LEADING RESEARCHERS CHALLENGE CONCLUSIONS FROM RECENTLY REPORTED VITAMIN E AND VITAMIN C STUDIES:
VITAMIN E AND VITAMIN C STILL SAFE TO TAKE AT HIGHER DOSES!

By James Meschino, D.C., M.S. N.D.

The authors of three recent studies, which received unprecedented media attention, suggested that vitamin E supplementation at or above 400 IU per day may produce dangerous and life threatening side effects. One study also suggested that vitamin C supplementation may also increase death from cancer. These reports have generated a significant amount of concern and confusion among members of the general public, many of whom take vitamin E supplements at or above 400 IU and/or vitamin C supplements for the purpose of reducing risk of degenerative diseases, and to derive other health and anti-aging benefits. Upon review of these three recently reported studies, researchers from the Council for Responsible Nutrition, and researchers associated with leading nutrition-based research universities, published a review article in the American Journal of Clinical Nutrition (April 2005) to set the record straight on these issues.

In their review of the totality of experimental and clinical trials pertaining to vitamin E and vitamin C, these authorities challenge the conclusions of these three highly popularized recent studies. Moreover, these leading nutrition authorities indicate that the established tolerable upper intake level (UL) for vitamin E and vitamin C, as set out in the year 2000 by the Food and Nutrition Board (FNB) of the Institute of Medicine, a part of the US National Academies, remains a safe guideline for healthy adults to follow. Based upon all available data the Institute of Medicine indicates that vitamin E is safe to ingest in doses up to 1,000 mg per day (1492.5 IU) and vitamin C is safe to ingest in doses up to 2,000 mg per day. They also indicate that many clinical trials show the safety of combinations of vitamin E and vitamin C at the amounts identified for their individual UL values. It is estimated that approximately 70% of the US population uses dietary supplements at least occasionally, and approximately 40% use supplements on a regular basis. The most commonly used supplements are multivitamins, vitamin C, vitamin E and calcium. As such, it is important for health practitioners to have accurate information upon which to make recommendations in regards to the use of these supplements by their patients

Vitamin E and All-Cause Mortality

In one of the recent studies, which was widely reported by the media, the authors indicate that a meta-analysis, that combined the results of 19 clinical trials of vitamin E supplementation for various diseases, including heart disease, end-stage renal failure, and Alzheimer's disease, showed that adults who took vitamin E supplements at or above 400 IU per day were 6% more likely to die of any cause than those who did not take vitamin E supplements (Miller ER III et al, 2005). In criticism of these findings, researchers from the Council for Responsible Nutrition and leading American universities indicate that further breakdown of the risk by vitamin E dose and adjustment for other vitamin and mineral supplements found that the increased risk of death in this meta-analysis was significant only for a dose of vitamin E at 2000 IU/day, which is higher than the UL for vitamin E, as set out by the Institute of Medicine. Reporting in the April issue of The American Journal of Clinical Nutrition, these authorities further point out that three other meta-analyses that combined the results of randomized controlled trials designed to evaluate the efficacy of vitamin E supplementation for the prevention or treatment of cardiovascular disease, found no evidence that vitamin E supplementation up to 800 IU per day significantly increased or decreased risk of cardiovascular disease or all-cause mortality. They conclude that at present, the evidence is not convincing that vitamin E supplementation up to 1,000 mg per day increases the risk of death due to cardiovascular disease or other causes, including cancer. They also point out that numerous studies suggest that vitamin E and/or vitamin C supplement use, may contribute to lowering risk of specific chronic degenerative diseases, such as Alzheimer's disease, age-related macular degeneration, some types of cancer, cataracts, and ischemic heart disease. A review of all studies involving vitamin E supplementation indicates that few reports have cited adverse side effects of long-term use of vitamin E at intakes up to many times the RDA (recommended dietary allowance). More than 20 published clinical trials involving over 80,000 subjects have documented the safety of vitamin supplements in doses ranging

from 100 IU to 3200 IU per day. The Institute of Medicine, however, suggests that doses of vitamin E above 1,000 mg per day may increase risk of bleeding complications. However, a large trial of patients taking long-term warfarin (an anti-coagulant drug), who also took 800-1200 mg of vitamin E per day showed no changes in coagulation variables that would suggest an increased risk of bleeding at a daily dosage as high as 1200 mg, when combined with other anti-coagulants.

