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INSIDE

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American Ginseng (*Panax quinquefolius*) for Upper Respiratory Tract Infections

By Tiffany Segre, MD, and Craig Schneider, MD

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HERBAL REMEDIES KNOWN AS GINSENG ARE BASED ON THE ROOTS of several distinct species of plants, mainly Korean or Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), and Siberian ginseng (*Eleutherococcus senticosus*). Each of these species is part of the Araliaceae family of plants: however, although American ginseng is closely related to *Panax ginseng*, neither should be confused with Siberian ginseng, which is actually an unrelated plant.

American ginseng has a long history of traditional use by Native Americans. Extensive cultivation now occurs in the American Midwest and Canada, and, unfortunately, it is becoming endangered in the wild due to over-harvesting and habitat loss. These supply and demand forces have led to several other plants being marketed as ginseng, but enactment of the Farm Security and Rural Investment Act in 2002 now permits only roots of *Panax* species to be labeled as ginseng.[1]

Ginsengs have traditionally been utilized as "adaptogens," or substances that help an organism respond to stress in the environment. Although there is abundant research on Asian ginseng, American ginseng has only recently been subjected to clinical investigation, and there is emerging evidence that it may reduce postprandial glucose levels in patients with Type 2 diabetes[2] as well as protect individuals from upper respiratory tract infections (URTIs).

This article will focus on the use of a specific American ginseng extract, CVT-E002 (COLD-fX®, CV Technologies Inc., Edmonton, Alberta, Canada), which has been studied in the prevention of URTIs.

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COLD-fX

CVT-E002 is a proprietary botanical extract of North American ginseng root (*Panax quinquefolius*) standardized to contain 80% polysaccharides and oligosaccharides (poly-furanosyl-pyranosyl-saccharides) and 10% protein. Batch-to-batch consistency is certified using ChemBioPrint® Technology.[3] Most studies have used a freeze-dried extract encapsulated to contain 200 mg per capsule.

Readers may be familiar with CVT-E002 from COLD-fX advertisements distributed in popular magazines featuring testimonial from hockey star Mark Messier.

Mechanism of Action/Laboratory Studies

American ginseng root contains triterpene saponins commonly known as ginsenosides. At least 30 ginsenosides have been reported to exist in the various ginseng species.[4] Individual ginsenosides are known to have distinct effects, with some opposing the actions of others. American ginseng also contains polysaccharides. There appear to be differences in ginsenoside content between wild and cultivated American ginseng, as well as between batches, plant parts, and preparation methods utilized.[5] CV Technologies claims that CVT-E002 differs from other Asian and American ginseng products in content of polysaccharides and ginsenosides.

Polysaccharides and oligosaccharides from ginseng are believed to be responsible for its immunomodulating activity.[6] Pre-clinical studies of American ginseng have reported activation of monocytes, induction of tumor necrosis factor-α and interferon-γ, as well as stimulation of natural killer cell activity and interleukin-2 (IL-2) production.[7,8] Stimulation of B-lymphocyte proliferation, serum immunoglobulin production, and macrophage production of IL-1 and IL-6 in vitro have also been reported.[6]

It remains unclear just how American ginseng impacts the development of URTIs or their course, as some of the effects described above would seem to be associated with improvements (e.g., increased γ-interferon production), while others might be expected to lead to worsening of symptoms (e.g., increased production of inflammatory cytokines).[9,10]

Clinical Evidence

There have been three randomized, double-blind, placebo-controlled trials recently published addressing the efficacy of American ginseng for the prevention of URTIs.

McElhaney et al published a small randomized, double-blind trial in 2006 evaluating the efficacy of CVT-E002 (400 mg/d) in reducing the incidence and duration of respiratory symptoms in healthy community-dwelling seniors older than age 65.[11] This placebo-controlled study included 43 volunteers from Edmonton, Canada, over a four-month period beginning in September 1998. Subjects received the influenza vaccine one month into the study. They were asked to self-assess and document the presence and duration of cold symptoms, any additional cold medications taken, and adverse effects experienced.

