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Antioxidant Vitamins Reduce Risk of Complications After Heart Surgery

Antioxidant vitamins—including vitamins C and E, coenzyme Q10, and others—are slowly being put to use in operating rooms around the world.

A number of recent studies have highlighted how vitamins can reduce the risk of complications and death during coronary artery bypass surgery, organ transplantation, and angioplasty. In other words, it's never too late to benefit from vitamin supplements.

Each of these surgical procedures generates large numbers of free radicals from "ischemia-reperfusion" injury. Ischemia interrupts blood flow and creates a relatively blood-free surgical environment. But it also increases production of free radicals, which deplete antioxidants.

Blood flow is reperfused, or restored, at the end of bypass surgery and transplants. Ironically, the rush of oxygen-rich blood to heart cells creates still more free radicals, causing myocardial stunning (depression of heart function) and arrhythmias (erratic heart beats).

Patients scheduled for coronary artery bypass graft surgery tend to have low blood levels of key antioxidants, including vitamins E and C, beta-carotene, and glutathione, according to a study by J. M. Braganza, MD, of Manchester, England, published in *Clinica Chimica Acta* (1996;252:181-95). Given the protective role of antioxidants in heart disease, this finding is not entirely surprising.

In a recent issue of *Transplantation* (1996;62:1197-9), Hans-Anton Lehr, MD, of Johannes Gutenberg University, Germany, explained that "boosting the antioxidant defense system by pretreatment with antioxidants...significantly attentuated ischemia/reperfusion injury in transplanted organs, resulting in extended graft and host survival."

Massimo Chello, MD, of the Medical School of Catanzaro, Italy, gave 15 patients 150 mg of CoQ10 daily for one week before surgery that involved clamping of the aorta, a major blood vessel. According to Chello's article in the *Journal of Cardiovascular Surgery* (1996;37:229-35), patients receiving the CoQ10 had lower free radical levels during the surgical clamping (which induces ischemia) and declamping (reperfusion), compared with 15 untreated surgical patients.

Modest amounts of vitamin C might also be of benefit. Haruo Tomoda, MD, of Tokai University, Japan, gave 500 mg of vitamin C daily to 59 patients immediately after balloon angioplasty. The procedure involves inflating a tiny balloon in blocked arteries to dilate them. Tomoda used 60 other patients as a control group for comparison.

Only 12 (or 20 percent) of the patients receiving vitamin C later suffered restenosis, or reclogging of the artery. In contrast, 22 (37 percent) of the patients not getting vitamin C developed restenosis. "The present study suggested the effectiveness of ascorbic acid in attenuating...restenosis," Tomoda wrote in the *American Journal of Cardiology* (1996;78:1284-6). "Ascorbic acid is inexpensive and without significant side effects, and thus, an increased dosage of ascorbic acid up to 1,000 mg/day starting before [angioplasty] may bring better results."

Other nutrients also are of value in minimizing surgical complications. A recent animal experiment found that antioxidant flavonoids, water-soluble pigments found in fruits and vegetables, reduced ischemia-reperfusion injury and arrhythmias (Facino RM, et al., *Planta Medica*, 1996;62:495-502). In recent years, researchers have also reported that vitamin E, alpha-lipoic acid, magnesium, and the omega-3 fatty acids reduce surgical complications.

The best approach, however, may be to use a combination of nutrients. Recently, Hans Rabl, MD, of the University of Graz, Austria, gave a combination of vitamins E, C, and A to 57 patients undergoing surgery on the carotid artery, which delivers blood to the brain. Patients receiving the vitamins had significantly lower levels of free radicals after surgery than did patients getting a placebo. In addition, only 13 percent of the vitamin-treated patients suffered headaches after surgery, an indicator of reperfusion injury. In comparison, 67 percent of the other patients developed headaches, according to an article by Rabl and his colleagues in *Medical Science Research* (1996;24:777-780).

Combination of Garlic and Fish Oil Lowers Cholesterol, Triglycerides

Fish oils lower triglycerides but raise cholesterol. Garlic lowers cholesterol but has no effect on triglycerides. The solution? According to Canadian researchers, it's a combination of garlic and fish oil capsules.

Adam J. Adler, PhD, and Bruce J. Holub, PhD, of the University of Guelph, Canada, treated 50 men with moderately high cholesterol for 12 weeks. They used garlic tablets, fish oil capsules, a combination of garlic and fish oil, or a placebo.

