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New Studies: Natural-Source Vitamin E Supplements Have Cardio Benefits

Two new studies, published in American Heart Association journals, have found that natural-source vitamin E supplements can have significant cardiovascular benefits.

In the first study, Robert J. Glynn, PhD, ScD, of the Harvard Medical School, and his colleagues tracked the health of 39,876 women, 45 years of age and older, who had been taking either 600 IU of natural-source vitamin E or placebos every other day for an average of 10 years.

Overall, women taking vitamin E supplements had a 21 percent lower risk of life-threatening blood clots –deep-vein thromboses or pulmonary embolisms – compared with women taking placebos.

Women who had experienced a serious blood clot before joining the study had a 44 percent lower risk of future clots if they took vitamin E supplements. Furthermore, women with a genetic susceptibility for serious clots – because of either factor V Leiden or a prothrombin mutation – benefited from a 49 percent reduced risk of clots if they took vitamin E.

Glynn and his colleagues also reported that women taking vitamin E had an 8 percent lower risk of hemorrhagic stroke, compared with those taking placebos. This was noteworthy because of a concern that vitamin E, a mild anticoagulant, might increase the risk of hemorrhagic stroke.

They did note that women taking vitamin E experienced a 6 percent higher risk of nose bleeds. Despite this finding, vitamin E was associated with a lower risk of bleeding risks compared with low-dose aspirin, according to the researchers.

In the second study, Andrew P. Levy, MD, PhD, of the Technion-Israel Institute of Technology, Haifa, Israel, and his colleagues studied 1,434 men and women, ages 55 and older, with type 2 diabetes and a genetic variation called Hp 2-2. People with the Hp 2-2 gene variation have less antioxidant protection, compared with people who have the Hp 1-1 gene.

Diabetes increases the risk of heart disease by about four times, and people with the Hp 2-2 gene variation have an additional two to five-fold greater risk of cardiovascular disease.

Levy and his colleagues gave the patients either 400 IU of natural source vitamin E or placebos daily.

After the first follow up, at 18 months, Levy found that only 2.2 percent of people taking vitamin E had suffered a heart attack, stroke, or cardiovascular-related death, compared with 4.7 percent of those taking placebos. That translated to a 53 percent lower risk of serious cardiovascular events after only one and one-half years. The study was terminated early because of the significance of the results.

References: Glynn RJ, Ridker PM, Goldhaber SZ, et al. Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism. Report from the Women's Health Study. *Circulation*, 2007;116:1497-1503. Milman U, Blum S, Shapira C, et al. Vitamin E supplementation reduces cardiovascular events in a subgroup of middle-aged individuals with both type 2 diabetes mellitus and the haptoglobin 2-2 genotype. A prospective double-blinded clinical trial. *Arteriosclerosis, Thrombosis and Vascular Biology*, 2008;28:epub ahead of print DOI:10.1161/ATVBAHA.107.153965. ❑

High Doses of Vitamin E May Not Be High Enough for Some People

Most clinical trials of vitamin E have used between 400 IU and 800 IU of the vitamin daily. But new research suggests that this range may not be enough, at least for some people.

L. Jackson Roberts, MD, of Vanderbilt University, Nashville, Tennessee, conducted two related studies. In one study, Roberts gave 3,200 IU of natural-source vitamin E to eight subjects daily for 20 weeks. In the other, he gave a range of doses, from 100 IU up to 3,200 IU to 35 subjects daily for 16 weeks.

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In both studies, Levy measured changes in the subjects' plasma F_2-isoprostanes, an indicator of oxidative stress (or free radical activity). All of the subjects had elevated cholesterol levels.

Vitamin E reduced plasma F_2-isoprostanes – but the reduction was significant only when people in the study took 1,600 IU and 3,200 IU of vitamin E for at least 16 weeks. These dosages were four to eight times higher than those used in most clinical trials.

