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A Review of the Use of Antioxidant Supplements in the Treatment of Human Oral Leukoplakia

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Abstract Over the past twenty years, research into the role of antioxidants in the prevention of cancer has increased dramatically. The use of antioxidant supplements to treat oral leukoplakia has gained acceptance due to the success demonstrated in several clinical trials. This review discusses the role of antioxidants in the development of cancer and their possible use in the treatment of oral leukoplakia. © 1993 Wiley-Liss, Inc.

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Oral leukoplakia (OL) is defined as a white patch within the oral cavity that cannot be identified as a separate entity [1]. OL is a clinical term with no specific histologic meaning. Histopathologic diagnoses range from hyperkeratosis through epithelial dysplasia to carcinoma. Both hyperkeratosis and epithelial dysplasia are considered premalignant lesions because of their potential to progress to carcinoma. OL has several different causes, but the specific etiology is typically uncertain in individual cases. Leukoplakic lesions that are either hyperkeratotic or dysplastic present treatment dilemmas. They occasionally involve extensive areas of the oral mucosa; they may progress to carcinoma, and surgeons and patients are reluctant to surgically excise premalignant lesions.

Antioxidants are essential in reducing free radical reactions which can cause DNA mutations, changes in enzymatic activities, and peroxidation of lipid membranes [2–4]. Beta-carotene (BC), retinol and its derivatives, ascorbic acid (vitamin C), and alpha-tocopherol (vitamin E) are all examples of antioxidants. Studies show an inverse relationship between low dietary and/or serum antioxidant levels and the probability of developing several different types of cancer [5].

Recent reports have documented the clinical success of various combinations of antioxidants in the treatment of oral leukoplakia [6–11]. This

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review evaluates the effectiveness of BC, retinol and its derivatives, vitamin C, and vitamin E in treating oral leukoplakia.

BETA-CAROTENE

BC is a carotenoid primarily found in green, orange, and yellow vegetables including spinach, carrots, sweet potatoes, and squash, as well as yellow fruits such as apricots and cantaloupes. The efficiency of BC absorption from the intestine dramatically decreases as the intake increases [12,13], which in part explains the lack of toxicity associated with BC. Serum levels of BC generally correlate with dietary intake [13, 14], but lower-than-expected serum values are found in men who smoke cigarettes [15–18], drink alcohol [15–17,19], or have a high body mass index [18,19].

There is no Recommended Daily Allowance (RDA) for BC. The average daily intake for adults in the United States is 3–5 mg/day [20]. Carotenodermia (yellowing of the skin) is the only known effect of excessive BC intake and it disappears several weeks after reducing intake [21]. The protective benefits of BC against cancer are probably related to its role in decreasing free radical damage and its ability to quench singlet oxygen, a reactive, unstable molecule [3]. BC also has immunoregulating properties which may retard the development of cancer cells [22–25].

Relationship to Human Cancer

Dietary studies have shown that low intake of BC is associated with increased risk of lung, laryngeal, gastric, ovarian, breast, and cervical cancer [14,26,27]. One group showed that a low intake of green vegetables and fruits was associated with an increased risk for oral cancer [28]. Another study revealed that the risk for oral and pharyngeal cancers decreased as the consumption of carrots, tomatoes, and green peppers increased [29].

The British United Provident Association (BUPA) study of 22,000 adult males showed that the mean serum BC level was significantly lower in cancer patients, most notably in patients with lung cancer [30]. Among the 2,974 males in the Basel study, an increased cancer risk was noted at several sites when serum BC concentrations were below 15 μg/dl [31]. An inverse correlation between the histologic severity of cervical dysplasia and serum BC levels has also been noted [32]. A limited amount of work has been done with tissue levels of BC, but one group has shown significantly lower levels in women with either benign or malignant uterine tumors [33].

Therapeutic Use in Oral Leukoplakia

There is considerable evidence that BC supplementation has minimal side effects and is possibly beneficial. The NCI accepted BC for "immediate intervention trials in humans...based on a strong protective effect reported in numerous epidemiologic studies" [34]. However, advising patients to increase their dietary intake of BC to achieve therapeutic levels is impractical; doubling the dietary intake would only increase serum BC levels by 29% [35]. Therefore, investigators use BC supplements to obtain higher serum levels [6,8,36].

