

The Nutrition Reporter™

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Should We Recognize Natural Vitamin E as the “Antiinflammatory” Vitamin?

The \$64,000 question: does vitamin E reduce the risk of coronary artery disease because of its anti-inflammatory properties?

Inflammation of blood vessel walls is recognized as one of the leading risk factors for coronary artery disease. A recent article in the *New England Journal of Medicine* found that high levels of C-reactive protein, a marker of inflammation, increased the risk of heart disease by four and one-half times.

At virtually the same time that report was published, two other journals reported vitamin E's potent antiinflammatory effects. In one study, Jane E. Upritchard, PhD, and her colleagues at the University of Otago, New Zealand, described a study of 57 people with adult-onset diabetes. They were given 800 IU of natural vitamin E, 500 mg of vitamin C, about a pint of tomato juice (containing the antioxidant lycopene), or a placebo daily for four weeks.

Upritchard's most significant finding was that the vitamin E reduced C-reactive protein levels by half. Vitamin E and tomato juice also slowed the free-radical oxidation of low-density lipoprotein (LDL) cholesterol by 54 and 46 percent, respectively. LDL oxidation is considered an early step in the development of heart disease.

In a separate study, Sridevi Devaraj, PhD, and Ishwarlal “Kenny” Jialal, MD, PhD, of the University of Texas Southwestern Medical Center, Dallas, compared inflammatory markers and free radical levels in 25 adult-onset diabetics with heart disease, 25 diabetics without heart disease, and 25 healthy subjects. The inflammatory markers included elevated levels of interleukin-1b and “soluble cell adhesion molecules (sCAMs),” both of which promote inflammation. Next, Devaraj and Jialal asked the subjects to take 1,200 IU of vitamin E daily for three months.

At the start of the study, the researchers found that both diabetic groups had higher levels of sCAMs than did the healthy group. Their white blood cells also released considerably more interleukin-1b and

superoxide free radicals, and these cells also were far more likely to adhere to blood vessel walls, compared with cells from the healthy subjects.

After taking vitamin E, the diabetic groups had a significant decrease in sCAMs, and all groups had significantly lower levels of interleukin-1b, tumor necrosis factor- α (another marker of inflammation), superoxide radicals, and white blood cell adhesion.

In addition, vitamin E supplementation significantly reduced LDL oxidation in all three groups. This change is important because oxidized LDL triggers an inflammatory response, prompting white blood cells to attack and engulf LDL. The white blood cells then migrate into the blood vessel wall, where they become stuck and form cholesterol deposits.

References: Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New England Journal of Medicine*, 2000;342:836-843. Upritchard JE, Sutherland WHF, Mann JJ. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care*, 2000, 23:733-738. Devaraj S, Jialal I. Low-density lipoprotein postsecretory modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications. The effect of α -tocopherol supplementation. *Circulation*, 2000;102:191-196. □

Antioxidants Improve Blood Cells, Ease Pain in Sickle-Cell Anemia

A half-century ago, Linus Pauling, PhD, identified sickle-cell anemia as a “molecular disease,” caused by an inherited genetic defect that deformed red blood cells. Affecting principally people of African descent, the condition causes severe pain when blood vessels become blocked by the deformed cells. Because afflicted red blood cells have an aver-

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age life span of only two weeks, compared with 17 weeks for normal cells, people with sickle-cell anemia suffer from chronic anemia.

However, a laboratory experiment and a small human trial have found that antioxidant supplements might strengthen the membranes of red blood cells in sickle-cell anemia, potentially preventing many of the disease's symptoms and complications.

S. Tsuyoshi Ohnishi, PhD, of the Philadelphia Biomedical Research Institute, and his colleagues tested the effects of antioxidants on the "dense cells" characteristic of sickle-cell anemia. They found that S-allyl cysteine (found in aged garlic extracts), fructosyl arginine, Pycnogenol®, green tea extract, black tea extract, and vitamin E were the most potent inhibitors of dense cells. Ginseng, ginkgo, and coenzyme Q10 also reduced dense-cell activity, though not as much.

