

## **Antioxidants: Vitamins C, E, and beta-carotene**

### **Background**

Oxidative damage is postulated to be the cause of many disparate disease processes including cancer, macular degeneration of the retina, and coronary atherosclerosis.

The oxidative hypothesis holds that aerobic metabolism produces free oxygen radicals (superoxide, singlet oxygen, hydrogen peroxide) which initiate lipid oxidation, possibly contributing to oxidative damage of DNA, proteins and carbohydrates within the cell.

Antioxidants are a diverse group of substances which have been shown to "scavenge" free radicals in vitro, thereby slowing the oxidative process. The best studied antioxidants are vitamin C, vitamin E, and beta-carotene.

A large body of observational data has suggested that people whose diet is rich in antioxidant vitamins have a lower incidence of cancer, macular degeneration, and coronary atherosclerosis. This has led to the hypothesis that diet supplementation with antioxidants could prevent these outcomes. Such observational studies are notoriously unreliable, however, as it is impossible to fully control for other factors which may be responsible for the effect which happen to be associated with antioxidant intake.

### **Summary of the Evidence**

- Clinical trials of antioxidants suggest that they may modestly slow the progression of macular degeneration, but trials of prevention have been inconclusive.
- Aside from a scant amount of preliminary data suggesting that vitamin E might reduce the risk of prostate cancer, trials have otherwise been strikingly negative for the prevention and treatment of coronary atherosclerosis, cancer, and dementia.
- There is alarming evidence that smokers who take beta-carotene supplements have an increased risk of lung cancer and heart disease. Its use should thus be discouraged.

### **Recommendations**

- With the exception of beta-carotene and high doses of vitamin A, vitamin supplements appear to be safe and are also relatively inexpensive. There is thus little reason to discourage their use.
- Very few patients in the trials below suffered from a chronic illness such as diabetes or had very low dietary intake of fruits and vegetables. In such patients, taking a single daily multivitamin is especially prudent.

### **Macular degeneration**

- In the United States, macular degeneration is the leading cause of blindness in those over age 65.
- A very large NIH-funded trial (AREDS 2001) randomized patients to antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg beta carotene, 80 mg zinc as zinc oxide with 2 mg copper as cupric oxide) or placebo.
- Over 6 years there was no preventive benefit in those with mild or no macular degeneration at baseline.
- Among those with moderate disease at baseline a reduction of 25% was seen in the risk of progressing to advanced disease.
- Patients with a significant smoking history should not take beta-carotene.

### **Coronary atherosclerosis**

- A large meta-analysis (Vivekananthan 2003) found remarkably consistent negative results. In 2 large primary prevention trials (patient with no history of heart disease) and 5 large secondary prevention trials (prior history of heart disease) beta-carotene, vitamin E, or the 2 together had no effect.
- This confirmed the analysis performed one year prior by the United States Preventative Task Force.

### **Cancer prevention**

- The United States Preventative Task Force performed an extensive review of a very large and complex amount of clinical trial data testing vitamins alone or in combination in the prevention of cancer and found no convincing evidence.

### **Beta-carotene – Adverse effects**

- Five RCT's have now found an increased incidence of lung cancer in smokers given beta carotene supplements. Among nonsmokers, trials have shown no effect on cancer incidence.
- The doses of beta-carotene tested were much higher than could reasonably be obtained from food.

### **Alzheimer's Dementia**

- A single large trial of vitamin E found it to be no better than placebo (Sano 1997).

### **Key Antioxidant References**

1. AREDS (Age-Related Eye Disease Study) Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. *Arch Ophthalmol.* 2001 Oct;119(10):1417-36.
2. U.S. Preventive Services Task Force. Routine Vitamin Supplementation To Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale. *Ann Intern Med* 2003; 51-55.
3. Vivekananthan DP, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet.* 2003;361(9374):2017-23.
4. Sano M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med.* 1997;336:1216-22.