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The Essential Antioxidants: an Update on Their Therapeutic Applications

Diane L. McKay, PhD and Jeffrey B. Blumberg, PhD, Antioxidants Research Laboratory
Jean Mayer, USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA USA

During the last 5 years, the rapid growth in knowledge about carotenoids and polyphenolic antioxidants, particularly the flavonoids, as well as advances in the therapeutic use of cellular antioxidants, such as a-lipoic acid and coenzyme Q10, appears to have distracted the attention of some healthcare professionals from the on-going evolution in the application of the essential dietary antioxidants, vitamins C and E and the trace mineral selenium. Historically, the research on these micronutrients has focused on the presentation of deficiency syndromes with very low dietary intakes. The most common, nutrient dense food sources of these compounds are listed in Table 1[1]. Recent studies, however, continue to reveal their promise as supplements for several therapeutic applications. While controversy has arisen from a few studies about a potential for harm from these nutrients as supplements, particularly regarding vitamin E[2], the vast majority of reports continue to support their long history of safety and a high benefit/risk ratio, e.g., as illustrated recently with the summary by Hathcock et al.[3] of 29 clinical studies of vitamin C with 25,815 subjects and 24 clinical studies of vitamin E with 86,092 subjects. This report provides a brief update on the therapeutic application of vitamins C, E and selenium supplements to a variety of conditions.

VITAMIN C

Pregnancy

In a randomized, double-blind, placebo controlled trial of 109 pregnant women attending a prenatal clinic in Mexico City, Casanueva et al.[4] found that a daily supplement of 100 mg vitamin C, in addition to a diet providing an average daily intake of 65 mg vitamin C, during weeks 20-36 of gestation effectively lowered the incidence of premature rupture of the chorioamniotic membrane (PROM) by 74% (RR: 0.26; 95% CI: 0.078, 0.837). PROM is an established cause of preterm delivery and is associated with increased rates of neonatal and maternal morbidity and mortality worldwide. Clinical evidence suggests that reactive oxygen species may contribute to PROM. After a 16-week intervention with vitamin C, the incidence of PROM in the supplemented group was 7.69%, compared to 24.5% in the placebo group (P = 0.018). Although the maternal plasma vitamin C concentrations were not affected by the supplement, presumably due to the effects of hemodilution and active transport to the fetus, leukocyte vitamin C concentrations did rise during the first 4 weeks of supplementation and were significantly elevated by week 8 (P = 0.005). The mean leukocyte concentration in the vitamin C group increased from 17.26 to 22.17 $\mu g/10^8$ cells, whereas levels in the placebo group decreased from 17.50 to 15.23 $\mu g/10^8$ cells (between subjects differences: P <0.001). Leukocytes concentrate and store vitamin C, thereby providing a more reliable indicator of vitamin C nutritional status than plasma. According to the authors, leukocyte ascorbic acid might be helpful as a functional indicator of PROM risk and indicate a recommendation for vitamin C supplementation.

Another major contributor to neonatal morbidity and mortality, preterm premature rupture of membranes (PPROM), is associated with 40-50% of premature deliveries requiring admission to the neonatal intensive care unit (NICU). In a double-blind, randomized, controlled trial by Borna et al.[5], 60 pregnant women admitted to hospital with PPROM during weeks 26-34 of gestation were given a daily combination of vitamin C (500 mg) and vitamin E (400 IU) or placebo until they delivered. Supplementation was found to significantly prolong the latency period in women with PPROM from 3.5 ± 4.0 days in the control subjects to 10.5 ± 5.2 days in the supplemented group (P = 0.03). Prolonging pregnancy in women with PPROM can decrease gestational age-related morbidity associated with preterm birth. While prolongation may also increase the risk of neonatal morbidity factors, no significant differences between groups were observed in this study with regard to chorioamnionitis, postpartum endometriosis, NICU admission, neonatal sepsis, respiratory distress syndrome, or neonatal death.

