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Vitamin E and Other Micronutrients Reduce Diabetic Complications and Insulin Resistance

Diabetics are routinely instructed on how to manage their carbohydrate, protein, and fat intake—but relatively little attention is paid to how vitamins and minerals can reduce their risk of disease complications.

As an example, the American Diabetes Association quickly distanced itself from new research on chromium picolinate, presented last year at an ADA meeting in San Francisco. Richard A. Anderson, PhD, a researcher at the U.S. Department of Agriculture, described a joint U.S./Chinese study in which diabetics received either daily supplements of chromium picolinate or placebos. Anderson reported that 200 mcg of chromium picolinate daily safely lowered and stabilized blood sugar levels in diabetics in just four months. People taking 1,000 mcg of chromium daily ended up with glucose and insulin levels comparable to those of normal people (Pramik J-J, *Medical Tribune News Service*, June 11, 1996).

In November, the ADA sponsored a scientific symposium on oxidants, antioxidants, and diabetic complications, held in Orlando, Fla. Although many researchers readily admitted taking vitamin E, they were reluctant to offer public recommendations. It was as if they said research is fine but clinical application is not.

Managing diabetes begins with controlling glucose, or blood sugar. Glucose is highly reactive and releases large numbers of free radicals, which damage blood vessels, according to Lester Packer, PhD, a professor at the University of California, Berkeley, and one of the speakers at the ADA meeting. These free radicals lead to a cascade of problems, including nerve and kidney damage, eye disease, and oxidized low-density lipoprotein (LDL) cholesterol and a high risk of coronary heart disease.

Many of these glucose-generated free radicals can be neutralized with vitamin E. "Vitamin E has been shown to have highly protective effects. The important thing is to take it," said Angelo Azzi, PhD, a professor at the Institute of Biochemistry and Molecular Biology in Bern, Switzerland (Challem J, *Medical Tribune* [Family Physician edition], Dec 12, 1996:18). Azzi stated a preference for natural vitamin E because it is better absorbed by the body.

"In my own practice, I suggest to my coronary artery disease patients that they take 400 IU of vitamin E (daily)," said Ishwarlal Jialal, MD, of the University of Texas Southwestern Medicine Center.

Stephan Jacob, MD, of Tübingen, Germany, reported

that supplements of alpha-lipoic acid, a nutrient and natural cell constituent, accelerated the removal of glucose from the blood, improved glucose tolerance, and reduced insulin resistance. That's significant because insulin resistance, which affects between one-fourth and one-third of Americans, is a major underpinning of adult-onset diabetes, hypertension, obesity, and coronary heart disease.

Among other recent findings...

- Diabetics suffer greater oxidative stress (more free radical damage) than nondiabetics, and a higher degree of oxidative stress is associated with a longer duration of the disease and greater complications. The researchers wrote that "antioxidant deficiency...may appear early on in non-insulin-dependent diabetes mellitus, before the development of secondary complications." Sundaram RK, et al., *Clinical Science*, 1996;90:255-60.

- High glucose levels increase the body's production of antioxidant enzymes (e.g., superoxide dismutase and glutathione), "suggesting that elevated glucose levels may produce an oxidative stress in the cells." Ceriello A, et al., *Diabetes*, 1996;45:471-7.

- In a study of 30 diabetics, researchers at the University of Vienna found that 2 grams daily of arginine significantly reduced lipid peroxidation (free radical damage to fats) after three months of treatment. Lubec B, et al., *Free Radical Biology & Medicine*, 1997;22:355-7.

- Researchers at Louisiana State University Medical Center reported that vitamin E prevented the glycosylation of protein in human blood. Glycosylation, the permanent binding of sugar and protein, is considered a fundamental cause of aging and diabetic complications. Jain SK and Palmer M, *Free Radical Biology & Medicine*, 1997;22:593-6.

- High blood levels of insulin, indicate of both insulin resistance and diabetes, decrease vitamin E levels in blood, possibly by generating free radicals. Galvin AQ, et al., *Metabolism*, 1996;45:998-1003.

- Women with diabetes have an increased risk of delivering infants with birth defects. In an animal study, researchers at the University of San Pablo, Spain, reported that vitamin E supplements decreased the rate of embryo malformations while also increasing embryo size and maturation. Viana M, et al., *Diabetologia*, 1996;39:1041-6.

Note: If you're diabetic, supplementation may lower your requirements for insulin or hypoglycemic drugs. □

Research summaries continue on next page

Sluggish Sperm? Antioxidants Might Help

If you're a man who has been diagnosed with infertility, antioxidant vitamins might give your sperm a lift. Several recent studies point to the role of free radicals in infertility—and the benefits of vitamin E and ferulic acid.

