteration and pathological states produced by free radicals depend on disequilibrium between free radical production and antioxidant levels leading to oxidative stress.

Key Words: Antioxidants, Coenzyme Q_{10} , Free radicals, Periodontal disease.

INTRODUCTION

Periodontal disease is an inflammatory disease process resulting from the interaction of a bacterial attack and host inflammatory response. Arrays of molecules are considered to mediate the inflammatory response at one time or another, among these are free radicals and reactive oxygen species (ROS). Periodontal pathogens can induce ROS overproduction and thus may cause collagen and periodontal cell breakdown. When ROS are scavenged by antioxidants, there can be a reduction of collagen degradation.

The majority of periodontal treatment modalities attempt to arrest the progression of periodontal destruction in order to avoid tooth loss. But there are some situations when periodontal therapy is not effective despite the provision of proper treatment. Therefore, periodontal research should attempt to identify background factors that may explain the response to therapy. Systemic factors such as a balanced nutrition or nutritional supplementation have not been thoroughly evaluated in periodontal research, although reports of the possible effects of nutrient deficiency and supplementation have appeared early in the periodontal literature.[1-4]

Address for correspondence*

Amit Bhardwaj

SGT Dental College, Gurgaon, Haryana; Private dental practitioner, Gurgaon,India

Email :amitmds1980@rediffmail.com

ROLE OF ANTIOXIDANTS

Antioxidant levels is as important as knowing your cholesterol levels, or your blood pressure. There are many studies linking free radical damage at the cellular level not only to premature aging, but also to virtually everything that ails us including periodontal disease. Free radicals are molecules or atoms that have lost an electron which causes them to become unstable and highly reactive. Antioxidants are the nutrients in fruits and vegetables that can neutralize free radicals by donating an electron without becoming unstable themselves. Unfortunately, because of depleted farm soils and early harvesting of crops to facilitate distribution to market, the fruits and vegetables that we find available to us today have significantly lower nutrient content then even 10 years ago and dramatically lower nutrient content from 50 years ago.

If your diet lacks certain nutrients, it may be more difficult for tissues in your mouth to resist infection. This may contribute to periodontal disease, a major cause of tooth loss in adults. Although poor nutrition does not cause periodontal disease directly, many researchers believe that the disease progresses faster and may be more severe in people with nutrient-poor diets because of compromised host response. Chronic subclinical inflammation is the driver of most, if not all, chronic diseases. It is a fact that the same basic inflammatory state underlies heart disease, cancer, Parkinson's disease, Alzheimer's disease, osteoporosis, osteoarthritis, chronic pain, and periodontitis.[5-8] The manifestation of the chronic inflammatory state is likely to differ depending

on our genetic disposition to disease expression. The term Genetic Polymorphism is used to describe the individual differences in our genes that can lead to the expression of various diseases.

ANTIOXIDANTS IN PERIODONTAL HEALTH

Oral biologists from University at Buffalo?s School of Dental Medicine have shown for the first time that a diet low in antioxidant vitamins can increase the risk of developing gum disease. The research was conducted in the University of Buffalo?s Periodontal Disease Research Center, They evaluated the examined serum levels of antioxidant nutrients and their relationship to periodontal disease, using data from 9,862 subjects between the ages of 20 and 90 who participated in study. To establish an antioxidant profile, researchers assessed levels of vitamins A, C and E; selenium; a-carotene; b-cryptoxanthin; lycopene; and lutein. Periodontal-disease status was established by combining mean periodontal-attachment level, plus the number and locations of detachments. The lowest and highest periodontal disease groups then were compared with antioxidant status. Results showed that selenium has the strongest association with gum disease, with low levels increasing the risk by 13-fold. Low levels of vitamins A and C, acarotene, and b-crytoxanthin also increased the risk of gum disease significantly. Low levels of most antioxidants are a risk factor for periodontal disease and infection. Free radicals are released as a result of bacteria clearance and killing. Periodontal tissue depends on natural antioxidants to overcome this oxidative stress and maintain homeostasis. When antioxidants are depleted, the ability of gum tissue to overcome oxidative stress, maintain normal tissue and control the bacterial damage appears to be compromised".[9]

