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PURPOSE OF PRESCRIBING ANTIOXIDANTS/VITAMINS ALONG WITH ORAL MEDICATIONS BY DOCTORS/DENTISTS

Clinical Research

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ABSTRACT

Antioxidants antagonize the effects of free radicals, and can be defined as "those substances which when present at low concentrations, compared to those of an oxidizable substrate, will significantly delay or inhibit oxidation of that substrate". They mainly include glutathione peroxidase, catalase and superoxide dismutase.

Moreover, during gingival inflammation, gingival crevicular fluid flow increases the change of saliva composition with products from the inflammatory response; this, in turn, could have some rôle in controlling and/or modulating oxidative damages in the oral cavity. Saliva is an excellent diagnostic tool of oral diseases because of its composition and easy collection. In addition to its other host-protective properties, saliva could constitute a first line of defence against free radical-mediated oxidative stress, since the process of mastication and digestion of ingested foods promotes a variety of reactions, including lipid peroxidation.This is the reason why the antioxidant capacity of saliva has led to increasing interest, and the development of techniques suitable for saliva antioxidant evaluation.

KEYWORDS

Antioxidants, Free radicals, Oxidative stress, Lipid peroxidation.

INTRODUCTION

Saliva, a heterogeneous fluid comprising proteins, glycoproteins, electrolytes, small organic molecules and compounds transported from the blood, constantly bathes the teeth and oral mucosa. It acts as a cleansing solution, an ion reservoir, a lubricant and a buffer.Different markers of protein oxidation, lipid peroxidation and DNA damage induced by reactive oxygen species [ROS] can be measured in saliva.

It is unclear that OS of local oral origin is caused by an overproduction of [ROS] reactive oxygen species due to infection and inflammation or by the lack of antioxidants. Studies indicate that antioxidant treatment could prevent or slow- down the progress of periodontitis and caries progression in experimental animals as well as in humans and that is why the clinical use of salivary markers for measuring the oxidative stress becomes even more attractive. This review summarizes basic information on the most commonly used salivary markers of oxidative damage, antioxidant status, and carbonyl stress and the studies analyzing these markers in patients with caries or periodontitis.[1]In endodontic infections the endodontic offenders and their products trigger theimmune-inflammatory response. The host attempts to localize the infection and prevent further dissemination at the expense of apical periodontal tissue breakdown, involving periodontal ligament, radicular cementum, and alveolar bone. In the chronic inflammation, the bone resorptive lesions are seen as an apical radiolucent area in a radiograph, which can progress to form an apical granuloma or a radicular cyst, a cavity lined by squamousepithelium.

Free Radicals are formed during cell metabolism and are responsible for different cellular signaling processes like transcription and transduction. Reactive oxygen species (ROS)does effect the different cell functions which causes inflammation and cell apoptosis.The catalytic pathways producing Reactive oxygen species involve the enzymes which are present intracellularly including respiratory enzymes, cytochrome P450monoxygenases, xanthine oxidase, and NADPH oxidase. It may be reactive oxygen species (ROS) or non-radicals. Reactive oxygen species have unpaired electrons in their outermost orbitals and are very reactive with normal species, this way it completes its octet. The examples are superoxide (O_2^{-}) and hydroxyl anion.

The Non-radical type of ROS are the oxidizing agents which are converted into reactive oxygen species easily,such as, hydrogen peroxide (H_2O_2). Someotherexamplesof non-radicals are nitrogen derived radical like nitric oxide and chlorine containing free radical like, hypochlorous acid. The effects of ROS can be antagonized by the Antioxidants and thus, antioxidants are the substances which when present in low concentrations, compared to an oxidizable substrate, will inhibit or delay the oxidation of the substrate. The MOA of antioxidants are via enzymatic and non-enzymatic reactions. The enzymes through which antioxidants act are catalase (CAT), superoxide dismutase (SOD), and thiol-dependent peroxidases namely peroxiredoxins and glutathione peroxidase. The non-enzymatic antioxidants are some metabolic antioxidants, such as coenzyme Q10, thiol antioxidants, uric acid, or bilirubin and the substances which are obtained exogenously from nutrients, namely water and fat-soluble vitamins, trace elements (carotenoids, ascorbic acid, tocopherols, polyphenols, folic acid, and cysteine) and polyphenolic compounds.showing ROS and antioxidant mechanisms interact in balance to maintain normal physiologic processes.