Several clinical trials investigated treating oral leukoplakia with BC supplements alone. These studies typically involved a small number of patients in a non-blinded, non-randomized trial with dosage regimens ranging from 26 to 120 mg BC/day. Patients with clinical improvement ranged from 14.8 to 71% [6,8,36,37]. Stich and colleagues [37–39] showed some success in treating oral leukoplakia with vitamin A and/or BC.

RETINOL AND RETINOIDS

Vitamin A (retinol) is an alcohol that can be converted into either an aldehyde (retinal) or retinoic acid [40]. Retinol is found in dairy products, eggs, and meats. The RDA for vitamin A is 5,000 IU/day; therapeutic doses are approximately 25,000 IU/day. In contrast to BC, the percentage of retinol absorption remains constant as the intake increases [12]. Hypervitaminosis A occurs when retinol intake exceeds the liver's capacity to remove or store it. Abnormal liver function tests have been reported in patients who consume as little as 50,000 IU/day of vitamin A; however, liver damage can occur at even lower levels if the patient drinks alcohol [41].

Retinoids are compounds consisting of natural or synthetic analogues of retinol [42]. Of the more than 1,500 synthetic analogues of vitamin A, 13-*cis*-retinoic acid (13-cRA, isotretinoin) has generated the most interest. Cheilitis, dry skin, hypertriglyceridemia, xerostomia, teratogenic effects, and symptomatic hyperostosis have been reported as side effects of retinoid supplementation [41].

Relationship to Human Cancer

The first study associating vitamin A deficiency with cancer appeared in 1941 [43]. Low intake of vitamin A has been linked with an increased risk for developing cancer of the lung, colon, breast, pharynx, larynx, esophagus, and bladder [44].

Therapeutic Use in Oral Leukoplakia

Using vitamin A supplements to treat oral leukoplakia began in the early 1960s [45] but was not widely accepted because of the side effects. An early report by Silverman and colleagues [45] showed that administering 300,000 to 900,000 IU of vitamin A/day supplied as 75,000 IU vitamin A ester troches (dissolved orally and the saliva-solute swallowed) resulted in 7/16 (43.8%) patients having partial or complete resolution of their leukoplakia. However, 3/4 patients with complete resolution had a recurrence within two weeks after discontinuing the troches. Half of the patients developed side effects. These two findings—recurrence within a short time after discontinuing the medication, and a high percentage of patients with side effects—appear throughout the reports that deal with therapeutic use of retinol and retinoids.

Two retinoids primarily used in the treatment of oral leukoplakia are 13-cRA (Accutane®) and tretinoin (Retin-A®). 13-cRA has been shown to cause temporary remission of oral leukoplakia; it also causes a high incidence of side effects when given at effective doses. Koch [46] treated 75 cases of oral leukoplakia with 80–100 mg of retinoic acid/day for eight weeks and noted that almost half the patients showed either partial or complete resolution of their lesions. However, almost half of his patients suffered from dizziness or headaches. Shah *et al.* [47] treated 16 patients with oral leukoplakia for six months using lozenges that were dissolved and swallowed to deliver topical doses of 13-cRA ranging from 3 to 10 mg/day. Five of the patients (31.2%) dropped out because of side effects; two of the three patients who showed complete resolution had recurrences within five weeks of discontinuing the medication.

A group from M.D. Anderson Cancer Center found a greater than 50% reduction in lesion size in 27/44 (67%) oral leukoplakias treated for three months with 1–2 mg/kg/day 13-cRA [9]. However, 79% of the patients had a variety of side effects. The point can be made here that the treatment should be no worse than the disease. The treatment of premalignant oral lesions with 13-cRA is difficult to justify: there is small likelihood such lesions will transform into carcinoma, the therapy causes a high percentage of side effects, and recurrences are noted when it is discontinued. Hays and colleagues [48] used 1.5 mg/kg/day of 13-cRA for three months to achieve clinical improvement in 62% of their patients with oral leukoplakia. The patients with clinical improvement were enrolled in the maintenance phase and randomly placed into a group receiving either 0.5 mg/kg/day of 13-cRA or 30 mg/day of BC for nine months. Relapse rates were significantly higher for patients receiving BC compared to those with 13-cRA (54% versus 10%, respectively). In another study, 3/9 patients whose oral leukoplakias did not respond to six months of BC supplementation (120 mg/day) showed clinical improvement with 13-cRA [36].