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The men who took 12 grams daily of fish oils, rich in the omega-3 fatty acids, had a 37.3 percent drop in triglyceride levels, but an 8.5 percent increase in the low-density lipoprotein (LDL) form of cholesterol. Those who took 900 mg of garlic capsules daily had an 11.5 percent decrease in total cholesterol and a 14.2 decrease in LDL.

The combination of fish oil and garlic provided the best overall benefits. Total cholesterol decreased by 12.2 percent, LDL by 9.5 percent, and triglyceride by 34.2 percent, according to Alder and Holub's article in the *American Journal of Clinical Nutrition* (Feb 1997;65:445-50). There were no significant changes in LDL cholesterol or triglyceride levels among men receiving the placebo.

Garlic, fish oil, and the combination of garlic and fish oil also resulted in a "small (2-4 percent) but significant" reduction in systolic, diastolic, and arterial blood pressures.

In a related editorial in the same issue (65:560-1), Penny M. Kris-Etherton, PhD, of Pennsylvania State University, described Adler and Holub's research as "exciting."

"The greater question is, Can these nutrients and dietary constituents be added to the diet in the form of food?" Kris-Etherton wrote. "This may simply mean eating more of certain foods...and potentially eating large amounts of these foods...Clearly, we are entering into an exciting era in which we will likely identify novel ways to lower risk of cardiovascular disease and other chronic diseases with diet."

Vitamins Slow Glycation, Benefiting Diabetics and Others

Glycation (sometimes described as glycosylation) refers to the permanent bonding of sugars and proteins, a process that promotes tissue damage and aging. Free radicals stimulate glycation by encouraging the oxidation of sugars. Among diabetics, glycation occurs at an accelerated rate, probably as a result of their high glucose levels, leading to the production of large numbers of "advanced glycation end products" and more rapid cellular aging.

Joe A. Vinson, PhD, of the University of Scranton, Pa., found that a variety of vitamins could slow glycation. The likely benefits would include fewer complications from diabetes and a slowing of the aging process.

In the laboratory experiments, Vinson incubated albumin, the most abundant protein in blood, with fructose. He selected fructose because it is found in tissues, but it reacts faster than does glucose. Vinson then tested whether various vitamins and minerals slowed the glycation of albumin.

He found that vitamins B3 and B6, used separately, completely inhibited the glycation process and almost completely stopped production of advanced glycation end products. Selenium yeast, vitamin C, carnosine (an antioxidant found in brain and muscle cells), and vitamin

E also inhibited glycation and the formation of advanced glycation end products. "All of the substances studied are naturally occurring vitamins and nutrients in the body and several of them are known to be lowered in the tissues of subjects with diabetes, such as ascorbate [vitamin C], pyridoxal [B6], and nicotinamide [B3]," Vinson wrote in *Nutritional Biochemistry* (1996;7:659-63).

In a human trial, Vinson gave seven college students and 11 middle-age subjects with normal glucose levels a dietary supplement containing both vitamin C and flavonoids. Five of the college students and all of the middle-age subjects had declines in glycation. The average decrease in glycation was 46.8 percent.

"The glycation-lowering effect in the supplement could be due to both the ascorbate and flavonoids in the mixture," Vinson wrote. Both nutrients have been shown to slow glycation.

Genistein Most Powerful of the Antioxidant Flavonoids in Soy

The isoflavones, a group of flavonoids found in soybeans, have been shown to protect against breast and prostate cancer. Researchers have generally believed they work because they block the cancer-promoting effects of the hormone estrogen.

But a recent study by Catherine Rice-Evans, PhD, of the International Antioxidant Research Center at Guy's Hospital, London, has confirmed that the isoflavones are also powerful antioxidants.

The isoflavones include genistein and daidzein, their glycoside (sugar-containing) molecules genistin and daidzin, and related compounds.

In experiments, Rice-Evans determined that genistein was the most potent antioxidant among them. It was followed by daidzein and genistin, which were about equal. Next came biochanin A and daidzin, which were virtually equal. Formononetin had still less antioxidant activity, and ononin had virtually no antioxidant activity.

Most of the isoflavones occur in the plant as glycosides, but bacteria in the intestine separate the sugar containing part of the molecule, yielding the more potent genistein and daidzein.

The research "supports the observation that genistein is the most potent antioxidant among this family of compounds studied," Rice-Evans wrote in *Free Radical Research* (1997;26:63-70).

GLA Eases Arthritic Symptoms

Gamma-linolenic acid (GLA) from borage seed oil can ease the symptoms of rheumatoid arthritis.