Battino et al. state that in gingivitis, the inflammatory infiltration consists mainly of lymphocytes, plasma cells and neutrophils. While vitamin E dramatically decreases, CoQ10 remains unchanged despite the increased amount of cells present in the periodontally affected tissues, indicating that the continuous oxidative stress which occurs in these structures affects the antioxidant pattern of the tissue.[10] Changes in the gingival microenvironment could impair apoptosis (programmed cell death) and promote enhanced release of reactive oxidative species (ROS) by phagocytes; decreased catalase (CAT) and superoxide dismutase (SOD) activity could promote accumulation of ROS and result in additional tissue destruction.[11]

Krol's study of total antioxidant status in peripheral and gingival serum correlated with periodontal clinical status showing significantly lower total antioxidant status in venous blood serum in each subgroup as compared with controls**.** He concluded that oxidative stress in periodontitis expressed by elevated concentrations of ROS and accompanied by suppressed antioxidant activity in gingival blood may accelerate lesion formation in periodontal tissues.[12] Further evidence for a role for ROS in tissue destruction with inflammatory periodontal disease was discussed by Waddington et al. Polymorphonuclear leukocytes (PMN?s) during an inflammatory response and are regarded as being highly destructive in nature. This is evidenced by ROS oxidation products, elevation of iron and copper ions (catalyzing theproduction of the most reactive radical species) and the identification of an imbalance in theoxidant/antioxidant activity within periodontal pockets, as well as the identification and characterization of connective tissue metabolites in gingival crevicular fluid (GCF) resulting from the degradation of periodontal tissues, notably alveolar bone.[13]

MICRONUTRIENT INTERACTIONS

Increased production of reactive oxidative species (ROS) necessitates an elevated need for zinc, copper and selenium, nutrients which are involved in antioxidant defenses. Systemic glutathione (GSH) is decreased with inflammation. The functions of GSH include antioxidant defense and immune regulation.[14] The vitamins pyridoxal phosphate (B6) and riboflavin (B2) are important in maintaining GSH status.[15] Selenium has important oxidation-reduction functions, and selenium-dependent GSH enzymes are involved in changing lipid and phospholipids hydroperoxides to harmless products,[16] neutralizing the inflammatory process at the cellular level. Therefore vitamins B2, B6, copper, zinc and selenium are needed to maintain systemic glutathione and selenium-dependent GSH enzymes for antioxidant defense, immune regulation, and neutralization of the inflammation process at the cellular level. Micronutrients—beta-carotene and vitamins A, C and E—can be depleted during inflammation.[17] As mitochondria (the power house of the cell) produce energy, they release ROS within the cell. In a study in Sagan et al suggested that dietary vitamin C enters the mitochondria and protects against oxidative injury.[18] These vitamins support immune functions and are involved in the maintenance of structural and functional integrity of epithelial tissues and physiological or metabolic parameters relevant to periodontal health.[8]

Lester Packer states vitamins C, E, CoQ10 (ubiquinone), alpha-lipoic acid, and selenium all function as part of an antioxidant network. When they neutralize a free radical they become a weak free radical themselves. But they function collectively and have the ability to recharge each other. Carotenoid antioxidants on the other hand are free radical traps and cannot be recharged. They are the first line of defense and have a protective effect on

vitamins C and E. When the carotenoid levels are diminished, the rest of the antioxidant network begins to unravel.[19] Svilaas et al demonstrated that carotenoids are predictors of overall antioxidant status.[20]

Enwonwo reports that deficiencies of several essential macro- and micronutrients adversely influence the prognosis of periodontal infections later he adds that good dietary practices and optimal nutritional status are important in mitigating the severity of inflammatory periodontal lesions but are likely of limited value if the stimuli from dental plaque are not removed.[21,22]

Periodontal diseases are associated with an imbalance between oxidants and antioxidants in favor of the former due to both an increase in free radical production and a defect in the total antioxidant activity of saliva.[23]