The membranes of sperm cells are rich in polyunsaturated fatty acids (PUFAs) and are highly susceptible to free radical damage, particularly from hydrogen peroxide. Free radical damage to these PUFAs weakens sperm cell membranes, inactivates enzymes, damage DNA, and causes cell death.

Ilter Alkan, MD, and his colleagues at the Marmara University School of Medicine, Turkey, analyzed free radical and antioxidant levels in 18 patients with idiopathic infertility (infertility of unknown cause). Sixteen (88.8 percent) of the 18 patients had higher levels of free radicals in their semen, compared with semen from 10 healthy men. The infertile men also had significantly lower levels of key antioxidants in their semen, including superoxide dismutase, catalase, and glutathione, according to Alkan's report in the *Journal of Urology* (Jan 1997;157:140-3).

In a separate study, Ami Amit, MD, of the Serlin Maternity Hospital, Israel, gave 200 IU of vitamin E daily for three months to 15 "fertile" men who had normal sperm counts but low fertilization rates.

Vitamin E reduced the amount of malondialdehyde, a marker of free radicals, in the semen. After just one month, it also improved the fertilization rate of the men by about 30 percent, according to Amit's article in *Fertility and Sterility* (Sept 1996;66:430-4).

In another study, researchers reported that the antioxidant ferulic acid, a polyphenolic flavonoid found in many medicinal herbs (including pine bark-derived flavonoids), can improve sperm motility. Rong-Liang Zheng, PhD, and Hong Zhang, PhD, of Lanzhou University, China, found that the sperm of infertile men contained high levels of thiobarbituric acid, a marker of free radicals.

Even fertile men might benefit from ferulic acid, according to Zheng and Zhang. "Ferulic acid is beneficial to sperm viability and motility in both fertile and infertile individuals..." the researchers wrote in *Free Radical Biology & Medicine* (1997;22:581-6). □

Garlic, Kale Top Veggies in Antioxidant Activity

Fruits and vegetables contain large quantities of antioxidants, but only some of their antioxidant activity may be related to vitamins C and E and beta-carotene. Other carotenoids and flavonoids may provide a greater share of the antioxidant activity in food.

Ronald L. Prior, PhD, of the USDA Human Nutrition Research Center on Aging, Tufts University,

analyzed the total antioxidant capacity of common vegetables and tea. Prior did so by measuring their ability to quench two types of free radicals, peroxy radicals and hydroxyl radicals.

Based on the fresh (wet) weight of the vegetable, Prior found that garlic was most active against peroxy radicals, according to his article in the *Journal of Agricultural and Food Chemistry* (Nov 1996;44:3426-31). After garlic, the most powerful peroxy scavengers were kale, spinach, Brussels sprouts, alfalfa sprouts, and sweet potato.

In contrast, kale had the greatest antioxidant activity against hydroxyl radicals, followed by Brussels sprouts, alfalfa sprouts, beets, spinach, and broccoli flowers. Hydroxyl radicals are considered the most dangerous type of free radicals.

When Prior ranked vegetables against the combined effect of peroxy and hydroxyl radicals, kale was the most potent, followed by garlic, spinach, Brussels sprouts, alfalfa sprouts, and broccoli flowers.

Green tea was several times more powerful than kale in quenching peroxy radicals. However, in the presence of copper, green tea increased free radical production. Garlic, broccoli flowers, and spinach had the greatest activity against copper-induced free radicals. □

Slow "Acetylators" Face a Higher Risk of Cancer

Some supplements, such as the amino acids carnitine and cysteine, are also sold in "acetylated" form—that is, as acetyl-L-carnitine and N-acetylcysteine. Acetylated forms are typically more expensive, but they are generally regarded as more potent. They may also be of particular benefit to people who don't do a particularly good job of acetylating nutrients and other compounds.

Acetylation is the process of adding a chemical "acetyl group" to an organic compound. The body routinely acetylates a variety of compounds, some of which are used to detoxify hazardous compounds.

If all this sounds rather abstract, consider the implications. Women born with "slow acetylating" genes are at a higher risk of breast cancer and other diseases, according to Christine B. Ambrosone, PhD, of the National Center for Toxicological Research, Jefferson, Ark.

Ambrosone investigated how one acetylated enzyme, N-acetyltransferase 2 (NAT2), detoxifies harmful compounds called aromatic amines, found in cigarette smoke. Similar substances, called heterocyclic amines, are created during the cooking of meat and may be a cause of colon cancer.

She found that about half of all Caucasian women have a genetic defect that interferes with their bodies' ability to efficiently acetylate and neutralize such amines. The consequence may be increased susceptibility to breast cancer, particularly among women who smoke.