Robert B. Zurier, MD, of the University of Massachusetts Medical Center, Worcester, gave either 2.8 grams of GLA or a placebo (consisting of sunflower seed oil) daily to 41 patients with rheumatoid arthritis. Over a six-month period, 14 (64 percent) of the 22 patients receiving GLA had at least a 25 percent improvement in their arthritic symptoms, according to Zurier's article in *Arthritis & Rheumatism* (1996;39:1808-17). Only four (21 percent) of the 19 patients getting the placebo improved.

Improvements were measured by both a physician's assessment and patients' subjective impressions of pain, joint tenderness and swelling, morning stiffness, and grip strength.

After six months, all patients were given GLA supplements, although they did not know whether they were taking GLA or placebo.

"Patients who were taking GLA during the first six months of study continued to improve during the second six months, and patients who were switched from placebo to GLA at six months exhibited improvement during the second six months that was comparable to that in patients who had been given GLA during the first six months," Zurier wrote.

GLA supplementation was stopped after 12 months, and within three months most patients had an exacerbation of symptoms.

Male Hormones Increase Free Radicals and Prostate Cancer Risk

High levels of male hormones (androgens) are strongly associated with a man's risk of developing prostate cancer. In fact, at least 75 percent of metastatic prostate cancers are fueled by androgens.

How do androgens increase the risk of prostate cancer? It's generally believed that these hormones signal cells to grow abnormally. But according to George Wilding, MD, of the University of Wisconsin, Madison, androgens also generate large numbers of free radicals, overwhelming the prostate's antioxidant defenses. These free radicals can then induce mutations in the DNA of prostate cells, resulting in cancer.

Wilding investigated how androgens affected the normal balance of free radicals and antioxidants. In an article in the *Journal of the National Cancer Institute* (Jan 1, 1997;89:40-8), he described how androgens increased the cellular consumption of oxygen.

His cell-culture study found that this oxygen consumption led to higher production of free radicals. Higher concentrations of androgens increased free radical production and lipid peroxidation (the oxidation of cell fats). Levels of the antioxidant glutathione decreased, likely as a result of quenching the free radicals.

Chronic Sinus Problems Seen as Another Oxidative Stress

Oxidative stress, caused by excessive numbers of free radicals, is involved in the development of heart diseases, cancer, rheumatoid arthritis, and lung disorders.

According to a recent study, oxidative stress may also be a factor in chronic sinusitis, a common condition characterized by nasal obstruction or discharge and headache.

Free radicals, such as superoxide and hydroxyl radicals, are produced when white blood cells destroy bacteria and virus-infected cells. However, free radicals are over-produced during localized inflammation and cause damage to cells.

"To prevent this oxidative damage, the mucosa contains a broad spectrum of naturally occurring protective antioxidants," wrote Gerrit-Jan Westerveld, MD, in *Archives* of Otolaryngology—Head and Neck Surgery (Feb 1997;123:201-4). "A disturbance in the delicate balance between oxidant production and local antioxidant defense, also known as oxidative stress, may result in pathologic conditions."

Westerveld, of the Vrije University Hospital, Amsterdam, obtained samples of nasal mucosa from nine patients with chronic sinusitis and compared them with samples from 10 healthy subjects. Patients with sinusitis had glutathione levels half those of healthy people, probably because it was used up scavenging free radicals. Glutathione is a powerful antioxidant produced by the body.

Levels of uric acid, another powerful antioxidant, were almost 20 percent lower than normal among patients with sinusitus, according to Westerveld. Although elevated levels of uric acid are often associated with gout, it protects vitamin C from oxidation and binds with metals to prevent free radical reactions.

Folic Acid Deficiency Hurts Anti-Cancer Gene

Folic acid, long considered a minor B vitamin, plays a major role in health: it keeps your body's cancerpreventing p53 gene from falling apart. But as many as 30 percent of apparently healthy adults may be deficient in the vitamin.

Animal and epidemiological studies have found that folic acid deficiency is associated with an increased risk of colon, cervix, lung, and brain cancers. But until recently, the exact mechanism had been unclear.

Folic acid is essential for the synthesis of deoxyribonucleic acid (DNA), which form the genes that program cell functions. Young-In Kim, MD, of the University of Toronto, Canada, recently investigated how folic acid deficiency specifically affected the p53 tumor suppressor gene. Defects in this gene have been implicated as a cause of more than 50 percent of all human cancers.