Childhood asthma

The combination of vitamins C and E was successful in decreasing the nasal inflammatory response to air pollutants among asthmatic children. Using a randomized, placebo-controlled study design, Sienna-Monge et al.[6] investigated the impact of daily supplementation with 250 mg vitamin C and 50 mg vitamin E for 4 months on the inflammatory response of the airways due to ozone exposure among 117 asthmatic children residing in Mexico City. The nasal acute inflammatory response was measured by analyzing interleukin (IL)-6 and IL-8, uric acid, and total glutathione obtained from a nasal lavage. The children who received the placebo had a significant increase in IL-6 and IL-8 in response to ozone exposure, while children receiving the antioxidant supplements did not. These clinical trial results are consistent with experimental and epidemiological studies that have suggested supplementation with antioxidants can modulate the acute changes in lung function observed among people exposed to pro-oxidant air pollutants.

Gout and kidney disease

According to Huang et al.[7], supplementation with 500 mg/day of vitamin C can reduce serum uric acid levels and, therefore, might prove beneficial in the prevention and management of gout and other urate-related diseases. High levels of uric acid in serum can become crystallized in the joint and kidney, leading to gout and the development of kidney stones. Hyperuricemia may also initiate or promote the progression of renal disease. In a randomized, placebo-controlled study of 184 nonsmoking adults from the Baltimore, MD area, supplementation with 500 mg/day of vitamin C for 2 months significantly lowered serum uric acid levels compared to a placebo (-0.5 mg/dL vs. +0.09 mg/dL; P <0.001). The difference between the two groups remained significant even after adjusting for age, gender, and baseline serum ascorbic acid and uric acid concentrations. Among the 21 subjects who were classified as hyperuricemic at baseline (serum uric acid >7.0 mg/dL), supplementation reduced serum uric acid even more (-1.5 mg/dL; P <0.001). The changes in serum uric acid were inversely correlated with changes in serum ascorbic acid. Supplementation also had a positive effect on glomerular filtration rate (GFR), which is a possible mechanism for the reduction in serum uric acid levels. The estimated GFR increased significantly with vitamin C supplementation compared to placebo (P = 0.02). These findings remained consistent after subgroup analyses, including age, gender, race, body mass index, chronic illnesses, diuretic use, and quartile of baseline serum uric acid and ascorbic acid as categories.

Atrial fibrillation therapy

In a trial by Korantzopoulos et al.[8], 44 patients with persistent atrial fibrillation (AF), the most frequently sustained arrhythmia encountered in clinical practice, were given electrical cardioversion to restore normal heart rhythm and then randomized to receive either 1000 mg/day vitamin C or no additional therapy for the next 7 days. Inflammatory indices, including white blood cell count (WBC), C-reactive protein (CRP), fibrinogen, and ferritin were examined over time post-cardioversion. These investigators found that vitamin C supplementation reduced the early recurrence rates after successful cardioversion and attenuated the associated inflammation. One week following successful cardioversion, AF recurred in 4.5% of patients supplemented with vitamin C and in 36.3% of patients in the control group (P = 0.024). No significant differences were observed in the inflammatory indices of the control group, while levels of WBC, CRP, and fibrinogen in the supplemented group were significantly lower when compared to baseline measurements.

VITAMIN E

Head and neck cancer therapy

The effects of vitamin E supplementation in patients with head and neck cancers who have suffered side effects from radiation treatments have been examined in two recent studies. Preliminary data from Chan et al.[9] suggest that daily supplementation with vitamin E may improve cognitive function in patients who develop temporal lobe radionecrosis after undergoing radiotherapy to treat brain lesions diagnosed as nasopharyngeal carcinoma. After one year, the 19 patients who received 2000 IU vitamin E daily scored significantly higher on tests measuring global cognitive ability (P = 0.035), verbal memory (P = 0.036), visual memory (P = 0.007), and executive function (as measured by the Cognitive Flexibility Test; P = 0.04) compared to control patients (n = 10).

Vitamin E has been shown in previous studies to act synergistically with pentoxifylline (PTX), a methylxanthine derivative, to exert an anti-fibrotic effect in patients with severe radiation-induced fibrosis and necrosis. More recently, Delanian et al.[10] demonstrated that this combination might also be effective in treating osteoradionecrosis (ORN). ORN, a severe delayed injury caused by the failure of bone to heal, typically occurs in the mandible and most often appears 6 months to 5 years after completing radiotherapy (RT) treatment for head and neck cancers. All 18 patients in this study had previously undergone RT treatment for malignant head and neck tumors, located mainly in the oral cavity or oropharynx. The mean latency period between the end of RT and the incidence of ORN was 4.1 ± 4.3 years (range 0.5-14 years). All patients were given a daily combination of 1000 IU vitamin E and 800 mg PTX for at least 6 months. The 8 most severe cases, i.e., those with active progressive ORN, were also given clodronate, a biphosphonate that inhibits osteoclastic bone destruction. At 6 months, the mean length of superficial soft tissue necrosis and relative regression was reduced 84%, subjective objective medical management and analytical evaluation of injury (SOMA) scores for symptom severity improved 67%, and 89% of patients had a complete recovery.