In contrast, women who are rapid acetylators can quickly detoxify and excrete hazardous compounds, including the aromatic amines in tobacco smoke. Rapid acetylators have a low risk of breast cancer, even if they smoke.

"Cigarette smoking appears to be a risk factor for breast cancer among postmenopausal, but not premenopausal white women with the NAT2 slow acetylation genotype," Ambrosone wrote in the *Journal of the American Medical Association* (Nov 13, 1996;276:1494-1501). "Among slow acetylators, smoking intensity, rather than smoking duration, most greatly affected breast cancer risk. Smoking at a young age also appeared to confer risk. Among rapid acetylators, neither intensity nor duration of smoking increased risk."

Although Ambrosone did not address the issue of acetylated forms of supplements, her findings support the claim that such products may have an advantage over nonacetylated amino acids, especially in people who are slow acetylators. □

Breast Cancer Prevention: Genistein Better than Other Flavonoids

Asian women who consume a lot of soy and relatively little fat are far less likely than American women, who have the opposite dietary pattern, to develop breast cancer. One of the principal components of soy is the isoflavonoid genistein, which has weak estrogenic effect and may block the activity of cancer-promoting estrogen hormones.

In a recent study David T. Zava, PhD, of the California Public Health Foundation, Berkeley, compared the activity of genistein to other flavonoids. The flavonoid equol was a good estrogen antagonist, but a poor inhibitor of cell growth. Quercetin and kaempferol were powerful inhibitors of cell growth, but weak estrogen antagonists.

Genistein accomplished both tasks. "Our results revealed that genistein has potent estrogen antagonist and cell growth-inhibitory actions" in amounts achievable through a soy-rich diet, Zava wrote in *Nutrition and Cancer*, 1997;27:31-40. □

Osteoporosis? Vitamin B12 May Help Build Stronger Bones

Calcium and vitamin D are well known for their essential roles in building strong bones and preventing osteoporosis. New research shows that vitamin B12 might also help.

G. S. Kim, MD, of the Asan Medical Center, Korea, studied the role of vitamin B12 in the development of osteoblasts, cells responsible for the formation of bone. Several recent studies have linked pernicious anemia, a severe B12 deficiency, to a heightened risk of osteoporosis and bone fractures. In one case history cited by Kim, a

woman treated with B12 for pernicious anemia had dramatic increases in bone density.

Kim investigated some of the detailed processes that occur in the development of human and rat osteoblast cells. He found that vitamin B12 directly stimulated both types of osteoblasts, according to his article in *Metabolism – Clinical and Experimental* (Dec 1996;45:1443-6).

In addition, Kim noted that osteoporosis is a common consequence of gastrectomy and gastric bypass surgery. Although some researchers have attributed these cases of osteoporosis to calcium deficiency, as many as 80 percent of gastrectomy patients suffer from B12 deficiency. "Taken together with our in vitro findings, it is suggested that vitamin B12 deficiency may contribute to osteoporosis and bone fractures in conditions such as pernicious anemia, gastrectomy, or gastric bypass," Kim wrote. □

Rutin Helps Repair Genes, Prevent Early Stages of Cancer

Polyphenolic flavonoids, found in fruits and vegetables, are not technically considered essential nutrients. However, the evidence strongly suggests that these powerful antioxidants are highly beneficial nutrients.

Rutin, one of these flavonoids, plays a crucial role in helping damaged genes repair themselves. In a recent study, R. K. Bhattacharya, PhD, of the Bhabha Atomic Research Centre, India, exposed laboratory rats to two cancer-causing chemicals, aflatoxin B₁ and N-nitrosodimethylamine. Both carcinogens resulted in breaks of deoxyribonucleic acid (DNA), which forms genes. Such DNA breaks are a primary cause of cancer.

"Resistance to this phenomenon (DNA breaks) depends in part upon the efficiency of enzymes involved in repairing lesions in DNA...Since DNA damage and inefficient repair are expected to initiate the process of carcinogenesis, modulation of these parameters could provide a potentially effective way for cancer control," Bhattacharya wrote in *Cancer Letters* (Dec 3, 1996;109:185-91).

When the rats' diet was supplemented with rutin, several DNA repair enzymes were activated. The enzymes "drastically" reduced the DNA damage. Rutin was somewhat more effective in reducing damage from N-nitrosodimethylamine than from aflatoxin B₁.

Rutin may inhibit the early stages of cancer in other ways as well. "For example, rutin and...quercetin were found to be effective inhibitors of lipid peroxidation, the action being possibly mediated through scavenging of free radicals. This action too can prevent damage to DNA," Bhattacharya wrote.