In a six-month trial, 10 patients took 6 grams of aged garlic extract, 6 grams of vitamin C, 1,200 IU of vitamin E, and 1,000 mcg of folic acid. The subjects' twin siblings took only folic acid. During the study, subjects taking the mix of vitamins and garlic had only one-third the number of painful sickle-cell episodes, compared with the other group.

"An interesting observation was that most of the patients in the supplement group felt much more energetic after they had started the regimen," wrote Ohnishi and his colleagues.

Reference: Ohnishi ST, Ohnishi T, Ogunmola GB. Sickle cell anemia: a potential nutritional approach for a molecular disease. *Nutrition*, 2000;16: 330-338. □

British Researchers Report that St. John's Wort Eases PMS Symptoms

The herb St. John's wort can significantly reduce symptoms of premenstrual syndrome (PMS), according to a study published in the July *British Journal of Obstetrics and Gynaecology*.

Edzard Ernst, MD, of the University of Exeter, United Kingdom, asked 19 women with carefully diagnosed PMS to take St. John's wort three times daily for two complete menstrual cycles. Each dosage contained 300 mg of standardized hypericin, a common marker of the herb's potency, adding up to 900 mg daily.

Ernst reported that St. John's wort reduced overall PMS symptoms by 51 percent – and that more than two-thirds of the women in the study had at least a 50 percent decrease in symptom severity. Virtually all PMS symptoms got better, with the greatest improvements being in anxiety, depression, nervous tension, confusion, and crying.

Early in July, the U.S. Food and Drug Administration approved Sarafem, a renamed form of Prozac,

for the treatment of PMS-related mood and physical symptoms. Studies have found that St. John's wort is at least as effective as Prozac in the treatment of depression and results in far fewer side effects.

Reference: Stevinson C, Ernst E. A pilot study of *Hypericum perforatum* for the treatment of premenstrual syndrome. *British Journal of Obstetrics and Gynaecology*, 2000;107:870-876. □

Higher Vitamin C Intake Linked to Longer, Healthier Lives in Men

Men with high blood levels of vitamin C were far more likely to live longer and to be free of cancer over a 12-16 year period. However, vitamin C levels were not associated with longevity in women.

Catherine M. Loria, PhD, of the National Heart, Lung, and Blood Institute and her associates studied 7,071 people participating in the second National Health and Nutrition Examination Survey.

The news for men with low vitamin C levels was not good. Adjusted for their ages, men were 57 percent more likely to die from all causes and 62 percent more likely to die from cancer.

On average, also, men had lower vitamin C levels than did women.

"Discussion concerning the role of antioxidants in chronic disease prevention has often focused on whether high antioxidant intakes are protective," wrote Loria and her colleagues. "Our findings as well as those of other studies suggest that, instead, we need to focus on the potential adverse effects of vitamin C intakes that are at or below those currently considered to be adequate."

Reference: Loria CM, Klag MJ, Caufield LE, et al. Vitamin C status and mortality in US adults. *American Journal of Clinical Nutrition*, 2000;72:139-145. □

Study Identifies How Beta-Carotene Might Protect Against Cancer

Research on beta-carotene and cancer risk has been nothing less than confusing. Some studies have found that beta-carotene supplements (i.e., the synthetic form) may increase the risk of lung cancer among heavy smoker-drinkers, but have no effect on light smokers/drinkers – and a reduced risk among former smokers. Adding to the confusion, beta-carotene enhances the activity of some immune cells, but in a free radical-rich environment (e.g., that created by tobacco smoke), it breaks down and generates still more cell-damaging radicals.

Now, in a detailed molecular biology study, researchers have reported that beta-carotene sometimes requires the presence of a specific cell protein to prevent cancer.

Lucia A. Stivala, PhD, and her colleagues at the

University of Pavia, Italy, cultured human skin cells. Through these cells, they investigated the interaction between beta-carotene and p21, a cell protein that inhibits a cancer-promoting gene.

By looking at the entire cell cycle – that is, from the origin of the cell through the time it divides and produces a second cell – they found that beta-carotene required the presence of p21 to block the growth of skin cells.