Free radicals cause tissue damage by a variety of different mechanisms which include

- DNA damage
- lipid peroxidation
- protein damage
- oxidation of important enzymes (e g anti proteases)
- stimulation of pro inflammatory cytokines release

It is interesting to note that the concentration of antioxidants in saliva does not appear to mirror those of plasma. Sculley et al stated that the influence of nutrition on antioxidant status may lead to a possible nutritional strategy for the treatment of periodontal disease (24) later they state that periodontal disease is associated with reduced salivary antioxidant status and increased oxidative damage within the oral cavity.[25]

CoQ_{10} and periodontitis

Chronic periodontitis is the direct result of accumulation of subgingival plaque. The microflora of this plaque is extremely complex causing problems in establishing which organisms are responsible for tissue destruction associated with the disease. Despite these problems, there is one point on which investigators agree, the subgingival flora of healthy gingival crevice is sparse and consists largely of aerobic and facultative bacteria, while in diseased state there is an increase in the proportion of anaerobic bacteria. These bacteria cause the observed tissue destruction directly by toxic products and indirectly by activating host defense systems, i.e. inflammation.[26] Inflammation represents the response of the organism to a noxious stimulus, whether mechanical, chemical, or infectious. It is a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue. Whether acute or chronic, inflammation is dependent upon regulated humoral and cellular responses, and the molecules considered to mediate inflammation at one time or another are legion. However, an event characteristic of mammalian inflammation, tissue infiltration by polymorphonuclear leukocytes and monocytes and subsequent phagocytosis features non-mitochondrial O_2 consumption, which may be 10 or 20 times that of resting consumption ultimately ends in generating free radicals (FRs) and reactive oxygen species (ROS), such as superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, and hypochlorous acid, all capable of damaging either cell membranes or associated biomolecules(26) Because of their high reactivity, several FRs and ROS can rapidly modify either small, free biomolecules (i.e., vitamins, amino acids, carbohydrates, and lipids) or macromolecules (i.e., proteins, nucleic acids) or even supramolecular structure (i.e., cell membranes, circulating lipoproteins). The type and the extent of damage depend upon the site of generation. Usually, the oxidative damage is perfectly controlled by the anti-oxidant defense mechanisms of the surrounding tissues but plaque microorganisms promoting periodontitis can unbalance this equilibrium. A massive neutrophil migration to the gingiva and gingival fluid leads to abnormal spreading of FR/ROS produced. Consequently, this led to a search for appropriate “antioxidant therapy” in inflammatory periodontal disease.[26]

A deficiency of coenzyme Q_{10} at its enzyme sites in gingival tissue may exist independently of and/or because of periodontal disease. If a deficiency of coenzyme Q_{10} existed in gingival tissue for nutritional causes and independently of periodontal disease, then the advent of periodontal disease could enhance the gingival deficiency of coenzyme Q_{10} In such patients,[27] oral dental treatment and oral hygiene could correct the plaque and calculus, but not that part of the deficiency of CoQ_{10} due to systemic cause; therapy with CoQ_{10} can be included with the oral hygiene for an improved treatment of this type of periodontal disease.[27] The specific activity of succinic dehydrogenase– coenzyme Q_{10} reductase in gingival tissues from patients with periodontal disease against normal periodontal tissues has been evaluated using biopsies, which showed a deficiency of CoQ_{10} in patients with periodontal disease. On exogenous CoQ_{10} administration, an increase in the specific activity of this mitochondrial enzyme was found in deficient patients.[27-30] The periodontal score was also decreased concluding that CoQ_{10} should be considered as an adjunct for the treatment of periodontitis in current dental practice.[31]

Not only succinate dehydrogenase CoQ_{10} reductase, but also succinate cytochrome c reductase and NADH cytochrome c reductase showed decreased

specific activity in periodontitis patients.[32] On exogenous administration of CoQ_{10} showed improved specific activity of these enzymes with significant reduction of motile rods and spirochetes.[33] The preliminary data indicated that CoQ_{10} may reduce gingival inflammation without affecting GCF total antioxidant levels [34], whereas one more study showed significant reduction in TBRAS in GCF in patients treated with scaling and root planning with CoQ_{10}.[35]