Reference: Roberts LJ, Oates JA, Linton MF, et al. The relationship between dose of vitamin E and suppression of oxidative stress in humans. *Free Radical Biology & Medicine*, 2007; 43:1388-1393. ❑

Perspectives

Good News About Vitamin E

Vitamin E has had a bumpy ride in recent years. Long criticized as a "cure in search of a disease," it was heralded by the American Heart Association as one of the top 10 heart-related developments in 1996. Then some studies reported only marginal benefits and, ridiculously, health hazards from vitamin E supplements. Suddenly, vitamin E was ignored in favor of dangerous medications, such as statins.

In a recent editorial in *Free Radical Biology & Medicine* (2007;43:1374-1376), Jeffrey Blumberg, PhD, and Balz Frei, PhD, two leading antioxidant researchers, distilled the significance of the previous study by L. Jackson Roberts. They pointed out that human studies have examined various end points, such as the risk of heart attack, but generally they have not correlated these end points to changes in oxidative stress.

This is a serious omission in clinical trials on vitamin E, the body's principal fat-soluble antioxidant. An analogy would be to conduct clinical trials on statin drugs without ever measuring cholesterol levels. Future studies would do well to test higher doses of vitamin E, measure F_2-isoprostanes as a marker of oxidative stress, and to correlate clinical changes with F_2-isoprostane levels.

Higher doses of vitamin E may be needed for a variety of reasons. Fat-soluble vitamins may be stored in fat tissue, reducing their availability to the rest of the body. With two-thirds of Americans now overweight or obese, this could be a significant issue limiting the benefits of vitamin E.

In addition, trans fats, which are still a common food additive, may increase vitamin E requirements through a number of mechanisms. For example, consumption of trans fats increases oxidative stress. Trans fats also interfere with the body's handling of omega-3 fatty acids, which vitamin E protects in cell membranes. *–JC*

Glycemic Index Turns Out to Be Highly Variable, Not Reliable

If you listen to the experts, the glycemic index – a measure of how carbs impact blood sugar – is an ideal way of judging the nutritional value of many foods. But it now turns out that the glycemic index varies considerably among individuals – and even in the same person on different days.

Alice H. Lichtenstein, DSc, and her colleagues at Tufts University, Boston, investigated the variability of glycemic responses in 23 apparently healthy men and women, who ranged from 20 to 70 years old. They were fed 50 grams of glucose as a reference food, then given 50 grams of carbohydrate as white bread on two or three separate days.

As a group, the subjects' average glycemic response to white bread was 71, virtually identical to the reference standard of 70. However, the glycemic response ranged among the subjects from 43 to 132 – from very good to very poor. In fact, based on their baseline characteristics, some of the subjects were likely prediabetic. Furthermore, individuals glycemic responses ranged by 18 percent on different days.

Lichtenstein and her colleagues wrote that, even with repeated testing, "glycemic responses to a single food, white bread, can be inconsistent, and a better understanding of the sources of this variability would be helpful in defining the utility of glycemic index values."

Reference: Vega-Lopez S, Ausman LM, Griffith JL, et al. Interindividual variability and intra-individual reproducibility of glycemic index values for commercial white bread. *Diabetes Care*, 2007;30:1412-1417. ❑

Long-Term Use of Beta-Carotene Supplements Improves Brain

Researchers have found that taking beta-carotene supplements for at least 15 years leads to improvements in mental function.

Francine Grodstein, ScD, of Harvard Medical School, and her colleagues used several tests to measure the cognitive function of 4,052 men, age 65 years or older, who had been taking either 50 mg of beta-carotene or placebos every other day for 15 to 20 years. They also tested the cognitive function of 1,904 men who had been taking either beta-carotene or placebos every other day for just three years.

The long-term users of beta-carotene did better in all of the cognitive tests, compared with men who were taking placebos. They performed significantly better on verbal-memory tests –that is, in remembering information they had heard. In contrast, men

who had been taking beta-carotene supplements for only three years did not appear to gain any advantage.

