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Antioxidants in Oral Healthcare

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Abstract :
The oral cavity is under constant bombardment from foods and drinks, as well as substances such as alcohol, tobacco products and nicotine, dental materials and much more. Bacteria and other disease-causing agents along with systemic conditions present further insult. Because the oral tissues are delicate, they are especially vulnerable to cell damage caused by free radicals and oxidative stress. Maintaining a good balance of oxidants and antioxidants is very essential for maintaining oral health. Factors such as pollutants, alcohol, nicotine , substances used in dental procedures can disturb the balance of oxidants in oral tissues. Antioxidants help to offset this imbalance.

Keywords:
Antioxidants, Oral cavity, Oral cancer, Periodontal disease, Dental caries.

INTRODUCTION

An antioxidant is a molecule which inhibits oxidation reaction. Antioxidants terminate the chain reaction caused by free radicals of oxidation reaction , preventing cell damage or death of the cells. Insufficient levels of antioxidants or inhibition of antioxidant enzymes causes oxidative stress and damage or kill the cells. It has been suggested that negative effects of nicotine are reversed by antioxidants (1). Antioxidants are available from different sources , including vitamins, minerals, enzymes and hormones, as well as food and herbal supplements. These supplements may be in bar, gel, capsule , drops and tablet forms. As an alternative medicine, herbal therapy is a treatment modality to remedy many medical and dental conditions. Antioxidants have also been used in combination with dried, fresh, and blended herbal paste. The majority of herbal supplements include green tea catechins(2), aloe vera ,star anise oil, myrrh gum, calendula extract, ammonium glycyrrhizate (from liquorice root), fennel oil, and neem extracts(3). Most recently, dental manufacturers and distributors have incorporated antioxidant supplements into toothpastes, mouth rinses/mouthwashes, lozenges, fluoride gels and dentifrices, oral sprays, breath fresheners, and other dental products for the control of gingival and periodontal diseases. While we are familiar with antioxidants taken systemically, such as foods and vitamin supplements, topical antioxidants may have an effect on oral cells. The success of topical antioxidants on skin cells suggests perhaps a similar effectiveness of topical compounds on cells in the oral cavity. Research studies are currently under way to examine the effectiveness of combinations of antioxidants applied topically to oral cells. Results from clinical studies, though incomplete, are positive. In addition, published research studies confirmed that antioxidants that work on skin cells also have an effect on oral, gingival, and periodontal cells(4,5,6).

I. EXTRACTS FROM NATURAL SOURCES

Many other extracts have been used in studies to demonstrate antioxidative potential. A recent study concluded that the lactoferrin and black tea polyphenols had protective effects against carcinogen activation, DNA damage, cell proliferation, invasion, and angiogenesis in an experimental oral carcinogenesis model(7). Phytochemical is found in black raspberries, which are a rich, natural source of vitamins and minerals. Specifically, the active compounds in black raspberries include vitamins A, C, and E, folic acid, calcium, selenium, beta-carotene, ellagic acid, coumaric acid, and quercitin, besides different anthocyanins and phytosterols. Freeze-dried black raspberries prevent the growth of oral, esophageal, and colon cancer in rodents, and human trials have shown a decreased expression of molecular biomarkers of dysplasia(8). Considerable evidence also has revealed that flavonoids possess antioxidant and anti-inflammatory properties that reduce inflammatory molecule expression in macrophages and monocytes within the gingival connective tissues. Some flavonoids such as luteolin, quercetin, and genistein have regulated the nitric-oxide production of LPS-stimulated human gingival fibroblasts. Luteolin is involved with LPS signaling pathways, decreasing the activation of various mitogen-activated protein kinase (MAP kinase) family members, and prevents inflammatory mediator expression(9). Ferulic acid is also a component of raspberries and is active against free radicals such as ROS. Animal studies and in vitro studies suggest that ferulic acid may have direct antitumor activity against breast and liver cancer, and can help in the fight against the effect of carcinogenic compounds like benzopyrene and 4-nitroquinoline 1-oxide. Ferulic acid has pro-apoptotic (programmed cell death) effects that will damage the cancer cells(10-13). The topical combinations of ascorbic acid, vitamin E, and ferulic acid may diminish oxidative stress and prevent the formation of thymine dimers (damage caused by ultraviolet light) in skin(14).