Kim reported in the *American Journal of Clinical Nutrition* (Jan 1997;65:46-52) that a lack of folic resulted in DNA strand breaks in the p53 gene—in effect, cutting it into pieces. Inadequate levels of the nutrient also interfered with the methylation of DNA, a key step in the synthesis of the p53 gene. These alterations to the p53 gene likely increase the risk of cancer, according to Kim.

• Dietary habits and gallstones

In a study comparing patients with gallstones and healthy subjects, Spanish researchers noted numerous differences in eating habits. For example, patients with gallstones consumed less fish and fruit than did healthy subjects. They also consumed less fiber, folic acid, and magnesium.Gallstone patients ate more cereals, oils, sugars, and meat than healthy subjects. "For all vitamins and minerals studied, [gallstone] patients showed a greater percentage of intakes below those recommended," the researchers wrote.

Ortega RM, et al., Journal of the American College of Nutrition, 1997;16:88-95.

• Capsaicin has anti-fungal activity

Capsaicin, the pungent component of chile peppers, has long been a folk medicine for the topical treatment of inflammation, sprains, and joint pain. Capsaicin is also an antioxidant, and it has moderate anti-fungal activity.

Chowdhury B, et al., *Medical Science Research*, 1996;24:669-70.

• Garlic increases antioxidant levels

In a cell-culture study, researchers exposed pulmonary artery endothelial cells to varying concentrations of aged garlic extract. Levels of glutathione and superoxide dismutase (SOD) increased, whereas levels of oxidized glutathione decreased, suggesting improved recycling of glutathione. The higher the dose and the longer the exposure, the higher glutathione and SOD levels rose.

Geng ZH and Lau BHS, *Phytotherapy Research*, 1997;11:54-6.

• Monosodium glutamate and oxidative stress

Monosodium glutamate (MSG) is a commonly used flavor enhancer that sometimes causes temporary aches and pains known as "Chinese restaurant syndrome." In an experiment with mice, researchers found that MSG increased lipid peroxidation (free radical damage to fats) in the animals' liver cells. Glutathione levels dropped, and levels of various glutathione enzymes (e.g., glutathione peroxidase and glutathione transferase) increased, indicating a heightened response to free radical insults.

Choudhary P, et al., *Toxicology Letters*, 1996;89:71-6. • Cuts and wounds increase free radicals

A minor wound to the skin, such as a cut, dramatically depletes levels of various antioxidants in the immediate area. Researchers noted 60-70 percent decreases in antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and glutathione-S-transferase. Other antioxidants, such as vitamins C and E, and glutathione, also decreased by about 60-70 percent. "The researchers wrote that "wounding results in loss of different free radical scavengers...which either partially or completely recover following healing."

Shukla A, et al., Free Radical Research, 1997;26:93-101.

• Vitamin C and radiation exposure

Supplemental vitamin C increased the survival of bone marrow cells in mice after they were exposed to a sublethal whole-body dose of x-ray radiation. However, vitamin C did not improve the survival of animals when they were exposed to a lethal dose of radiation.

Harapanhalli RS, et al., Research Communications in Molecular Pathology and Pharmacology, 1996;94:271-87.

• L-Arginine may help in colon cancer

The amino acid L-arginine increases the ability of lymphocytes to attack cancer cells. In a study of 18 patients, Scottish researchers found that 30 grams of arginine daily increased the activity of tumor-infiltrating lymphocytes in patients undergoing surgery for colorectal cancer. "These findings have important implications for new strategies in anticancer treatment," wrote the researchers.

Heys SD, et al., *British Journal of Surgery*, 1997;84:238-41. • **Reversing flouride poisoning**

Fluorosis, which is generally considered irreversible, is common in many developing nations where drinking water is contaminated with fluoride. In a double-blind trial, researchers gave children ages 6-12 years supplements of vitamin *C*, calcium, and vitamin D. Follow-up exams indicated a significant improvement in the dental, skeletal, and clinical symptoms of fluorosis. "Thus," the researchers observed, "the study indicated that fluorosis can be reversed, at least in children by a therapeutic regimen that is fairly cheap, simple and easily available and without any side effects."

Gupta SK, Acta Paediatrica Japonica, 1996;38:513-19.

• Diet and breast cancer

A number of dietary habits were associated with an increased risk of breast cancer in women. Women who used salad dressings other than low-fat varieties had about a 30 percent increased risk of breast cancer. Women who ate the skin on poultry had a 70 percent increased risk. And women who did not use lean or extra-lean ground beef had more than twice the risk of developing breast cancer.

Byrne C, et al., Journal of Nutrition, 1996;126: 2757-64.



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