It appears that various forms of vitamin A can reverse and/or prevent epithelial keratin formation; however, the biochemical mechanism is unknown.

ASCORBIC ACID

L-Ascorbic acid (L-AA), commonly known as vitamin C, is found in citrus fruits and cruciferous vegetables [49]. The adult RDA ranges from 60 mg/day for nonsmokers to 100 mg/day for smokers. Absorption is approximately 90% if intake is less than 100 mg/day, declining sharply when the intake exceeds 180 mg/day [50]. Toxicity is not a problem because the water solubility and absorption efficiency of ascorbic acid decline with increased intake [49].

Relationship to Human Cancer

Many studies have shown that a low intake of ascorbic acid is associated with increased risk for cancers of the stomach, esophagus, oral cavity, larynx, and cervix [51,52]. The protective effect of dietary ascorbic acid is attributable more to fruits than vegetables [52,53]. Unfortunately, the typical American diet often lacks fruit, based on the report of one survey showing that 41% of Americans on a particular day did not consume any fruit or fruit juice [53].

Therapeutic Use in Oral Leukoplakia

We are unaware of any investigations involving ascorbic acid as the sole treatment for oral leukoplakia. The association between vitamin C and oral carcinoma is based solely on dietary assessments that found an increased risk when fruit and vegetable intakes were low.

ALPHA-TOCOPHEROL

Alpha-tocopherol (AT), the most active form of vitamin E, is found in plant oils, margarine, shortening, wheat germ, and green leafy vegetables [54]. The RDA is 10 mg/day for adult males and 8 mg/day for adult females. Absorption of AT ranges from 20 to 80%; efficiency decreases as intake exceeds 30 mg/day [50,54]. Supplements are more effective in achieving high serum AT levels than are modifications of the diet [55]. Doses of up to 3,200 mg/day of AT have been well tolerated by adults with no sign of toxicity [54,56,57].

AT is an effective antioxidant at high oxygen pressures [58]. It protects the conjugated double bonds of BC from oxidation and also protects cellular membranes from lipid peroxidation [2,59,60]. Additionally, its ability to enhance mitogenic response, inhibit certain prostaglandins, and improve T-cell-mediated responses increases the patient's immune response [61–64].

Relationship to Human Cancer

One study showed that patients with low serum levels of AT had a relative risk of >2.0 for gastrointestinal cancers [65]. In contrast, another study found that a higher intake of AT increased the possibility of colonic cancer [51]. The use of vitamin E supplements correlated with a diminished risk for oral and pharyngeal cancer in a study evaluating more than 2,000 cases [60].

Therapeutic Use in Oral Leukoplakia

One study evaluating the effects of 800 IU AT/day for 24 weeks found that 20/31 (64.5%) evaluable patients showed clinical improvement [66]. However, the data are difficult to interpret because 12 other patients were not clinically assessed due to problems encountered in this multicenter study. A variety of mild side effects was reported among the patients in the study.

ANTIOXIDANT COMBINATIONS

Considerable data support the concept of a synergistic effect between the antioxidants. A mild deficiency of either BC, ascorbic acid, or AT decreases the bioactivity of the others. Other investigators have shown a synergistic effect in animal tumor prevention when using a combination of BC and AT [67,68]. It has been speculated that BC, ascorbic acid, and AT jointly participate in cancer prevention by immunosurveillance against tumors [55]. The antioxidant functions of BC and the retinoids are maximal at low oxygen pressures, while AT is more effective at high oxygen pressures [58]. BC, ascorbic acid, and AT are free radical scavengers with different subcellular distributions [2].

Therapeutic Use in Oral Leukoplakia

We recently completed analyses of 79 patients with histologically verified hyperkeratosis or epithelial dysplasia treated for nine months with 30 mg of BC, 1000 mg ascorbic acid, and 800 IU AT/day. Clinical improvement, observed in 55.7% of the patients, was most likely to occur in those who reduced their use of alcohol or tobacco ($p = 0.0056$) and those diagnosed with epithelial dysplasia ($p = 0.02$). Although risk factor reduction was important, approximately half of the patients who did not alter exposure to either alcohol or tobacco showed clinical improvement. The benefit of antioxidant supplementation in the treatment of oral leukoplakia is uncertain, but evidence suggests that it does play a role.

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