II. VITAMIN SUPPLEMENTS

Recent studies have indicated that vitamin E may have therapeutic effects in treating and preventing periodontal pathology(15,16). Vitamin E is a powerful lipid-soluble antioxidant that is valuable in decreasing wound-healing time(17). To determine whether free radicals have an effect on the normal process of the cell cycle and whether vitamin E inhibits cell damage, normal human oral epithelial cells were treated with hydrogen peroxide (H2O2) in culture in the presence or absence of vitamin E. Cultures exposed to H2O2 showed characteristic features common among premalignant epithelial lesions. Therefore, the conclusion is that vitamin E may have the potential to reduce oxidative

damage caused by hydroxyl radicals(18). Another vitamin supplement that is essential is folic acid. Low serum folate levels have been associated with an increased risk of periodontal disease in older adults as shown in a recent population-based, cross-sectional study(19). The role of folic acid in combination with oral hygiene measures was investigated in a 1-year follow-up study on epileptic children treated with phenytoin (an anticonvulsant). This study led to the conclusion that the combined effects of systemic folic acid and phenytoin slow down the onset and decrease the incidence and severity of phenytoin-induced gingival overgrowth(20).

III. SALIVARY ANTIOXIDANTS

Saliva is rich in antioxidant compounds. The primary antioxidants include uric acid, albumin, ascorbic acid, glutathione and antioxidant enzymes. Antioxidants are critical to the body's defense system because of their ability to neutralize free radicals—reactive oxygen species and reactive nitrogen species —and counteract oxidative stress.

IV. ANTIOXIDANTS AND PERIODONTAL DISEASES

Periodontal diseases are inflammatory disease process resulting from interaction between bacterial attack and host inflammatory response. Free radicals and reactive oxygen species (ROS) are responsible for the inflammatory response. Periodontal pathogens can induce ROS overproduction and thus may cause collagen and periodontal tissue breakdown. When ROS are scavenged by antioxidants, collagen breakdown can be minimised. 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 (21-24). Low levels of vitamins A and C, β carotene, and β 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" (25). 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 (26). The vitamins pyridoxal phosphate (B6) and riboflavin (B2) are important in maintaining GSH status (27). Selenium has important oxidation-reduction functions, and selenium-dependent GSH enzymes are involved in changing lipid and phospholipids hydroperoxides to harmless products (28), 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 (29). 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 (30). 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 .

V. ANTIOXIDANTS AND DENTAL CARIES

Dental caries is one of the most common oral health problem and its prevention is one of the most important strategies in many countries. It affects all people regardless of their sex, socioeconomic strata, race, and age. It is also profoundly affected by other factors like oral hygiene and saliva(31). Recently, it has been claimed that the imbalances in levels of free radicals, reactive oxygen species, and antioxidants in saliva may play an important role in the onset and development of dental caries(32). Hence, evaluation of those factors in saliva that may increase the risk of individuals to dental caries, can pave way to make recommendations that will cater specifically to needs of an individual(33).

Most important would be the function of salivary peroxidase system, which constitutes one of the major salivary antioxidant systems. Salivary peroxidase brings about the control of oral bacteria that form dental plaque, to imbalances in the ecology, and which lead to dental caries. Salivary peropxidase catalyzes the peroxidation of thiocyanate ion (SCN^-) to generate oxidation products (more stable $OSCN^-$); this inhibits the growth and metabolism of many micro-organisms thereby inhibiting caries or atleast slowing down the progress of caries(34).

VI. ANTIOXIDANTS AND ORAL CANCER

Oral cavity cancer is one of the ten most frequent cancers in the world as to 25% of all malignancies are found in the oral cavity(35). Tobacco is the predominantcause of this cancer. About 48.2% of cancers in men and 20.5% in women are related to tobacco, a major proportion of which is in the oral cavity, pharynx, larynx, oesophagus (74.7%), while lung cancers account only for 15%(36). The role of antioxidants in cancer chemoprevention is by inhibiting oral carcinogenesis by reversing of premalignant lesions like oral leukoplakia. Oxidative damage is recognized as playing a role in the pathogenesis of cancer which could arise from incorrect nutritional habits and lifestyle practices. This process can cause DNA damage, which is a basic mechanism in cancer induction. Sufficient antioxidative status is crucial in free radical defence. To reduce the risk of oral and pharyngeal cancer, especially oral cell carcinoma, diet must be optimized, primarily to reduce calorie intake, monosaturated fat and red or

