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## Vitamin C and Oral Health:-Recent Concerns on Supplementation and Toxicity.

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### ABSTRACT

Some clinicians enthusiastically recommend repeated dosages of vitamin C tablets for alleviation of periodontal symptoms and gingival hypertrophy. Case selection in order to choose surgical or medicinal treatment is the need of the hour. The amount of a vitamin C required by an individual varies considerably, however the current recommended dietary allowance ( RDA) is 75 mg for women and 90 mg for men. The review attempted to shed light on the fact that ascorbic acid deficiency hampers dentin formation, interferes with bone formation and ruins the host immune response in periodontal patients. Evidence from animal models and human studies suggest an inverse relationship between levels of vitamin C and ischemic heart disease, hyperglycemia, cancers of mouth, esophagus, stomach and pancreas. Antioxidants have been demonstrated to inhibit HIV replication in vitro. An adequate intake is linked to reduced mortality from heart disease, enhancement of immune function in tumors and definitely improved periodontal health. Several populations have a higher requirement of vitamin supplementation to maintain optimal plasma vitamin C concentrations. Above a tolerable upper intake level ie.2 mg, the potential toxicity is also discussed. Furthermore, mega doses of ascorbic acid are unrelated to the betterment of periodontal health.

**Keywords:** Vitamin C; Supplement; Periodontal health

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## INTRODUCTION

A healthy diet rich in fruits and vegetables and a satisfactory nutritional status are indispensable in maintaining a natural and functional dentition. Vitamins are essential to maintain normal metabolic processes and homeostasis within the body. The amount of a vitamin C required by an individual varies considerably, however the current recommended dietary allowance (RDA) is 75 mg for women and 90 mg for men. Fruits and vegetables are rich in vitamin C. While prolonged storage of unprocessed fruits and vegetables leads to loss of vitamin C; boiling, steaming, freezing and canning do preserve it to a great extent. Most vitamins are stored minimally in human cells, but some are stored in liver cells to a greater extent. Vitamins A and D may be stored in sufficient amounts to maintain an individual without any intake for 5 to 10 months and 2 to 4 months, respectively. However the lack of vitamin C will manifest within weeks and may result in death in 5 to 6 months. In addition, the deficiency increases the oxidation of tetrahydrofolate to inactive folate metabolites and predisposes the patient to macrocytic/ megaloblastic anemia. With regards oral health, the recent reports infer that ascorbic acid deficiency hampers dentin formation. Moreover, one who takes the lowest levels of the vitamin, and who also smokes, is likely to show adverse changes on periodontal tissues. Since, research has suggested the association between periodontal status and cardiovascular disease, diabetes and viral infections, this review article also discusses the role of vitamin C in preventing or treating these chronic conditions, as well as, in others where higher intake is needed. High intakes of the vitamin was thought to be well tolerable but it's now known that gastrointestinal upset accompanies dosages above 2 g.

### Mechanisms of Action

Vitamin C readily undergoes reversible oxidation and reduction and plays an important role as a redox agent in biological systems [1]. Its best understood function is in the synthesis of collagen, which promotes the formation of hydroxyproline. Collagen is a protein responsible for maintenance of the framework and tone of tissue, and it exhibits a wide range of diversity [2]. Nonhydroxylated form is unstable and cannot form the triple helix required for normal structure of subcutaneous tissue, cartilage, bone and teeth. The failure of cells to deposit collagen fibrils and intracellular cement substance leads to delayed wound healing. The inability of osteoblasts to form new bone matrix between cells prevents ossification, which may lead to bone fractures by preventing bone healing. Scurvy is the classic disease associated with vitamin C deficiency, the earliest symptom being fatigue followed by follicular hyperkeratosis, perifollicular hemorrhage, petechiae, purpuras, ecchymoses beginning on back of the lower extremities, and xerosis. Hemorrhage into the muscles of arms and legs and joints may lead to phlebothrombosis.

Since foods like mushrooms, broccoli, cereals fortified with folic acid and oranges that contain vitamin C also contain folic acid, a diet that causes scurvy may also lead to folic acid deficiency. In addition, the vitamin also regulates iron distribution and storage by maintaining a normal ratio of ferritin to hemosiderin. It also appears to participate in the synthesis of brain neurotransmitters and pituitary peptide hormones.