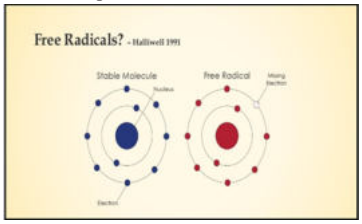
ROLE OF SALIVA

Saliva is a heterogeneous biological fluid that comprises enzymes, hormones, antibacterial constituents, electrolytes as well as small organic molecules and compounds transported from the blood. It also acts as a cleansing solution, a buffer, an ion reservoir, and a lubricant. Saliva constitutes as first line of defense against free radicalmediated oxidative stress, because the process of mastication and digestion of food promotes various reactions, including lipid peroxidation.4 Pereslegina reported that unstimulated saliva was better in the determination of antioxidant defense parameters when compared with stimulated saliva, as TAC was found to be higher in unstimulated saliva.5 Since saliva has found application as a diagnostic aid in an increasing number of clinical situations (Mandel), including dental caries and the possible therapeutic effects of antioxidants in maintaining a balance between ROS and antioxidants, there is an increasing interest in the evaluation of antioxidant capacity of saliva and its relationship with dental caries.

VITAMINS / ANTIOXIDANTS, FREE RADICALS AND OXIDATIVE STRESS:

HOW ARE THEY RELATED?

Free radicals are an atom or group of atoms that have one or more unpaired electrons generated in various normal physiological activities of cells. They are defined as "any molecular species capable of independent existence that contains an unpaired electron in an atomic orbit." They have either a positive, negative, or neutral charge. They are formed in enzymatic and nonenzymatic reactions. Some of the free radicals have positive effects: they kill the bacteria, control tone of smooth muscles and give strength to the immune system of the body to fight inflammation. Free radicals are extremely reactive and unstable as they have unpaired electron in their outermost orbit. Thus, they either donate or accept an electron.



The concept of free radicals was given by Denham Harman in 1956 for their role in the aging process. Superoxide anion, peroxide, hydrogen peroxide, hydroxyl ion, hydroxyl radicals which are the byproducts of oxygen metabolites, are known as reactive oxygen species (ROS). During all normal cellular activities like cell cycling and signal transduction ROS and Reactive nitrogen species(RNS) are formed. So, oxidative stress is caused by cellular damage that occurs due to increase in level of free radicals.In oral diseases these free radicals cause Periodontitis, Dental caries, oral precancer, gingival inflammation and in systemic heart diseases , cancers etc.

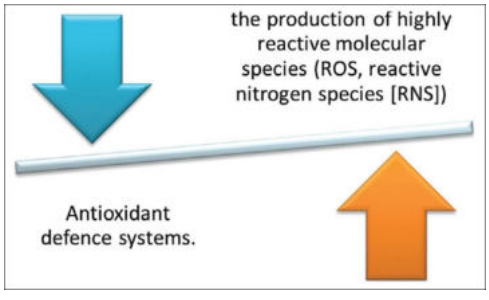
One of the earliest studies done to evaluate the relation between the physicochemical properties of saliva, such as flow rate, buffering capacity, pH, calcium level, total protein, and total antioxidant status with dental caries, age, and gender in children was by Tulunoglu et al in 2006. The authors concluded that the total protein and total antioxidant in saliva were increased with caries activity and that the higher total antioxidant values in caries active children may be attributed to elevated protein levels.[8]

Local oral pathologies and systemic diseases such as periodontitis, oral carcinoma, aphthous stomatitis, and diabetes mellitus are associated with an increase of OS markers in saliva, which has been proved by various studies.