processed meat. The important dietary micronutrients that are antioxidant in action include vitamin A, β carotene, lycopene, Vitamin C, vitamin E (alpha- tocopherol), Zinc and selenium. Considerable evidence exists suggesting a role for nutrients, particularly the so called antioxidants vitamin A, β carotene, vitamin C, vitamin E, lipoic acid, zinc, selenium and spirulina in the prevention of this disease(37). A recent study has suggested that these anti-oxidant nutrients act to inhibit the development of cancer cells and to destroy them through apoptosis (programmed cell death), by their stimulation of cytotoxic cytokines, by their action on gene expression, by preventing the development of tumor's necessary blood supply or by cellular differentiation. A report has also shown a reduction in adverse effects of chemotherapy when given concurrently with antioxidants(38). Retinoids are the natural and synthetic derivatives of vitamin A. The retinoids in the body originate from retinyl esters, carotenoids, and retinal in diets. The effects of retinoids are mediated by retinoid acid receptors (RARs) and retinoid X receptors (RXRs). Three subtypes, designated as α, β and both RARs and RXRs, have been described. Recently, retinoids have been implicated in the induction of cell death in many tumor-derived culture cell systems in both retinoid receptor-dependent and independent manners. The continued development of new synthetic drugs to up-regulate RA receptors and receptor independent drugs would be valuable. It appears that exploiting the apoptotic potential of Oral Squamous Cell Carcinoma would lead to contemporary therapies that might be less toxic to normal cells due to their physiologically controlled survival pathways. It is suggested that these newer therapies would also be effective in treatment of epithelial dysplasia. Ideally, the root of cancer control lies in instituting chemoprevention. In addition to the chemotherapeutic and chemopreventive agents, a number of dietary components and micronutrients are emerging with considerable potential for the induction of apoptosis. These agents include green tea constituents (EGCG and others), and a number of other phytochemicals, such as carotenoids (lycopene) and retinoids (39). βcarotene is a vitamin A precursor commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya and oranges. Main actions of beta carotene include

Anti-oxidant and free radical scavenging
Immunomodulation, stimulation of increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors
Inhibition of mutagenesis
Inhibition of cancer cell growth.

B carotene is especially used for scavenging free radicals in areas of low oxygen concentration. Results from a recent study has demonstrated that one third of patients (15 out of 46) that used 360 mg â carotene per week during 12 months presented a complete resolution of oral leukoplakia (OL)(40). Lycopene is a prominent carotenoid in serum which is the red antioxidant pigment . This is a fat-soluble red pigment found in some fruit and vegetables. The primary sources of lycopene include tomatoes, apricots, papaya and other yellow fruits. In particular, lycopene and other carotenoids rich foods also are inversely related to upper digestive tract neoplasms including oral cancer. Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. Lycopene has the uncommon feature of getting bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent(41).

VII . Reversal Of Oral Leukoplakia With Antioxidants

The reversal or regression of premalignant lesions such as leukoplakia is an important stategery for cancer prevention. Any agent selected for trial in premalignant lesion, the ultimate goal of which is application for cancer prevention, should have minimal or preferably no toxicity because many subjects whose lesions are unlikely to progress to cancer will be exposed to the intervention. If the object is to develop agents for use by general population to reduce the incidence of oral cancer, then agents preferred are antioxidants such as β carotene and vitamin E. Intervention trials on betel, quid-tobacco chewers show that administration of Vitamin A cause complete remission of leukoplakia. The most commonly used synthetic retinol, 13 cis- retinoic acid, is toxic even when given at very low dose. There is an increasing emphasis on the use of relatively non-toxic antioxidants such as beta-carotene and Vit.E(42,43). A study showing Lycopene effect on oral cancer has proved that high doses of Lycopene (8 mg/ day) are useful in improvement of oral health(44).

VIII . Conclusion

It appears that diets low in antioxidant vitamins cannot only increase the risk of developing gum disease but influence its severity as well and that this has implications beyond gum diseases. 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. The root of cancer control lies in early diagnosis and treatment. The knowledge of antioxidants is useful in reducing the incidence of oral cancers at initial stages though non invasive techniques. Recent clinical studies have shown the beneficial effects of these antioxidants in oral leukoplakia, a characteristic oral precancerous lesion. Hence, natural products like fruits and vegetables helps in preventing oral cancers at an early stage. Nutrients will be widely utilized and will play an important role in preventing cancers once their effectiveness is conclusively demonstrated by prospective clinical studies, and when their mechanisms of actions are more clearly understood.

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