## Vitamin in Oral health

### *Macroscopic Structural Integrity*

Collagen is the major organic matrix component of dentin. It has been shown that in vitro treatment with ascorbate enhanced the formation of mineralized nodules and collagenous proteins [3]. Animal studies suggest ascorbic acid deficiency hampers dentin formation. It is shown that a mutant strain of Wistar rat, characterized by hereditary lack of L-gulonogalactone oxidase, is unable to synthesize ascorbic acid when given an ascorbic acid-free diet and showed a significant reduction in both size and mineral apposition rate of dentin and a reduction in bone formation in mandible [4]. A national survey in Great Britain which assessed the relationship between the food selection, nutrient status and the dental status in the elderly population, concluded from the dental examination, blood and urine tests that vitamin C were significantly lower in edentulous as compared to dentate subjects. People with 21 or more teeth consumed more of most nutrients, particularly non-starch polysaccharides. Plasma ascorbate and retinol in the hematological analysis were significantly associated with dental status. Thus, maintaining a natural and functional dentition defined as having more than twenty teeth into old age plays an important role in having a healthy diet rich in fruits and vegetables, a satisfactory nutritional status, and an acceptable BMI [5]. Ascorbic acid affects in vitro growth of bacteria and may also act in vivo to decrease caries activity.

Based on the evidence from the double-blind study [6], which compared the caries status and selected bacteriological variables of dentate adult subjects (with low levels of vitamin C in plasma ie.  $< \text{or} = 25 \text{ } \mu\text{mol/ L}$ ) with those of controls ( plasma levels  $>\text{or} = 50 \text{ } \mu\text{mol/ L}$ ) matched for age, sex and number of teeth; it was evaluated that the relative numbers of caries lesions were inversely related to the vitamin C in plasma. The initial inflammatory stage of bone healing is characterized by the formation of granulation tissue and the induction of precursor cells that differentiate into fibroblasts, chondroblasts, osteoblasts, osteoclasts and cells essential for capillary proliferation. It was found that the ascorbate modulates the chondrocyte gene expression and that type X collagen predominates in calcifying cartilage under the influence of alkaline phosphatase, which is induced by ascorbate [7]. In another study [8], it was found the vitamin C supplementation showed faster bone healing .The deficiency has also been associated with lower bone density in both human studies [9] and animal trials [10,11].

### *Periodontal Health*

Periodontal disease ( peri = around; dont=tooth, refers to the gingiva, periodontal ligament, cementum and alveolar bone ) is by nature, an entity of multifactorial origin with the role of putative and/ or anaerobic bacteria debated unequivocally. The host immune response in itself or in complex interaction with pathogens, stress, smoking and nutritional inadequacies have been the basis of recent research. In an attempt done to assess the attitudes of general dental practitioners and hygienists towards the role of nutrition in periodontal health; out of the eight hundred and seventy-nine questionnaires completed, sixty-six percent of respondents believed nutrition plays a role in periodontal health. Dietary factors that were considered most important were vitamin C (70%), fruit and vegetables

(64%) and antioxidant vitamins (45%) [12]. The suggested mechanisms through which ascorbic acid effects the periodontal status are:-

- Low levels of ascorbic acid influence the metabolism of collagen within the periodontium, affecting the ability of the tissue to regenerate and repair itself. Furthermore, collagen fibres in the periodontal ligament of scorbutic monkeys are the last affected before death [13].
- The deficiency increases the permeability of oral mucosa to tritiated endotoxin and tritiated inulin and of normal human crevicular epithelium to tritiated dextran. Optimal levels of vitamin C thus would maintain epithelium's barrier function to bacterial products [14].
- Increasing levels of ascorbic acid enhance both the chemotactic and the migratory action of leucocytes without influencing their phagocytic activity [15].
- An optimal level of ascorbic acid is apparently required to maintain the integrity of the periodontal microvasculature, as well as the vascular response to bacterial plaque and wound healing [16].
- Depletion of vitamin C may interfere with the ecologic equilibrium of bacteria in plaque and therefore increase its pathogenicity. However, no evidence demonstrates this effect.
- Ascorbic acid deficiency interferes with bone formation, leading to loss of periodontal bone. Osteoporosis of alveolar bone in scorbutic monkeys results from increased osteoclastic resorption and is not associated with periodontal pocket formation.<sup>13</sup> Oral human manifestations of scurvy include gingival edema, bleeding and ulcerations, secondary bacterial infections; and loosening of teeth [17].