In the first eight weeks of the study, the number of acute respiratory infection (ARI) symptoms was similar in both groups. However, during the last two months of the study, significantly fewer subjects in the ginseng group reported ARI symptoms compared to placebo (32% vs. 62%, P = 0.05). The ginseng group reported 55% fewer days of ARI symptoms than did the placebo group. Incidence of adverse effects was similar in the two groups. The authors concluded that CVT-E002 could be effective in reducing the frequency as well as the duration of ARI symptoms in healthy community-dwelling seniors; however, the small sample size and lack of a validated instrument for evaluating ARI symptoms limit the impact of the author's conclusions. Of note, there was no influenza circulating in the community during the period in which the study was conducted.

Predy et al conducted a larger randomized, double-blind study during influenza season in the Edmonton area comparing CVT-E002 (400 mg/d) to placebo for the prevention of URTIs in healthy community-dwelling

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adults ages 18-65.[12] The primary endpoint of this 2005 study was the number URTIs, and secondary endpoints included the severity and duration of URTI symptoms. Subjects (130 in the ginseng group and 149 in the placebo group) were asked to complete a daily log of their cold symptoms, severity, and duration. They contacted an investigator as soon as cold symptoms started and colds were verified per modified Jackson criteria (two-day symptom scores >14).

The mean number of colds verified was lower in the ginseng group, but this difference was not significant. However, the ginseng group did have a significantly reduced rate of recurrent colds (10% in the ginseng group vs. 22.8% in the placebo). There was also a significant decrease in the total number of cold symptoms experienced (31% lower) and their overall duration (34.5% less days). The incidence of adverse effects was similar for the two groups. The investigators concluded that in a healthy adult population, CVT-E002 could safely reduce the risk of recurrent colds as well as the number of colds per person and their duration. This study was well designed, attending to adherence with study protocol and using standardized criteria to evaluate cold symptoms. Intention-to-treat analysis was used, and both study participants and statisticians remained blinded. Unlike the other CVT-E002 studies, participants were excluded from this study if they had received the influenza vaccine in the last six months.

In 2004, another group, also led by McElhaney, investigated whether taking CVT-E002 as prophylaxis in the influenza season decreased the incidence of ARI in institutionalized older adults.[13] This study was originally designed as two randomized, double-blind trial arms testing CVT-E002 200 mg orally twice daily against placebo. The first trial lasted eight weeks, beginning in mid-February 2000 and included 89 mostly female subjects (average age 81 years) from three nursing home and assisted living facilities in Canada. The second study consisted of a similar participant profile and lasted 12 weeks, starting in late December 2000. About 90% of the subjects in both groups had been vaccinated for influenza. Clinical assessments for ARI occurred twice a week. ARI was defined as two respiratory symptoms or one respiratory symptom and one constitutional symptom. Symptomatic participants were cultured for influenza, respiratory syncytial virus (RSV), parainfluenza, and rhinovirus. Serology testing was also used to test for influenza. The primary outcome for the study was clinically confirmed ARI.

Results demonstrated no significant difference between the placebo and CVT-E002 groups for the number of clinical cases of ARI or the severity or duration of the symptoms in either of the two arms. The number of laboratory-confirmed ARI in each of the two trials alone was too low to detect meaningful differences. Therefore, the authors used a combined analysis (the Mantel-Haenszel odds ratio) to evaluate the endpoints. Once again, clinically symptomatic ARI was not significantly reduced in the treatment group. However, the authors point out that the incidence of laboratory-confirmed ARI due to influenza (odds ratio [OR] 0.14) as well as influenza and RSV (OR 0.11) was significantly higher in the placebo group. The number of adverse events was high, but similar in both the placebo and CVT-E002 groups.