Topical application of CoQ_{10} to the periodontal pocket was evaluated with and without subgingival mechanical debridement. In the first three-week period, significant reduction in gingival crevicular fluid flow, probing depth and attachment loss were found and significant improvements in modified gingival index, bleeding on probing and peptidase activity derived from periodontopathic bacteria were observed only at experimental sites (CoQ_{10} with subgingival mechanical debridement).[36] It suggested that the research literature on coenzyme Q_{10} 's periodontal effect does not extend to International English language dental literature. The review of available literature does not give any ground for the claims regarding benefit of coenzyme Q_{10} and has no place in periodontal treatment.[37]

A study evaluated the periodontium condition after oral applications of coenzyme Q_{10} with vitamin E. The total antioxidant status (TAS) in the mixed saliva by the colorimetric method was determined twice. The average value of plaque index decreased from 1.0 to 0.36, average value of interdental hygiene index was reduced from 39.51–6.97%, gingival index values decreased from 0.68 to 0.18, and the values of sulcus bleeding index decreased from 7.26 to 0.87. Periodontal pockets also shallowed by 30%. The laboratory examination result improved by 20%. It concluded that coenzyme Q_{10} with vitamin E had a beneficial effect on the periodontal tissue [38].Because it is an antioxidant, coenzyme Q_{10} has received much research attention in the medical literature in the last several years. Although coenzyme Q_{10} may have been viewed as an alternative medication, it is used routinely, both topically and systemically, by many believing dentists and periodontists. However, there is a dearth of new information for coenzyme Q_{10} in the treatment of periodontal conditions. A deficiency of CoQ_{10} has been found in the gingiva of patients with periodontal disease.[27,28] Gingival biopsies from patients with inflamed periodontal tissues showed a deficiency of CoQ_{10}, in contrast to patients with normal periodontal tissues. Many clinical trials with oral administration of CoQ_{10} to patients with periodontal disease have been conducted. The results have shown that oral administration of CoQ_{10} increases the concentration of CoQ10 in the diseased gingiva and effectively Suppresses advanced periodontal inflammation and periodontal microorganisms.[39,40] Clinical study with interpocket application has shown CoQ_{10} is an effective adjunctive in the treatment of chronic periodontitis and also found to enhance the resistance of the periodontal tissues to periodontopathic bacteria (unpublished data).

RECOMMENDATION FOR THE PERIODONTAL THERAPY

1. Control bacteria with improved oral hygiene
2. Remove irritants with scaling and root planning
3. Strengthen the host defense response with appropriate supplementation and track baseline and subsequent antioxidant status using non-invasive measurement of skin carotenoids.
4. Surgery when necessary - surgical objectives:

1. soft tissue regeneration
2. pocket reduction
3. bone regeneration
4. periodontal plastic surgery procedures

Antioxidant levels appear to be a significant factor in weakening or bolstering host resistance to periodontal disease. In fact, they may just be the missing link. And considering the emerging body of evidence tying periodontal disease to other serious health problems, when we improve host resistance, we may not simply be improving periodontal status, we may be improving the quality of and even saving lives.

CONCLUSION

It appears that diets low in antioxidant vitamins can not only increase the risk of developing gum disease but influence its severity as well and that this has implications beyond gum disease since periodontal pathogens have been shown to play a role in heart disease, lung disease and diabetes in addition to destroying periodontal tissue and bone. It therefore seems prudent to address host resistance specifically with regard to antioxidant status along with our periodontal protocols. Nutritional counselling and supplementation may very well reduce inflammation and thereby enhance outcomes of conventional periodontal therapy.

REFERENCES

1. Aurer-Kozelj J, Kralj-Klobucar N, Buzina R, Bacic M. The effect of ascorbic acid supplementation on periodontal tissue ultrastructure in subjects with progressive periodontitis. Int J Vitam Nutr Res 1982; 52: 333-341.
2. Nakamoto T, McCroskey M, Mallek H M. The role of ascorbic acid deficiency in human gingivitis- a new hypothesis. J Theor Biol 1984; 108: 163 171.
3. Alvares O, Siegel I. Permeability of gingival sulcular

epithelium in the development of scorbutic gingivitis. Oral Pathol 1981; 10: 40-48.