Grodstein and her colleagues wrote that beta-carotene might help the brain by scavenging harmful free radicals. In addition, some beta-carotene is converted to vitamin A, which normalizes the activity of beta-amyloid precursor protein. An accumulation of beta-amyloid protein is one of the hallmarks of Alzheimer's disease.

The 50 mg dose of beta-carotene converts to 83,000 IU. Synthetic beta-carotene was used in this study.

Reference: Grodstein R, Kang JH, Glynn RJ, et al. A randomized trial of beta-carotene supplementation and cognitive function in men. The Physicians Health Study II. *Archives of Internal Medicine*, 2007;167: 2184-2190. ❑

Phosphatidylcholine May Help People with Ulcerative Colitis

Phosphatidylcholine is widely recognized as one of the beneficial fats found in the brain. It's also found in colonic mucus, where it helps maintain a protective barrier.

In a recent study, researchers from University Hospital Heidelberg, in Germany, found that supplements of phosphatidylcholine can be of great benefit to people suffering from chronic ulcerative colitis.

Wolgang Stremmel, MD, and his colleagues, asked 60 patients to take either 500 mg of phosphatidylcholine or placebos four times daily for 12 weeks. All of the patients were described as "steroid-refractory," meaning that they did not benefit from the medications usually used to treat chronic ulcerative colitis.

Eighty percent of the patients receiving phosphatidylcholine were able to discontinue steroid therapy without any increase in symptoms, compared with only 10 percent of those taking placebos. In fact, 40 percent of the patients taking phosphatidylcholine achieved a "clinically inactive state" – in effect, they no longer had any signs of ulcerative colitis. The results were especially impressive because patients receiving phosphatidylcholine began the study with more severe symptoms than those given placebos.

The phosphatidylcholine supplements were a proprietary product designed to release in the lower intestine.

Reference: Stremmel W, Ehehalt R, Autschbach F, et al. Phosphatidylcholine for steroid-refractory chronic ulcerative colitis. A randomized trial. *Annals of Internal Medicine*, 2007;147:603-610. ❑

Glucosamine Supplements Lower Chances of Joint Replacement

People who have taken glucosamine sulfate supplements – and stopped – have a substantially lower risk of undergoing total joint-replacement surgery.

Olivier Bruyere, PhD, of the University of Liege, Belgium, and his colleagues tracked 272 patients from two earlier clinical trials that gave subjects either 1,500 mg of glucosamine sulfate or placebos daily for one to three years. The patients stopped taking the supplements (or placebos) after the trials.

When Bruyere followed up five years later, he found that patients who had taken glucosamine sulfate were 57 percent less likely to have undergone total joint-replacement surgery. In contrast, people who had taken placebos were more than twice as likely to undergo this type of surgery.

Bruyere also noted that people who took placebos had joint-replacement surgeries throughout the entire follow-up period. However, those who took glucosamine sulfate tended to have both a lower incidence of surgery and at later dates.

Reference: Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomized, placebo-controlled trials. *Osteo-arthritis and Cartilage*, 2007:doi:10.1016/j.joca. 2007/06.011.

Tryptophan May Help with Varied Mood Issues in Men and Women

A new study indirectly suggests that supplements of the amino acid (protein building block) tryptophan may be helpful in some mood disorders in men and women.

Tryptophan and 5-hydroxytryptophan (5-HTP), a closely related compound, are precursors to serotonin, a neurotransmitter that regulates feelings of depression and anxiety.

Espen Walderhaug, PhD, of the University of Oslo, Norway, and his colleagues conducted a tryptophan-depletion study on 39 male and 44 female college students described as "normal." Walderhaug used the Profile of Mood States (POMS) test to measure the students moods before and six hours after taking an amino acid mixture without tryptophan.