The authors concluded that CVT-E002 may provide a safe option for preventing ARI in an institutional setting, even when people have been vaccinated. CVT-E002 may be helpful in decreasing laboratory-confirmed ARI; however, the trial was not statistically powered to evaluate this secondary endpoint. In addition, there were no significant differences in clinical symptom scores between the groups, so the clinical utility of laboratory-confirmed ARI is unclear. Altogether, though the results are suggestive of minimal benefit, it is difficult to draw definitive conclusions from this study.

Adverse Effects

In these studies, American ginseng was reported to cause adverse gastrointestinal effects (nausea, heartburn, diarrhea), dry mouth, myalgias, and arthralgias at rates similar to placebo.

Conclusion

CVT-E002 is a well standardized product with known phytochemical composition and limited lot-to-lot variability. It appears to be well tolerated and safe to use for up to 16 weeks. Data from three industry-sponsored studies (two by the same lead author) suggest that in healthy adults American ginseng in the form of CVT-E002 may be beneficial in decreasing the number of recurrent colds and the duration of symptoms if introduced early in the cold season. Further well-designed, non-industry sponsored studies would contribute greatly to revealing the true utility of American ginseng for prevention of upper respiratory tract illness.

Recommendation

CVT-E002 appears to be safe and well tolerated for use during cold and flu season. As preliminary evidence suggests it may reduce the frequency of recurrent colds and the duration of symptoms, a trial by well-informed and otherwise healthy adults is reasonable at 400 mg/d. ❖

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Nuts Reduce Cardiovascular Disease Risk

By Amy E. Griel, PhD, and Penny M. Kris-Etherton, PhD, RD

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PART 2 OF A SERIES ON CARDIOVASCULAR DISEASE

[Note: Part 1 of this series appeared in the February issue of Alternative Medicine Alert *and contained information on epidemiological and clinical nutrition studies as well as a discussion of results from clinical trials that specifically examined walnut consumption. This second part commences with a review of almonds.]*

ALMONDS HAVE BEEN EVALUATED EXTENSIVELY AND have been shown to lower total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels due to their nutrient content, including their fatty acid profile (they are a rich source of monounsaturated fatty acids [MUFA] and are low in saturated fatty acids [SFA]). As a result, almonds can be used as a fat source to achieve a moderate fat diet that is low in SFA. Almonds also contain a significant amount of α-tocopherol, a potent antioxidant, and many other proposed cardioprotective components, including folic acid, calcium, potassium, magnesium, copper, zinc, and specific phytochemicals.

To determine which individual components of almonds contribute to the reduction observed in lipids and lipoproteins, some studies have assessed whether the processing of almonds has an effect on the lipid-lowering effect. Comparing whole almonds vs. almond oil provides information about whether effects are due specifically to the oil fraction or whether there are benefits from both the fat and components of the total nutrient package. Employing a two-period six-week randomized crossover design, Hyson and colleagues tested whether the incorporation of whole almonds (66 g) vs. almond oil (35 g) into a habitual diet would have similar effects on blood lipids and lipoproteins.[1] The only difference in the composition of the diets was a 36% increase in fiber with the incorporation of whole almonds, compared to both baseline and the almond oil

diet. The incorporation of both whole almonds and almond oil diets significantly ($P < 0.05$) reduced TC (4%, 4%), LDL-C (6%, 7%), and triglycerides (TG, 14%, 15%), and increased high-density lipoprotein-cholesterol (HDL-C, 4%, 7%), respectively, compared to baseline. Thus, the results of this study indicate that the lipid-lowering effect of almonds is due primarily to the constituents in the lipid fraction of almonds, with no measurable added benefits from the non-lipid fractions.