Can you boost p21 levels? Stivala noted that a recent study found that vitamin E increased activity of the p21 protein, suggesting that the two nutrients worked in tandem (aside from their antioxidant properties). In addition, research has also found that dietary fiber increases the activity of p21 in the colon and may reduce the risk of colon cancer.

Reference: Stivala LA, Savio M, Quarta A, et al. The antiproliferative effect of β -carotene requires p21 waf1/cip1 in normal human fibroblasts. *European Journal of Biochemistry*, 2000;267:2290-2296. □

Red Delicious Apples, With Skin, Contain Potent Antioxidant Levels

If an apple a day keeps the doctor away, the reason likely goes beyond the fruit's vitamin C content.

The typical apple contains only about 5.7 mg of vitamin C per 100 mg (roughly 3.5 ounces) of the fruit. It turns out that the lion's share of an apple's antioxidant capacity is the result of its naturally occurring phenolics and flavonoids.

Rui Hai Liu, MD, PhD, and his collaborators at Cornell University, Ithaca, N.Y., measured the total antioxidant capacity of Red Delicious apples. Apples with skin contain about 290 mg of phenolics and 219 mg of flavonoids per 100 grams of apple—the equivalent antioxidant capacity of 1,500 mg of vitamin C. Without skins, the apples contained only 142 mg of phenolics and 98 mg of flavonoids.

In a laboratory study, Liu and his associates found that fresh apple extracts inhibited the growth of colon-cancer and liver-cancer cells. Higher concentrations of the apple extracts were far more effective than lower doses. In addition, extracts made from apples with skins were far more potent than extracts made from skinless apples.

"We suggest that this strong inhibition of tumour cell proliferation in vitro could be due to apples' combination of phytochemicals (phenolic acids and flavonoids), as these are natural antioxidants," wrote the researchers.

Reference: Eberhardt MV, Lee CY, Liu RH. Antioxidant activity of fresh apples. *Nature*, 2000; 405-903-904. □

Studies Confirm the Cholesterol-Lowering Effect of Soy Isoflavones

Two new studies support previous findings that soy foods, particularly those rich in antioxidant isoflavones, reduce cholesterol levels.

Mindy S. Kurzur, PhD, of the University of Minnesota, and her colleagues asked 13 healthy women, ages 18-35 and all with normal cholesterol levels, to consume isoflavone-rich soy isolate extracts daily for three menstrual cycles. The women consumed approximately 10 mg, 65 mg, and 129 mg of isoflavones daily in the crossover study (in which each subject ate each test food for a defined period).

Only women consuming the greatest amount of soy isoflavones had statistically significant changes in their blood fats. After consuming the isoflavones, they had 7.6 to 10 percent reduction in their low-density lipoprotein (LDL) cholesterol. In addition, their ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol improved by 10 percent, and the ratio of LDL to HDL cholesterol improved by 14 percent.

In a separate crossover study, Helen Wiseman, PhD, of King's College, London, led a team of researchers that asked 24 subjects to eat either high- or low-isoflavone diets for 17 days. Wiseman and her colleagues then measured levels of isoprostanes, a marker of free radical activity, and LDL oxidation before and after the subjects followed the soy isoflavone diets.

Subjects who ate the high-isoflavone diet had isoprostane levels about one-fourth lower than those eating the low-isoflavone diet. People who ate the high-isoflavone diet also had LDL that became more resistant to free-radical oxidation.

References: Merz-Demlow BE, Duncan AM, Wangen KE, et al. Soy isoflavones improve plasma lipids in normocholesterolemic premenopausal women. *American Journal of Clinical Nutrition*, 2000;71:1462-1469. Wiseman H, O'Reilly JD, Adlercreutz H, et al. Isoflavone phytoestrogens consumed in soy decrease F2-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. *American Journal of Clinical Nutrition*, 2000;72:395-400. □

Five-Year Cancer Survival Has Little Basis in Science, Researchers Find

Surviving cancer for five years is commonly equated with being cured. However, a new analysis of cancer-survival data shows that five-year survival has more to do with better diagnosis than with successful cures.