Vitamin E and Heart Disease

Media attention was also recently focused on the Heart Outcomes Prevention Evaluation Study (HOPE Study), which reported that vitamin E supplementation at 400 IU per day may pose a heath threat. This study was an evaluation of the angiotensin-converting enzyme inhibitor (ACE-inhibitor) drug known as ramipril, vitamin E at 400 IU/d, or both, in 9541 patients with multiple cardiovascular risk factors. Although media reports suggested that vitamin E was associated with negative outcomes in this study, the authors conclude that vitamin E was “well tolerated” because the number of adverse events associated with the vitamin E treatment was not significantly greater than that with the placebo over the mean follow-up of 4.5 years.

In contrast to the HOPE study, a number of other studies suggest that vitamin E supplementation reduces risk of heart disease as well as other types of cardiovascular disease. Although not all studies have shown positive results, a significant body of evidence continues to suggest that vitamin E supplementation at 100-800 IU per day may reduce risk of heart and cardiovascular disease.

In the Nurses’ Health Study (Stampfer MJ, 1993) women who took vitamin E supplements for short periods had little benefit, but those who took at least 100 IU per day for more than 2 years experienced reductions of 40% or more in the risk of coronary (heart) disease, after adjustment for age, cardiac risk factors, exercise, alcohol intake, regular use of aspirin, postmenopausal hormone use, and intake of vitamin C and beta-carotene.

Similar findings have emerged from the Health Professionals' Follow-up Study (Rimm EB, 1993) in an analysis of nearly 40,000 U.S. male health professionals aged 40-75, who were free of heart disease, diabetes, or hypercholesterolemia at the beginning of the study in 1986. After adjustment for age, smoking, and other cardiac risk factors, those in the highest vs. the lowest 20% of vitamin E intake showed a significant reduction in risk of heart disease. As in the Nurses” Health Study, the relation was strongest for supplement use; men who took at least 100 IU per day for at least 2 years had a 37% reduction in risk of heart disease compared with men who did not take vitamin E supplements

The relationship between vitamin E and cardiovascular disease was also examined in an elderly cohort study. The Established Populations for Epidemiologic Studies of the Elderly (Klipstein-Grobusch K, 1996), which followed 11,178 U.S. men and women aged 67-105 for up to 10 years, found a 47% decreased risk of fatal heart attack and a 34% reduction in overall mortality among those reporting vitamin E supplement use.

In a secondary prevention trial known as the Cambridge Heart Antioxidant Study (Stephens NG, 1996), which randomized 2002 British patients with angiographically proven atherosclerosis to natural vitamin E (400 or 800 IU daily) or placebo for a median treatment duration of 1.4 years, individuals assigned to vitamin E had a significantly lower risk of sub-sequent nonfatal heart attacks and a 57% reduction in combined outcomes involving nonfatal heart attack and cardiovascular death.

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico Prevention Trial (GISSI-Prevenzione Investigators, 1999), 11,324 men and women who survived an acute non-fatal heart attack were randomized to synthetic vitamin E (300 mg daily), n-3 polyunsaturated fatty acids (1 g daily), both, or neither in an open-label design. After 3.5 years, secondary analysis of the group receiving vitamin E treatment alone revealed significant declines in cardiovascular risk, ranging from 20% for all cardiovascular deaths to 35% for sudden death.

The Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease (Boaz M, 2000) trial randomized 196 hemodialysis patients with cardiovascular disease to natural vitamin E (800 IU/day) or placebo. After 1.4 years of treatment, vitamin E treatment was associated with significant reductions in fatal and nonfatal heart attack, ischemic stroke, peripheral vascular disease, and unstable

angina. The overall reduction in cardiovascular risk for these combined outcomes was 54%. Those assigned to the vitamin E group were 70% less likely to experience a heart attack. The results of this small Israeli trial are consistent with those of Cambridge heart study, which also employed a higher dose of vitamin E than GISSI or HOPE and which was also of 1.4 years duration.