Antioxidants are present in all body fluids and tissues that protect against endogenously formed free radicals. They scavenge FR or ROS and prevent the damage caused by them. Free radicals are normally neutralized by efficient systems in the body that include antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase), as well as the nutrient-derived antioxidant small molecules (vitamin E, vitamin C, carotenes, flavonoids, glutathione, and uric acid). In apparently healthy individuals, a delicate balance exists between free radicals and antioxidants.

Many studies have shown that disruption of relations of free radicals and antioxidants play an important role in the pathogenesis of inflammatory diseases of oral tissues. Periodontal diseases are inflammatory diseases that have a multifactorial etiology. The inflammatory and immune responses to the bacteria as well as viruses that colonize the periodontal and associated tissues involve the systemic circulation and ultimately the peripheral systems of the body. Loss of balance between ROS and antioxidant defense also is a factor causing various endodontic and periodontal diseases. It may be seen as an increase in oxidativestress, or decrease in individual antioxidant level.Increased generation of ROS can cause toxic effects by damage of proteins, lipids and DNA. Oxidative damage of these biomolecules contributes to disease development.[19] OS in periodontitis expressed by elevated concentrations of ROS and accompanied by suppressed antioxidant activity in saliva and blood may accelerate progression of periodontal disease.

Imbalance between antioxidants and reactive oxygen species



OXIDATIVE STRESS IN ORAL DISEASES :

Dental caries

Dental caries is the most prevalent oral disease worldwide affecting both, children and adults and leading to pain and tooth loss. Overall review that deals with the epidemiology, pathogenesis, diagnosis, treatment of dental caries has been published previously [25] .

Dental caries is an inflammatory disease that is caused by various factors. The primary trigger, however is the acid that is produced by the fermentable bacteria.The destruction of dental hard tissues is discussed in a recent review.High sucrose levelsinhibits dentinal fluid movementthat is in turn caused by down-regulation of parotid hormone from hypothalamic signaling. Teeth become susceptible to bacterial acids due to this. The important role of ROS and antioxidants on the regulation of parotid hormone was hypothesized in a review dealing with the systemic theory of dental caries [38]. Dental caries is the most common, chronic, noncommunicable, preventable oral disease worldwide. Oxidation may play an important role in dental caries initiation and progression.

Pathogenesis of inflammatory response in Dental Caries and increase ROS production :

As the caries process reaches to dentin, degradation of dentin matrix starts. ROS activate matrix metalloproteinases (MMPs) in dentin matrix. Though activated MMPs are tightly regulated by tissue inhibitors of metalloproteinases and alfa-macromolecules in normal physiological conditions, but certain localenvironmental changes (pH changes and ROS) results in imbalance and the regulatory mechanism is bypassed leading to tissue destruction.[17]

During endodontic infection, ligation of Toll-like receptors (TLRs) on phagocytes' surface by bacterial motifs or dying cells triggers activation, phagocytosis, synthesis of ROS, activation of humoral and cellular responses, and production of inflammatory mediators, such as, cytokines and matrix metalloproteinases (MMPs)

Given the close relation between inflammation and oxidative stress the role of ROS and antioxidant systems in the pathogenesis of periodontal tissue injury has regained attention in the last years. Malondialdehyde (MDA), a product of polyunsaturated fatty acid peroxidation, was reported to be significantly elevated and GSH-PX activity reduced in periapical granulomas compared to healthy gingival tissue, reflecting an oxidative imbalance[15]. PMN obtained from apical granulomas showed increased production of hydrogen peroxide and superoxide anion, which tended to normalize after surgical treatment[17]. The imbalance between the generation and elimination of ROS in periapical lesions can also be assessed by the total oxidant status (TOS) and total antioxidant status (TAS)[20]. In fact, TOS was reported to be significantly higher in ALs than in healthy periodontal ligament controls. Analysis of oral gingival crevicular fluid showed reduced TAS levels in asymptomatic AP teeth and were restored to normal levels after endodontic treatment[21]. These reports evidence the existence of local oxidative stress in ALs, either at the expense of ROS increments and/or reduced antioxidant defense.