A similar study tested the effects of incorporating 100 g of either roasted salted almonds, roasted almond butter, or raw almonds into a cholesterol-lowering diet.[2] All three test diets were matched for total fat (~44%), SFA (~8%), MUFA (~22%), and PUFA (~10%). There was a significant reduction ($P < 0.05$) in LDL-C from all forms of almonds (12% for raw almonds and 7% for roasted almonds and almond butter); the reduction in TC was greatest following the raw almond diet (7%; $P < 0.01$) and similar for the roasted almond (5%; $P < 0.05$) and almond butter diets (5%). There were no significant changes in TG or HDL-C following the three different diets.

In addition to testing the different almond products, researchers also have evaluated the effects of incorporating almonds into a blood cholesterol-lowering diet on lipids and lipoproteins. When compared to a dairy-based diet (35% total fat, 17% SFA, 15% MUFA, and 3% PUFA), an almond-based diet (40% total fat, 5% SFA, 28% MUFA, and 7% PUFA) produced the greatest reductions in TC (16%) and LDL-C (19%) ($P < 0.001$).[3] Within the context of a cholesterol-lowering diet, a dose-dependent relationship also has been observed with the consumption of increasing doses of almonds. Following the consumption of a Step II diet plus either 1) 73 g/d of whole almonds, 2) muffins, or 3) half portions of almonds (37 g/d) and muffins, a dose-response relationship was observed.[4] The full portion of almonds was associated with a 5.6% reduction in TC, a 9.4% reduction in LDL-C, an 8.4% reduction in the ratio of TC:HDL-C, and a 3.8% increase in HDL-C, compared to baseline.

This dose-response effect was then tested by comparing the addition of two different levels of almond intake to a Step I diet.[5] Twenty-five healthy individuals consumed a Step I diet (30% total fat), low-almond diet (35% total fat), and high-almond diet (39% total fat) in a randomized crossover study. Almonds represented 0%, 10% (~34 g/2,000 kcal), and 20% (~68 g/2,000 kcal) during the Step I, low-almond, and high-almond diets, respectively. Levels of TC, LDL-C, and apolipoprotein B, and the LDL-C:HDL-C ratio were reduced in a dose-response manner (TC: 5.41, 5.36, 5.17 mmol/L; LDL-C: 3.74, 3.70, 3.48 mmol/L, respectively, for Step-1, low-almond, and high-almond diets). There were no significant differences in levels of HDL-C or TG.

The results of these studies suggest that the incorporation of almonds into either a Step I or Step II diet will provide additional improvements to the lipid and lipoprotein profile, above those seen with the traditional Step I or Step II diet in a dose-dependent manner.

Macadamia Nuts

Macadamia nuts are a rich source of MUFA; thus, when they are substituted for other fats in the diet they can facilitate a shift to a fatty acid profile that is higher in MUFA and lower in SFA. To date, three clinical trials have evaluated the effect of macadamia nuts on the lipid and lipoprotein profile.

The results of a supplement trial by Garg et al show that the addition of macadamia nuts (40-90 g/d; 15% of the total energy intake), significantly decreased TC (3.0%) and LDL-C (5.3%), and increased HDL-C (7.9%) in hypercholesterolemic men.[6]

Two controlled feeding studies have demonstrated similar improvement in the lipid and lipoprotein profile following the incorporation of macadamia nuts into a cholesterol-lowering diet. In one study, investigators compared a high-carbohydrate diet (HCD; 21% total fat) and a macadamia-enriched diet (MD; 42% total fat) to the subjects' typical food intake (37% total fat).[7] Both the HCD and MD elicited a significant reduction in TC (-7.9%) and LDL-C (-10.7%) when compared to typical food intake. The MD reduced TG levels by 20.9% and maintained levels of HDL-C; the HCD however elicited a 13.1% reduction in HDL-C.

In a later study, Curb et al compared a macadamia nut-based diet (37% total fat) to a typical American diet (37% total fat) and a Step 1 diet (30% total fat).[8] Compared to the typical American diet, both the macadamia-based diet and the Step 1 diet reduced TC (5%, 4%; $P < 0.01$), LDL-C (4%, 5%; $P < 0.05$), and HDL-C (4%; $P < 0.01$, 6%; $P < 0.001$), respectively. TG levels were higher on the Step 1 diet (8%; $P < 0.05$), when compared to the typical American diet; however, the macadamia nut diet significantly reduced TG levels (9%; $P < 0.05$).