Hepatitis C

Lipid peroxidation may play an important role in the evolution of liver damage, i.e., fibrogenesis and the progression of cirrhosis, in patients infected with the hepatitis C virus (HCV). Ota et al.[11] examined the effects of vitamin E supplementation (500 mg/day of d-α-tocopherol) among 8 HCV patients and compared the results to the effects of supplementation among 9 healthy control subjects. All patients were treated as outpatients at Kawasaki Medical School Hospital in Japan. Vitamin E was administered 3 times daily – 200 mg in morning and afternoon, 100 mg in evening for 12 weeks. Arachidonic acid, docosahexanoic acid, and the polyunsaturated:saturated fatty acid ratio in red blood cell membrane phospholipids were significantly lower at baseline in the HCV patients compared to the control subjects. At 8 and 12 wk after vitamin E supplementation, these measures were elevated in the HCV patients to the same levels as the control subjects, i.e., no significant differences were observed between patients and control subjects after the intervention suggesting a restoration of more normal function in the HCV patients.

Prostate cancer

To determine the effect of selenium and vitamin E in blood and prostate tissue, Kim et al.[12] randomized 39 patients with clinically localized prostate cancer to receive vitamin E (400 IU *all rac*-α-tocopherol acetate), selenium (200 µg L-selenomethionine), a combination of both or placebo for 3-6 weeks prior to prostatectomy. Each patient also received a multivitamin and vitamin C (250 mg) supplement. Age-matched, disease-free men served as controls (n = 29) in this 2 x 2 factorial, preoperative feasibility study complementary to the ongoing, phase III Selenium and Vitamin E Cancer Prevention Trial. Weighted voting analyses of mass profiling of low molecular weight lipophilic serum proteins (2 – 13.5 kDa) showed a change in proteomic pattern classification from cancerous to healthy for some patients with prostate cancer after the supplementation, with the combination treatment inducing the most significant shift to patterns associated with prostate cancer-free status.

SELENIUM

Immunity

In the U.K., Broome et al.[13] assessed the effects of selenium supplementation on functional changes in immune status in a double-blind study.

Apparently healthy adults with plasma selenium concentrations <1.2 µmol/L were randomized to receive 50 or 100 µg selenium (as sodium selenite) or placebo daily for 15 weeks. After 6 weeks, all subjects were given an oral, live attenuated poliomyelitis vaccine virus. The researchers found that selenium supplementation augmented the cellular immune response to the polio vaccine through an increased production of interferon-γ (IFN-γ) and other cytokines, an earlier peak T cell proliferation, and an increase in T helper cells. T cell proliferation occurred one week earlier in the supplemented groups than in the placebo group suggesting that supplemented subjects had the ability to mount an earlier immune response to the viral challenge. Peak IFN-γ release was greater in the group supplemented with the 100 µg dose than in the placebo group, suggesting a dose-response relationship for selenium and immune responsiveness. Supplemented subjects also showed a more rapid clearance of the poliovirus. Interestingly, in placebo subjects, mutations of the attenuated polio virus were observed, an effect which was not apparent in the selenium supplemented groups.

Chromosome breaks

In a pilot study by Kowalska et al.[14], the frequency of chromosome breaks was measured in BRCA1 carriers following oral selenium supplementation. The product of the BRCA1 gene is involved in the repair of double-stranded DNA breaks. Evidence suggests that increased susceptibility to DNA breakage contributes to the cancer phenotype in women who are born with constitutional heterozygous mutations of this gene, greatly increasing their risk of breast and ovarian cancer. At baseline, the BRCA1 mutation carriers showed significantly greater mean frequencies of bleomycin-induced chromosome breaks per cell than did healthy non-carrier relatives who served as controls (26 case-control pairs). Among the 35 women with BCRA1 mutations who were given 0.4 mL of an oral, ethanolic solution of sodium selenite providing about 276 µg selenium daily for 1-3 months, the frequency of chromosome breaks was greatly reduced to levels comparable with the non-carrier controls. In every case, the post-supplementation level of chromosome breaks showed a significant decline from the baseline level. The investigators suggest that BRCA1 carriers are particularly sensitive to oxidative stress and DNA injury, and this condition may be mitigated by dietary selenium.