Scurvy is uncommon in the pediatric population. But a recent finding reported a 10-month-old boy with inflammatory and necrotic gingival lesions, fever, irritability, and pseudo paralysis of the legs. Laboratory examinations revealed moderate anemia and skeletal x-rays showed osteopenia, scorbutic rosary at the costochondral junctions, and "corner sign" on the proximal metaphyses of the femora. The boy had been fed only with diluted cow's milk. He had never taken solid food, vitamin C, or iron complement. Seventy-two hours after starting oral vitamin C supplementation, there was significant improvement in the patient's gingival lesions and general health [18].

### **Association with Cancer**

Case-control studies indicate that vitamins C along with E, A and carotenoids decrease risk of oral premalignant lesions and oral cancer. The authors prospectively evaluated the association among 42,340 participants in the health professionals follow-up Study who provided information on supplement use and diet every 2-4 years by food frequency questionnaire. Dietary vitamin C was significantly associated with reduced risk (quintile 5 vs. 1, RR = 0.52, 95% CI 0.31-0.85, p(trend) = 0.04), however no association with supplemental vitamin C was observed [19]. The possible anticarcinogenic effect appears to be related to its ability to detoxify carcinogens or block carcinogenic processes through its action as an antioxidant or as a free-radical scavenger. Other proposed mechanisms include enhancement of the immune system, stimulation of collagen formation necessary for "walling off" tumors, inhibition of hyaluronidase which may keep the ground substance

around the tumor intact and prevent metastasis, inhibition of oncogenic viruses and improved wound healing after cancer surgery [20]. A condition frequently observed in palliative care patients is xerostomia, which is the subjective feeling of mouth dryness, caused by the decrease of saliva quality or quantity having physical, social and psychological consequences. One treatment modality is mechanical stimulation obtained by chewing gum and gustatory stimulation may be reached by sucking Vitamin C tablets [21]. It is further proposed that vitamin C contributes in the enhancement of the effect of certain chemotherapeutic drugs, reduction in their toxicity, particularly adriamycin and neutralization of carcinogenic substances [22].

### **Cardiovascular disease**

There is sufficient evidence that the extent of periodontal disease may be associated with coronary heart disease(CHD). Researches state there may be a greater risk for CHD-related events such as myocardial infarction when periodontitis affects a greater number of teeth in the mouth, compared with subjects having the infection at fewer teeth, with regards to severity in bleeding indices, pocket formation and loss of attachment around the teeth [23,24]. Periodontal disease predisposes the patient to an increased incidence of bacteremia with virulent gram -negative organisms which act as a reservoir of endotoxins. An estimated 8% of all cases of infective endocarditis are associated with dental or periodontal diseases, without the preceding dental procedure [25]. Recognition of this fact is implicit in the American Heart Association recommendations on prevention of bacterial endocarditis, which stress on the importance of establishing and maintaining the “best possible oral health to reduce potential sources of bacterial seeding”. It has been shown that oxidation of low-density lipoprotein (from the endotoxins) and lipid membranes play a crucial role in the formation of atherosclerotic plaques, which in turn impair endothelium-dependent vasodilation in human coronary and peripheral blood vessels. Although the mechanism is still unclear, it has been suggested vitamin C can protect circulating and membrane lipids from free radicals. It does appear to improve the endothelium- dependent vasomotor capacity of coronary arteries in hypertensives and patients with ischemic heart disease. Vitamin C is also believed to protect lipids indirectly by sparing or reconstituting the active forms of vitamin E [26].

### **Diabetes mellitus**

In addition to the five classic complications, namely retinopathy, nephropathy, neuropathy, macrovascular disease and altered wound healing, the American Diabetes Association designated periodontal disease as the sixth complication of diabetes [27]. Also, a two- way risk exists as periodontitis increases the tissue resistance to insulin, preventing glucose from entering target cells causing elevated blood glucose levels, and requiring increased pancreatic insulin production. The complications, in part, are believed to result from either the intracellular accumulation of sorbitol or the nonenzymatic glycoxidation of proteins or both. In type 1 diabetics, vitamin C supplementation is necessary to prevent protein glycoxidation and to optimize aldose reductase inhibition and a tight glycemic control. The ascorbate supplementation does not only improve the gingival and periodontal status as stated earlier in the article, but also has been shown to improve endothelium-

dependant vasodilation in type 1 or type 2 diabetics [28] apart from treating tissue scurvy resulting from hyperglycemia.