The lack of tryptophan resulted in striking mood changes. Men became more impulsive, and women became more depressed and cautious. Mutations in a gene involved in serotonin transport also contributed

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Quick Reviews of Recent Research

• Pycnogenol® reduces osteoarthritis pain

A team of researchers from Iran, Germany, and the United States used 50 mg of Pycnogenol or placebos three times daily to treat men and women with osteoarthritis of the knees. All of the subjects continued taking nonsteroidal anti-inflammatory drugs (NSAIDS) or COX-2 inhibitors as needed during the 90-day study. Based on self-administered questionnaires, patients taking Pycnogenol had reductions of 43 percent in pain and 35 percent in stiffness. They had a 52 percent improvement in physical function and an overall 49 percent improvement. In addition, the patients' use of NSAID and COX-2 inhibitor drugs decreased while taking Pycnogenol.

Farid R, et al. *Nutrition Research*, 2007;27: 692-697.

• Silymarin helps in type 2 diabetes

Researchers from Iraq treated 59 patients with type 2 diabetes who had been taking 10 mg of glibenclamide (also known as glyburide) daily and trying to control their diet, but still had poor glycemic control. They were divided into three groups and given 200 mg of silymarin with glibenclamide, placebo with glibenclamide, or continued therapy with glibenclamide for 120 days. Patients taking silymarin had significantly reduced fasting and postprandial glucose, glycated hemoglobin (HbA1c), and body mass index (BMI) compared with the other patients. Silymarin is an extract of the herb milk thistle (*Silybum marianum*). Other studies have also found it helpful in treating diabetes.

Hussain SAR, et al. *Journal of Medicinal Food*, 2007;10:543-547.

• Folic acid can reduce cardio risk factors

Spanish researchers used 2.5 mg of folic acid daily to treat 61 patients diagnosed with coronary heart disease. A group of 63 patients not receiving supplements (or placebos) was used as a control group. All of the patients had normal vitamin B12 levels, and they were also being treated with statins, anticoagulants, and other drugs. Levels of homocysteine, a risk factor for cardiovascular disease, decreased in patients taking folic acid. In general, there were no changes in carotid intima-media thickness, a marker of cardiovascular disease, in any of the patients. However, in a subgroup of 12 patients with the MTHFR 677TT gene mutation, carotid intima-media thickness decreased by an average of 13 percent. The MTHFR 677TT mutation interferes with the formation of folic-acid-dependent enzymes and significantly increases the risk of cardiovascular diseases.

Fernandez-Miranda C, et al. *International Journal of Cardiology*, 2007;118:345-349.

• Omega-3 fats lower risk of type 1 diabetes

Researchers from Denver, Colorado, tracked 1,770 children at high risk of developing type 1 diabetes because of a genetic susceptibility or because a sibling or parent had been diagnosed with the disease. The children's diets were assessed at one year of age. When followed up on at age six, 58 of the children tested positive for pancreatic islet autoimmunity (IA). IA is a marker for antibodies that attack the insulin-producing cells of the pancreas, and it often precedes type 1 diabetes. Children who had consumed the largest amounts of omega-3 fatty acids, found in coldwater fish, were 55 percent less likely to have developed IA. When two or more medical tests were used to determine IA, high intake of omega-3 fatty acids were associated with a 77 percent lower risk of developing IA. Children with high blood levels of omega-3 fatty acids had a 37 percent lower risk of being diagnosed with IA.

Norris JM, et al. *JAMA*, 2007;298;1420-1428.

Tryptophan and Mood...

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to feelings of depression in some of the women.

Although the study did not test the effects of tryptophan or 5-HTP supplements, it did suggest that they might be of benefit in people with low levels of tryptophan and mood disorders.

Reference: Walderhaug E, Magnusson A, Neumeister A, et al. Interactive effects of sex and 5-HTTLPR on mood and impulsivity during tryptophan depletion in healthy people. *Biological Psychiatry*, 2007;62:593-599. ❑

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