Lymphedema

Lymphedema develops when excessive interstitial tissue fluid accumulates due to interruption of lymphatic flow in lymph nodes. In cancer patients, secondary lymphedema can occur after surgically induced damage to lymphatic vessels, e.g., lymph node dissection, or radiotherapy. The treatment of lymphedema in head and neck cancer patients with selenium has been explored in two recent German studies. In the affected limb of patients with chronic lymphedema, the production of free radicals is increased as a result of lymphostasis, mechanical tissue compression, and chronic inflammation triggered by an excess of interstitial protein and cellular debris. This condition promotes a variety of degenerative processes, worsening lymphostasis, and inflammation by tissue fibrosis.

Bruns et al.[15] treated 36 head and neck cancer patients with persistent, extensive or progressive lymphedema of the head and neck region daily with 350 µg sodium selenite/m^2 body surface for 4-6 weeks. Self-assessed quality of life values improved significantly between baseline and end of treatment. After 4 weeks, 75% of patients had an improvement of one grade or more according to the Miller scoring system, while 63% had an improvement of one stage or more when assessed with the Foldi scoring system. After selenium supplementation, 65% of the 20 patients who initially presented with interstitial endolaryngeal edema had their swelling reduced to normal levels. Microlaryngoscopic findings were used to assess the level of swelling in the endolaryngeal airways and confirm that tracheostomy was no longer necessary for these patients. The selenium supplement was reported to be well tolerated and absent of adverse side effects. The authors of the study concluded that selenium supplementation has a beneficial effect on secondary head and neck lymphedema caused by radiotherapy alone or combined after surgery.

CONCLUSION

These recent studies indicate a growing role for supplementation with vitamins C and/or E or selenium in the treatment of a wide variety of conditions in addition to the most frequently examined outcomes of cancer and cardiovascular disease. While these clinical intervention trials are relatively small in size, the rigor of their design (including randomization and placebo control), and the benefits obtained strongly warrant continuing investigation for the application of these essential antioxidants as supplements.

Table 1. Food Sources of the Essential Antioxidant Micronutrients

Micronutrient (units)	Units/common measure	% RDA
Vitamin C (mg)		
Sweet pepper, red	283 mg /cup	377
Peaches, sliced, frozen	236 mg /cup	315
Orange juice	124 mg /cup	165
Pepper, green	120 mg /cup	160
Strawberries, raw	98 mg /cup	131
Brussels sprouts, cooked	97 mg /cup	129
Oranges, raw	95 mg /cup	127
Grapefruit juice	94 mg /cup	125
Broccoli, raw	79 mg /cup	105
Peapods, boiled	77 mg /cup	103
Vitamin E (alpha-tocopherol, mg)		
Tomato paste, canned	11.3 mg /cup	75
Sunflower seeds, dry roasted	7.4 mg /cup	49
Almonds	7.3 mg /oz	49
Sunflower oil	5.6 mg /Tbsp	37
Tomato products, canned	5.1 mg /cup	34
Safflower oil	4.6 mg /cup	31
Turnip greens, frozen	4.4 mg /cup	29
Hazelnuts	4.3 mg /oz	29
Spinach, cooked	3.7 mg /cup	25
Dandelion greens, cooked	3.6 mg /cup	24
Selenium (µg)		
Brazil nuts	543 µg /oz	987
Mixed nuts	119 µg /oz	216
Chicken giblets, cooked	86 µg /cup	156
Whole wheat flour	85 µg /cup	155
Tuna fish salad	85 µg /cup	155
Turkey giblets, cooked	84 µg /cup	153
Barley, raw	75 µg /cup	136
Orange roughy, cooked	75 µg /3 oz	136
Halibut, cooked	40 µg /3 oz	73
Salmon, cooked	40 µg /3 oz	73

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