4. Dilley J G, Koerber L G, Roche J R. The effects of dietary supplement of fresh oranges on the oral health of children. ASDC J Dent Child 1977; 44: 35-41.

5.Seaman DR. Clinical Nutrition for Pain Inflammation and Tissue Healing. 1998. Privately published

6. Seaman DR. "Nutrition Considerations for Pain and Inflammation." In: Liebenson CL, Editor.Rehabilitation of the Spine: A Practitioner's Manual. Baltimore: Williams & Wilkins; 2006: p. 728-40.

7. Seaman DR. "Nutritional Considerations in the Treatment of Soft Tissue Injuries." In: Hammer WI, Editor. Functional Soft Tissue Examination and Treatment by Manual Methods, 3rd ed. Boston: Jones and Bartlett;2007

8. Chapple IL. Role of free radicals and antioxidants in the pathogenesis of the inflammatory periodontal diseases. Clin Mol Pathol 1996;49:M247-M255.

9. Nishida M, Grossi SG, Dunford RG, How A, Trezisan M, Genco RJ. Dietary vitamin C and the risk for periodontal disease, J Periodontol. 2000 ;71:1215-23.

10. Battino M, Bompadre S, Politi A, Fioroni M, Rubini C, Bullon P. Antioxidant status (CoQ10 and Vit.E levels) and immunohistochemical analysis of soft tissues in periodontal diseases. Biofactors 2005;25:213-17.

11. Elles SD, Tucci MA, Serio FG, Johnson RB. Factors for progression of periodontal diseases. J Oral Pathol Med. 1998;27:101-15.

12. Krol K. [Reactive oxygen species and antioxidant mechanisms in the pathogenesis of periodontitis] Ann Acad Med Stetin, 2004;50:135-48.

13. Waddington RJ, Moseley R, Embery G. Reactive oxygen species: a potential role in the pathogenesis of periodontal diseases. Oral Dis. 2000;6:136-51

14. Sen CK. Nutritional biochemistry of cellular glutathione. Nutr Biochem 1997;8-:660-72

15. Grimble RF. Modification of inflammatory aspects of immune function by nutrients. Nutr Res 1998;18:1297-317.

16. Rayman MP. The importance of selenium to human health. Lancet 2000;356:233-41

17. Semba RD, Tang AM. Micronutrients and the pathogenesis of human immunodeficiency virus infection. Br J Nutr 1999;81:181-9.

18. Sagan KC, Carcamo JM, Golde DW. Vitamin C enters mitochondria via facilitative glucos etrans porter 1(glut1) and confers mitochondrial protection against oxidative injury. FASEB J 2005;19:1657-67.

19. Packer L, Colman R.The antioxidant miracle. In: "The Controversial Carotenoids: Alpha Carotene, Beta Carotene, Cryptoxanthin, Lutein, Lycopene, and Zeaxanthin." New York (NY):John Wiley & Sons Inc.; 1999. p 133.

20. Svilaas A, Salhl AK, Anderson AF, Svilaas T, Strom E, Jacobson Jr. DR, Ose L, Blomhoff R. Intakes of Antioxidants in „Coffee, Wine, and Vegetables Are Correlated with Plasma Carotenoids in Humans, J Nutr 2004;134:562-7.

21. Enwonwu CO. Cellular and molecular effects of malnutrition and their relevance to periodontal diseases. J Clin Periodontol. 1994;21:643-57. 22. Enwonwu CO. Interface of malnutrition and periodontal diseases. Am J Clin Nutr. 1995;61:430S-436S.

23. Diab-Ladki R, Pellat B, Chahine R. Decrease in the total antioxidant activity of saliva in patients with periodontal diseases. Clin Oral Investig. 2003;7:103-7.