In the recent Antioxidant Supplementation in Atherosclerosis Prevention (Salonen JT, 2000) trial, 3 years of supplementation with both vitamin E (136 IU twice per day) and vitamin C (250 mg twice per day), but not with either vitamin alone, significantly slowed the progression of common carotid atherosclerosis among 256 middle-aged Finnish men, which is an important indicator for risk of stroke. Supplementation with a combination of vitamin E (400 IU twice per day) and vitamin C (500 mg twice per day) has also been shown to reduce the early progression of transplant-associated coronary arteriosclerosis in a small trial of 40 cardiac transplant recipients, most of whom were men (Fang JC, 2000).

Taken together, there is sufficient evidence to indicate that vitamin E supplementation, ranging from 100-800IU per day may reduce risk of cardiovascular disease and possibly improve the management of certain existing cardiovascular conditions. As well, a number of studies have also shown that supplementation with 900 IU of vitamin E per day can improve insulin function in diabetics, which is associated with improved blood sugar regulation and lipid and cholesterol blood levels and lower cardiac risk (Paolisso G, 1994).

Antioxidants and Cancer

In criticism of the recent meta-analysis by Bjelakovic et al (2004), which suggested that there is no evidence that antioxidant supplements prevent gastrointestinal cancers, but instead, seem to increase overall mortality, researchers from the Council for Responsible Nutrition and from leading U.S. nutrition-based research universities, indicate that this meta-analysis was strongly biased by including studies that were not scientifically combinable. In contrast to this report these researchers indicate that when proper scientific protocol is followed (regarding what are acceptable studies to combine in a meta-analysis) the most highly aggregated meta-analysis on this subject shows a nonsignificant protective effect for antioxidants against cancer when all trials, all treatments, and all types of cancer are considered.

A number of studies have provided evidence that vitamin E supplementation and other supplements can reduce risk of specific cancers and help to reverse a precancerous condition in the mouth known as leukoplakia. For example researchers from the Fred Hutchinson Cancer Research Center in Seattle conducted a case-control study involving 251 men and 193 women diagnosed with colon cancer in 1985-1989 and 233 male and 194 female control subjects from the general population.

From their data (White E, 1997) they determined that the daily use of multivitamins for 10 years was associated with a 50% reduction in risk of developing colon cancer among men and women compared to non-multivitamin users. There was also strong evidence for the use of Vitamin E supplementation (average daily dosage of 200 IU) for over 10 years. Vitamin E supplement users demonstrated a 57% reduction in risk of colon cancer compared to nonusers of Vitamin E supplements. A clear dose-dependent response trend was observed for Vitamin E, meaning that higher vitamin E daily dosages were associated with a greater protection than lower daily dosages.

According to a review of clinical trials (Garewal H, 1995) the combination of beta-carotene and vitamin E has led to complete or partial remissions in six of eight trials studying people with oral leukoplakia. In one trial, administration of 50,000 IU of beta-carotene, 1,000 mg of vitamin C, and 800 IU of vitamin E per day for nine months led to improvement in 56% of people with leukoplakia, with stronger effects in those who also stopped using tobacco and alcohol (Kaugars GE, 1994).

Summary

In conclusion, the body of evidence continues to suggest that vitamin E and vitamin C can be taken safely across a broad range of intakes and that these supplements have the potential to reduce risk of several common degenerative diseases. The Institute of Medicine indicates that daily supplementation of up to 1,000 mg of vitamin E and 2,000 mg of vitamin C is safe for use by the general population. The three

recently cited studies, which received a great deal of media attention for their suggestion that commonly used doses of vitamin E and vitamin C supplements increase risk of cardiovascular and cancer death have been shown to have inherent flaws in the study design and/or have drawn unsubstantiated conclusions from the actual study findings. Health practitioners and the general public alike, should be aware of the flawed conclusions of these widely popularized recent studies and be aware of the recommendations set out by the Institute of Medicine in regards to safe intake levels of vitamin E and vitamin C, which more accurately reflect the totality of experimental and clinical evidence to date.

For more information on this or other related topics, visit Dr. Meschino's website at: http://www.meschinohealth.com/

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