

# The Whitehall-Robins Supplement

## A Selection of Recent Findings in the Field of Nutrition

Feb 2009 - Volume 13, Number 1

### **Vitamin E supplementation reduces cardiovascular events in subgroup of middle-aged individuals with both type 2 diabetes mellitus and haptoglobin 2-3 genotype. A prospective double-blinded clinical trial.**

Several observational and preclinical studies reported that vitamin E is beneficial in preventing cardiovascular disease. Recent randomized clinical trials investigating whether vitamin E supplementation provides cardiovascular benefits did not confirm such benefits. A possible explanation for the findings from the clinical trials is inadequate patient selection in these studies. It is plausible that high antioxidant intake may be more beneficial to individuals with high levels of oxidative stress. The haptoglobin (Hp) genotype may help in identifying patients with high levels of oxidative stress who are more likely to benefit from vitamin E supplementation. The Hp gene is polymorphic with 2 common alleles denoted as 1 and 2. Hp2 allele protein has inferior antioxidant properties compared to Hp1 protein. These differences in antioxidant protection are markedly accentuated in diabetes mellitus (DM) which result in an increase in oxidative stress in individuals with Hp2 genotype. Hp 2-2 DM individuals have a 2-5 fold increase in cardiovascular events compared to other Hp genotypes. This randomized placebo-controlled trial of 1,434 DM individuals with the Hp2-2 genotype were randomized to 400 IU/d of vitamin E or placebo. The primary composite outcome was myocardial infarction, stroke, and cardiovascular death. Eighteen months after initiating the study and at the first evaluation of events, the primary outcome was significantly reduced in individuals on vitamin E supplementation. Based on this immediate benefit the study was terminated early. The authors conclude "Vitamin E supplementation appears to reduce cardiovascular events in individuals with DM and the Hp2-2 genotype."

[Milman U, et al. *Arterioscler Thromb Vasc Biol* 2008; 28:341-347]

### **Dietary antioxidants and the long-term incidence of age-related macular degeneration. The Blue Mountains Eye Study.**

Age-related macular degeneration (AMD) is one of the leading causes of blindness. Currently, there are limited treatment options. The exact etiology of AMD is unknown; however, oxidative stress is hypothesized to be one of the mechanisms in AMD. This study investigated the association between antioxidants intakes from daily foods and supplements and the 10-year incidence of AMD in an older Australian cohort. High intakes of beta-carotene, zinc and vitamins C and E were particularly assessed. In this study, individuals in the highest category of total zinc intake (mean intake  $\geq 15.8$  mg/day) were less likely to develop AMD compared to individuals with low zinc intake, and this association was statistically significant. Similarly, high intake of lutein and zeaxanthin (mean intake  $\geq 942$  mcg/day) was associated with a lower risk of AMD. Surprisingly, high beta-carotene was associated with an increased risk of AMD. The authors acknowledge that there were no prior studies reporting higher risk of AMD with increasing beta-carotene intake, and they have no biological explanation for this finding. Sensibly, the authors are advising caution in interpreting the beta-carotene finding. Nevertheless, it is encouraging that this study confirmed earlier reports of a beneficial effect of higher zinc, lutein and zeaxanthin intakes in reducing the risk of AMD.

[Tan JSL, et al. *Ophthalmology* 2008; 115:334-341]

### **Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial.**

The relation between solar radiation and the reduction in cancer mortality in North America was reported by Apperly more than 60 years ago. In 1980, Garland and Garland were the first to propose that vitamin D was specifically associated with colon cancer. Since then, the inverse association between solar radiation and cancer mortality has subsequently been described for breast, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, and uterine cancers, as well as for non-Hodgkin lymphoma and multiple myeloma. This protection was presumed to be mediated by the effect of solar radiation on vitamin D status. Several observational studies reported that calcium and vitamin D supplementation are associated with a reduced risk of common cancers. This effect was not tested in interventional studies. This population-based, double-blind, randomized placebo-controlled trial in postmenopausal women, investigated the effect of calcium alone (1,400 mg-1,500 mg), and calcium plus vitamin D (1,100 IU) in reducing the incident cancer risk of all types. The supplemental vitamin D level was sufficient to raise serum 25(OH) D to  $> 80$  nmol/L which is a level widely believed to be associated with the many reported benefits of vitamin D. In this study improved vitamin D status was associated with a decrease in all-cancer risk. Furthermore, baseline and treatment-induced serum 25(OH) D concentrations were strong predictors of cancer risk. These findings support the importance of optimizing vitamin D status and maintaining a high serum 25(OH) D concentration. There was a marginal protective effect for the calcium only group. The authors conclude "Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women."