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Quick Reviews of Recent Research

• Cow's milk increases diabetes risk in children

Several investigations have shown a strong association between cow's milk consumption during infancy and the later development of Type I (juvenile-onset) diabetes. Researchers studied the siblings of several hundred children who had Type I diabetes. Cow's milk consumption increased the risk of diabetes in these siblings by more than five times.

Virtanen SM, et al. *Diabetes*, 2000;49:912-917.

• Cell study finds vitamin E inhibits prostate cancer

Researchers studied the effects of natural vitamin E succinate (d-alpha tocopheryl succinate) on the growth of prostate cancer cells. Vitamin E stopped the growth of two different types of prostate cancer cells and prompted these cells to self-destruct. However, vitamin E had no deleterious effect on normal prostate cells.

Israel K, et al. *Nutrition and Cancer*, 2000;36:90-100.

• Vitamin supplements help drug addicts

Researchers studied 70 male heroin addicts, some of whom were given large daily dosages of vitamin C and moderate amounts of vitamin E, or conventional medications. The dosages were approximately 21 grams of vitamin C and 350 mg of vitamin E for a 150-pound adult. About one-half of the addicts receiving vitamins C and E experienced mild withdrawal symptoms, in contrast to only 6 percent of the conventionally treated group. Only 10-16 percent of the men taking vitamins had serious

withdrawal symptoms, in contrast to more than half of those in the conventionally treated group.

Evangelous A, et al. *In Vivo*, 2000;14:363-366.

• Natural beta-carotene reduces DNA damage

Eight healthy men and women were given individual supplements of natural beta-carotene, lutein, and lycopene—each at 15 mg daily for three weeks. White blood cells from the subjects were exposed to hydrogen peroxide, a generator of free radicals, before and after taking each of the supplements. Hydrogen peroxide increased the number of DNA breaks in the cells. However, DNA strands were best able to repair themselves after the subjects took beta-carotene supplements.

Torbergson AC, et al., *European Journal of Nutrition*, 2000;39:80-85.

• Genistein may protect against neck cancers

Genistein, the predominant antioxidant isoflavone found in soybeans, has been shown to inhibit the growth of breast and prostate cancers in test-tube experiments. In this study, researchers explored the effect of genistein on squamous cell carcinoma cells from the head and neck. Genistein increased the activity of the p21 cell protein, which inhibits the activity of a cancer-promoting gene. In addition, genistein reduced levels of the Bcl-2 cell protein, a change that would trigger the self-destruction of cancer cells.

Alhasan SA, et al., *International Journal of Oncology*, 2000;16:333-338.

• Elderly have low vitamin B1 levels

Researchers compared functional blood levels of vitamin B1 (by measuring thiamine pyrophosphate levels) in 222 elderly subjects and 100 volunteer blood donors. Forty-three percent of the elderly subjects had extremely low vitamin B1 levels, and over three years, these levels declined by another 20 percent.

Wilkinson TJ, et al. *Age and Ageing*, 2000;29:111-116.

Five-Year Cancer Survival...

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H. Gilbert Welch, MD, MPH, of the Veterans Affairs Medical Center, White River, Vt., and his colleagues analyzed cancer-patient data from 1950 to 1995. While there was an increase in five-year survival for the 20 most common types of cancer, the increases ranged from a negligible 3 percent (for pancreatic cancer) to 50 percent (for prostate cancer).

"Although the expectation might be that large increases in five-year survival would be associated with declining mortality...no obvious relationship is evident..." wrote Welch. The reason was that mortality rates decreased for 12 types of cancer but increased for 8 others. In addition, the large increases in five-year survival appeared to be associated with an increased incidence or diagnosis of cancer.

Reference: Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *JAMA*;283:2975-2978. □

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Post Office Box 30246 • Tucson AZ 85751-0246 USA

Editor and Publisher: **Jack Challem**

Copy Editor: **Melissa Diane Smith**

Medical Advisors:

Lendon H. Smith, MD Portland, Oregon • **Richard P. Huemer, MD** Lancaster, California
Ralph K. Campbell, MD Polson, Montana • **Peter Langsjoen, MD** Tyler, Texas
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