This flavonoid is a glycoside (sugar-containing molecule) of quercetin and closely related to hesperidin. It is particularly rich in buckwheat, comprising 3 percent of its dry weight. Rutin and quercetin are also found in berries, grapes, and broccoli. □

Quick Reviews of Recent Research

• Grape skin compound helps prevent cancer

Resveratrol, a substance naturally found in grape skins and other plants, possesses anti-inflammatory and anti-cancer properties. It also functions as an antioxidant and antimutagen. As an anticarcinogen, resveratrol inhibits cancer at three stages: initiation, promotion, and progression. Resveratrol is part of a family of plant compounds called phytoalexins, which protect plants from infection.

Jang M, et al., *Science*, Jan 10, 1997;275:218-20.

• Ginkgo boosts antioxidant protection

Ginkgo biloba protects pulmonary artery endothelial cells from free radical damage. It also increases levels of glutathione, a powerful antioxidant, and protects cells against free radical damage.

Rong YQ, et al., *Nutrition Research*, 1996;16:1913-23.

• Quality of hospital diets often falls short

Only four out of 57 hospitals queried achieved key dietary recommendations, such as providing low-fat foods and several servings of fruits and vegetables daily. Twenty-two of the hospitals provided patients with too much fat, 27 with too much saturated fat, 46 with too much cholesterol, and 31 with too much sodium.

Singer AJ and Nestle M, *New England Journal of Medicine*, 1996;335:1466-7.

• Vitamin E succinate inhibits breast cancer cells

In an experiment, researchers determined that the d-alpha tocopheryl succinate form of vitamin E inhibited the growth of human breast cancer cells. The vitamin E worked by protecting "transforming growth factor- β ," which regulates cell growth. Transforming growth factor- β may also play a protective role in three-fourths of the breast, prostate, lung, colon, and skin cancers that occur in men and women.

Charpentier A, et al., *Nutrition & Cancer*, 1996;26:237-50.

• Carotenoids might prevent colon cancer

In an animal study, lycopene and lutein showed the greatest ability of several carotenoids to inhibit precancerous changes to colon cells. "The results," researchers wrote, "suggested that lycopene and lutein in small doses may potentially prevent colon carcinogenesis."

Narisawa T, et al., *Cancer Letters*, 1996;107:137-42.

• Magnesium reduces risk of cerebral palsy

The risk of delivering an infant with cerebral palsy or mental retardation can be reduced by giving pregnant women magnesium sulfate. Infants were 90 percent less likely to have cerebral palsy and 70 percent less likely to be mentally retarded if their mothers received magnesium sulfate. Magnesium was most beneficial among women at risk for delivering low-birth-weight infants.

Schendel DE, et al., *Journal of the American Medical Association*; 1996;276:1805-10.

• Macadamia nuts contain potent antioxidants

Macademia nuts, a tasty Hawaiian export, are rich in polyphenolic flavonoids, which act as antioxidants. Some of the polyphenols are benzoic and cinnamic acids.

Quinn LA and Tang HH, *Journal of the American Oil Chemists Society*, 1996;73:1585-8.

• Vitamins can make up for a bad diet

Taking vitamins C and E before eating a high-fat meal can counter some of the negative health effects of the fat, according to a presentation at the annual meeting of the American Heart Association, held in New Orleans in Nov 1996. The research team, led by Gary Plotnick, MD, of the University of Maryland School of Medicine, Baltimore, found that the vitamins prevent triglycerides from interfering with how blood vessels relax and dilate.

Khan J, Medical Tribune News Service, Nov 13, 1996.

• Natural beta-carotene protects against radiation

Natural beta-carotene supplements derived from algae contain roughly equal amounts of all-trans and 9-cis isomers, whereas synthetic beta-carotene contains only the all-trans isomer. (Isomers are the same molecules, but with different structures.) In laboratory rats exposed to whole-body radiation, levels of 9-cis beta-carotene and vitamin A decreased more than did all-trans beta-carotene. The findings suggest that the 9-cis isomer, found in algae but not in synthetic beta-carotene, might be more effective than the all-trans isomer in protecting against radiation-induced free radical damage.

Ben-Amotz, A, et al., *Radiation and Environmental Biophysics*, 1996;35:285-8.

• Monounsaturated fats prevent LDL oxidation

Oxidation of the low-density lipoprotein (LDL) form of cholesterol is considered a major cause of coronary heart disease. Vitamin E and other antioxidants are known to slow and prevent the oxidation of LDL. Researchers found that a diet rich in monounsaturated fatty acids (found in olive oil) further protected LDL against oxidation.

Reaven P, et al., *Arteriosclerosis, Thrombosis & Vascular Biology*, 1996;16:1465-72. □

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