### **Viral Infections**

In vivo, vitamin C and E have been shown to reduce oxidative stress in HIV infected patients and to reduce the overall viral load [29]. Other antioxidants such as N- acetyl cystiene, glutathione and glutathione-esters appear to have cooperative interactions with ascorbate to inhibit HIV replication in vitro. A fundamental immunologic abnormality lies in the progressive decrease and functional impairment of CD4+ lymphocytes, which is critically dependent on intracellular redox balance and oxidative stress. In another study, the efficacy of a systemic bioflavonoid-ascorbic acid complex was evaluated in the treatment of episodes of recurrent herpes labialis [30]. Twenty episodes were treated with a complex of 600 mg bioflavonoids and 600 mg of ascorbic acid, administered three times daily. Twenty episodes were subjected to a complex of the potency each of 1000 mg. While the other ten episodes were treated with a placebo. It was observed that both the regimens were statistically superior to the placebo (  $p < 0.01$  ), in that, there was a reduction in vesiculation, but no significant difference in the remission of symptoms within both the regimens was stated. Bioflavonoids maintain normal capillary permeability and ascorbic acid maintains the normal mechanical strength of capillaries, as well as, promotes collagen formation. The role of long term supplementation of vitamin C in the prevention and treatment of common cold remains controversial and further research would be beneficial.

### **Special patient category**

Malnutrition associated with alcoholism may predispose an individual to scurvy. Several populations warrant special attention with respect to vitamin C requirements; which include smokers [19], elderly [31], pregnant and lactating women. The current and former tobacco users who take less dietary vitamin C have an increased risk for periodontal disease. The current RDA for smokers is 110mg/ day for women and 125 mg/ day for men, which is required to maintain plasma vitamin c concentrations compared to non smokers. The concentration is inversely related to cigarette consumption. There has been evidence that a high plasma vitamin C concentration lower the prevalence of cognitive impairment and the same oxidative processes mentioned earlier are implicated in aging [31]. Pregnant or lactating women also require a higher intake due to active placental vitamin transport, whereby the concentrations are significantly higher in cord blood and newborn than in mothers. Vitamin c in renal transplant recipients has been shown to improve flow mediated, endothelium- dependent vasodilatation and increase the resistance of lipoproteins in dilute serum to oxidation [32].

### **Vitamin C toxicity**

The intestinal absorption of vitamin C is 80-90% efficient and it is actively co-transported with sodium against an electrochemical gradient into intestinal epithelial cells, where intracellular dehydro-L-ascorbic acid (DHAA) converts by reduction to ascorbate. A Similar mechanism is responsible for the near complete ascorbate resorption in kidneys. Ascorbate and one of its metabolites, namely oxalate is found in the urine in excess states.

The latter is pertinent as it accounts for one of the few potential toxicities of vitamin C supplementation, oxalic acid renal stones. The tolerable upper intake level for adults is 2000 mg and the levels above 1 gram/ day can cause nausea [33]. Another problem with pharmacological doses is “rebound scurvy”, which occurs when the intake of high levels is stopped abruptly. The ascorbic acid is required in human diet, as well as, in other primates, guinea pigs and flying mammals. With regards to oral health, although several epidemiological surveys in developed countries have analyzed the association between the vitamin and periodontal status, however, these failed to establish a causal relationship [34]. It is noteworthy that mega doses of vitamin C have been found to be unrelated to better periodontal health [35]. In their comprehensive approach to patient care, clinicians should therefore base the need for recommending dosages in excess of the RDA only on sound data supported by nutritional analysis.

### SUMMARY

Vitamin C is an essential antioxidant to maintain normal metabolic processes and homeostasis within the body. Severe deficiency in humans results in scurvy; a disease characterized by hemorrhagic diathesis and delayed wound healing. Oral manifestations include bleeding, ulcerated and swollen gingiva, secondary bacterial infections and ultimately loosening of teeth. Advances in science and technology have greatly expanded our knowledge of the pathogenesis of dental and periodontal diseases. Animals placed on a diet deficient in vitamin C exhibit adverse changes in periodontium with respect to impaired collagen formation, distorted nuclear morphology of leucocytes and reduced chemotactic responses. The recent analysis of literature which indicates a strong association between systemic and oral health, has also shown that vitamin C tends to improve congestive heart failure, improve upon hyperglycemia in diabetes, fastens bone healing and reduces oxidative stress and also viral load in infections. While higher dosages are tolerated generally, a tolerable upper level is to be known. Even in smokers, elderly, lactating and pregnant, who warrant special attention to supplementation, the data do not support recommending the routine daily intake of more than 200mg. Clinicians should be cognizant in the comprehensive approach to patient care and provide the latter with evidence based prescriptions.

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