24. Sculley DV, Langley-Evans SC. Salivary antioxidants and periodontal disease status. Proc Nutr Soc. 2002;61:137-43.

25. Sculley DV, Langley-Evans SC. Cling Sci (Lond). 2003;105:167-72.

26. Battino M, Bullon P, Wilson M, Newman H. Newman Oxidative injury and inflammatory periodontal diseases: The challenge of anti-oxidants to free radicals and reactive oxygen species. Crit Rev Oral Biol Med. 1999;10:458–76.

27. Nakamura R, Littarru GP, Folkers K, Wilkinson EG. Deficiency of coenzyme Q in gingival tissue from patients with periodontal disease. Int J Vitam Nutr Res. 1973;43:84–92.

28. Littarru GP, Nakamura R, Ho L, Folkers K, Kuzell WC. Deficiency of coenzyme Q10 in gingival tissue from patients with periodontal disease. Proc Nat Acad Sci USA. 1971;68:2332–5.

29. Wilkinson EG. Bioenergetics in clinical medicine. II. Adjunctive treatment with coenzyme Q in periodontal treatment. Res Commun Chemic Path Pharm. 1975;12:111–24.

30. Nakamura R, Littarru GP, Folkers K, Wilkinson EG. Study of CoQ10-enzymes in gingiva from patients

with periodontal disease and evidence for a deficiency of coenzyme Q10. Proc Natl Acad Sci U S A. 1974;71:1456–60.

31. Wilkinson EG, Arnold RM, Folkers K. Bioenergetics in clinical medicine. VI. Adjunctive treatment of periodontal disease with CoQ10. Res Commun Chem Path Pharmac. 1976;14:715–9.
32. Shizukuishi S, Inoshita E, Tsunemitsu A, Takahashi K, Kishi T, Folkers K. Therapy by Coenzyme Q10 of experimental periodontitis in a dog-model supports results of human periodontitis therapy. In: Folkers K, Yamamura Y, editors. Biomedical and clinical aspects of Coenzyme Q. Amsterdam: Elsevier; 1984. pp. 153–62.
33. McRee JT, Hanioka T, Shizukuishi S, Folkers K. Therapy with Coenzyme Q10 for patients with periodontal disease. 1. Effect of Coenzyme Q10 on subgingival micro-organisms. J Dent Health. 1993;43:659–66.
34. Denny N, Chapple IL, Matthews JB. Antioxidant and anti-inflammatory effects of coenzyme Q10: A preliminary study. J Dent Res. 1999;78:543.
35. Kuru B, Yildiz D, Kayalý R, Akçay T. Gingival lipid peroxidation and glutathione redox cycle before and after periodontal treatment with and without adjunctive Coenzyme Q10. Turkiye Klinikleri J Dental Sci. 2006;12:1–8.
36. Hanioka T, Tanaka M, Ojima M, Shizukuishi S,Folkers K. Effect of topical application of coenzyme Q10 on adult periodontitis. Mole Aspects Med. 1994;15:s241–8.
37. Watts TL. Coenzyme Q10 and periodontal treatment: Is there any beneficial effect? Br Dent J. 1995;178:209–13.
38. Brzozowska TM, Flisykowska AK, OEwitkowska MW, Stopa J. Healing of periodontal tissue assisted by Coenzyme Q10 with Vitamin E: Clinical and laboratory evaluation. Pharmacol Rep . 2007;59:257–60.
39. Shizukuishi S, Hanioka T, Tsunemitsu A, Fukunaga Y, Kishi T, Sato N. Clinical effect of Coenzyme 10 on periodontal disease; evaluation of oxygen utilisation in gingiva by tissue reflectance spectrophotometry. In: Shizukuishi S, Hanioka T, Tsunemitsu A, editors. Biomedical and clinical aspects of Coenzyme Q. Vol. 5. Amsterdam: Elsevier; 1986. pp. 359–68.
40. McRee JT, Hanioka T, Shizukuishi S, Folkers K. Therapy with Coenzyme Q10 for patients with periodontal disease. 1. Effect of Coenzyme Q10 on subgingival micro-organisms. J Dent Health.