The present study was conducted to evaluate OS in dental caries patients by measuring the levels of Salivary Malonialdehyde MDA and salivary antioxidants, i.e., Glutathione peroxidase and the correlation of root canal treatment with caries and OS in saliva. There is increasing evidence that OS is an important contributing factor in the pathogenesis of caries and periodontal disease.[8] In accordance with the present study, Ozturk et al, 2008 implicated OS in the pathogenesis of caries and ↓ GSH in caries group i.e. negative correlation between GSH ($p < 0.05$) and DMFT. The study conducted in adults by Ozturk et alwas the first study to establish the role of salivary glutathione (GSH) as an antioxidant in relation to dental caries . Lower GSH concentrations was seen in adults with caries compared to subjects without caries, a negative correlation was analyzed between GSH and clinical indices. In this study no difference in lipid peroxidation was seen between subjects without and withcaries.[16]Rai et al have studied TBARS in the saliva of caries active patients. Greater lipid peroxidation was detected in caries active patients than in control patients. AhmadiMotamayel et alhave analyzed TAC in caries active and caries free students .[22] In this study greater levels of TAC was found in the group with caries, especially in males.

In the most recent study by S. Karger, AGBasel showed greater levels of serum and salivary MDA in the case group compared to the healthy control group. The ROS marker was significantly greater in the caries group compared to the healthy control group. Antioxidants were not significantly different between the two groups. MDA can be produced by dental caries, causing disease progression. Further studies are necessary to analyze whether MDA is the cause or effect of the disease. In the present study, levels of salivary Glutathione peroxidase were significantly decreased in patients diagnosed with caries compared to individuals with an apparently healthy periodontium. Novaković*et al*conducted a study which also showed decrease in the levels of uric acid and albumin in patients with chronic periodontitis compared to healthy individuals. This is in accordance with the findings of Talaviya,

Shetty.[8] In 2011, Mathur *et al*conducted a study to analyze the effect of antioxidant therapy on the progression of endo-perio disease and to investigate if any correlation existed between antioxidant levels in saliva and periodontal attachment loss .

In the present study, we found that subjects with caries tended to have greater oxidative injury and lower levels of Glutathione peroxidase before therapy compared to after root canal treatment [RCT]in subjects.

This is in accordance with the findings of Novakovic et al who in 2013 showed the correlation between GPx, SOD, uric acid,albumin, TAS (before and after non-surgical treatment). The study stated that there is increase in level of uric acid,albumin ,GPx, TAS after treatment.

In the present study, saliva was used as a diagnostic fluid because it can be collected in a safe and easy manner requiring no special training and whole saliva is a mixture of oral fluids and includes secretions of the major and minor salivary glands in addition to constituents of non-salivary origin derived from GCF, expectorated bronchial secretions, serum and blood cells from oral wounds, as well as bacteria and bacterial products, viruses and fungi, desquamated epithelial cells, and food debris. This is in accordance with the findings of Chiappin*et al* and Mathur *et al*. A study by Sculley *et al*also suggested that whole saliva may contain simply measured indicators of oxidative processes and may provide a tool for the development and monitoring of new treatment strategies.

CONCLUSION

Thus, it can be proposed that, in the future, antioxidant supplementation may be used in the treatment or prevention of caries and periodontitis. There is evidence that production of excessive free radicals and ROS may be substantially elevated in certain inflammatory diseases, including dental caries, and it is the antioxidant defense system that maintains the balance between them. Various factors such as age factor, gender, dietary habits, immunity, severity of dental caries, type of dentition, site of infection, and method of measuring TAC, it is difficult to correlate the increase or decrease in salivary antioxidant capacity with the onset and progression of dental caries. More researches must be conducted in order to understand the mechanism behind the fluctuating level of total antioxidants in the presence of dental caries.

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