[Lappe JM, et al. *Am J Clin Nutr* 2007; 85:1586-1591]

### **Cholecalciferol significantly increases 25-hydroxyvitamin D concentrations in adults with cystic fibrosis.**

Persons with cystic fibrosis (CF) tend to have low bone mineral density. Low bone mineral density is a multifactorial condition; however, vitamin D is widely believed to be an important causative factor. Vitamin D deficiency is frequently encountered in CF despite routine supplementation as per the treatment guidelines. In CF a serum 25(OH)D concentration  $< 50$  nmol/L is considered deficient; however, it is widely reported in the literature that vitamin D concentrations  $> 75$  nmol/L are needed to optimize calcium absorption and normalize parathyroid hormone. This study determined the prevalence of 25 (OH) D deficiencies in a large cohort of CF subjects and evaluated the effectiveness of vitamin D supplementation with vitamin cholecalciferol (D3) in 360 adults with CF followed at a large CF center.

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In this study, a significant (69%) proportion of adults with CF have 25(OH) D concentration  $\geq$  50 nmol/L, despite vitamin D supplementation. This finding strongly suggests that the current recommended dosage of 400 to 800 IU is inadequate to normalize concentration. The findings from this study are suggesting that, on average, an additional 1,000 IU/day might be required to increase concentrations in most subjects. Subjects with the lowest concentrations had the greatest response to supplementation. The authors conclude "A significant proportion of adults with cystic fibrosis have serum 25(OH) D concentrations  $\geq$  50 nmol/L. Cholecalciferol increases serum 25(OH) D concentrations significantly and the maximum response occurs in persons with the lowest baseline concentrations."  
*[Stephenson A, et al. Am J Clin Nutr 2007; 85:1307-1311]*

### **Suggested Readings**

**Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure.**

*[Moan J, et al. PNAS 2008; 105:668-673]*

**Dietary patterns and the risk of Barrett's esophagus.**

*[Kubo A, et al. Am J Epidemiol 2008; 167:839-846]*

**Vitamin D and adipogenesis: new molecular insight.**

*[Wood RJ. Nutr Rev 2008; 66:40-46]*

**Low vitamin B-12 status and risk of cognitive decline in older adults.**

*[Clarke R, et al. Am J Clin Nutr 2007; 86: 1384-1391]*

**Proton pump-inhibiting drugs, calcium homeostasis, and bone health.**

*[Wright MJ, et al. Nutr Rev 2008; 66:103-108]*

**The science behind dietary omega-3 fatty acids [Review].**

*[Surette ME. CMAJ 2008; 178:177-180]*

**Dietary Choline and betaine intakes in relation to concentrations of inflammatory markers in healthy adults: the ATTICA study.**

*[Detopoulou P, et al. Am J Clin Nutr 2008; 87:424-430]*

**Preconception B-vitamin and homocysteine status, conception, and early pregnancy loss.**

*[Ronnenberg AG, et al. Am J Epidemiol 2007; 166:304-312]*

**Maternal periconceptional alcohol consumption and risk of orofacial clefts.**

*[Romitti PA, et al. Am J Epidemiol 2007; 166:775-785]*

**Effect of high-dose  $\alpha$ -tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease.**

*[Devaraj S, et al. Am J Clin Nutr 2007; 86:1392-1398]*

**Cereal grains, legumes, and weight management: a comprehensive review of the scientific evidence.**

*[Williams PG, et al. Nutr Rev 2008; 66:171-182]*