Pecans

Pecans are a rich source of MUFA and contain a number of cardioprotective compounds, including plant sterols, vitamin E, folic acid, calcium, magnesium, phosphorus, zinc, vitamin A, and several B vitamins. In addition, one serving of pecans provides approximately 10% of the daily value for both zinc and fiber. To date, two controlled feeding trials have assessed the lipid-lowering effect of pecans in healthy and hypercholesterolemic

individuals. When compared to a self-selected diet, an eight-week supplement of 68 g/d of pecans resulted in a 6% reduction in LDL-C.[9]

In a later study, Rajaram et al employed a two-period crossover design to study the cholesterol-lowering effect of pecans.[10] When compared to a Step I diet, the pecan-enriched diet (72 g of pecans per 2,400 kcal) elicited a 10.4% reduction in LDL-C in hypercholesterolemic individuals. In addition to the substantial reduction in LDL-C, several other lipid and lipoprotein risk factors were affected, including TC (-6.7%), HDL-C (+5.6%), LDL-C:HDL-C (-15.7%), TG (-11.1%), apolipoprotein B (-11.6%), and lipoprotein(a) (-15.1%).

Pistachio Nuts

Pistachio nuts are low in SFA and rich in MUFA and cholesterol-lowering phytosterols. One serving (~30 g; approximately 49 nuts) of pistachios contains 13 g of total fat (of which only 1.5 g is saturated fat); more than 10% of the daily value for dietary fiber, vitamin B_6, thiamin, phosphorus, and copper; and 61 mg plant sterols. To date, two studies have tested the cholesterol-lowering effects of pistachio nuts.

In a two-period, three-week randomized crossover study, researchers assessed the effects of a 100 g (20% energy) supplementation of pistachio nuts on plasma lipids and lipoproteins.[11] When compared to a habitual diet (37% total fat, 11% SFA, 11% MUFA, and 5% PUFA), the pistachio-enriched diet (39% total fat, 8% SFA, 15% MUFA, and 7% PUFA) reduced LDL-C (-11%), TC (-3.7%), TC:HDL-C (-14.6 %), and LDL-C:HDL-C (-9.4%).

In a similar study, the substitution of pistachios for 20% of the daily caloric intake resulted in significant reductions in the ratios of TC:HDL-C and LDL-C:HDL-C ($P < 0.001$ and $P < 0.01$, respectively), and small non-significant reductions in TG and LDL-C.[12] Because pistachios contain the highest levels of plant sterols among nuts it is likely that other mechanisms in conjunction with those associated with their fatty acid profile account for their blood cholesterol-lowering effects.

Hazelnuts

Hazelnuts contain about 91% MUFA, mostly oleic acid, and less than 4% SFA. Hazelnuts also contain many cardioprotective compounds, including fiber, vitamin E, arginine, folate, vitamin B_6, calcium, magnesium, and potassium. To date, only one study has evaluated the effects of hazelnuts on blood lipids and lipoproteins. Nineteen individuals with Type 2 diabetes consumed a high-carbohydrate diet (60% carbohydrate, 25% total fat, 10% SFA, 10% MUFA, and 5% PUFA) for 30 days, followed by a 15-day washout period before consuming a hazelnut diet (40% carbohydrate, 45% total fat, 9% SFA, 27% MUFA, and 9% PUFA) for 30 days.[13] LDL-C and TC were significantly reduced ($P < 0.01$) following the hazelnut diet (26%, 12%, respectively) compared to baseline. The high-carbohydrate diet significantly reduced LDL-C (16%; $P < 0.01$) and minimally reduced TC (5%) compared to baseline. The changes observed in apolipoprotein B (+7%, -8%), HDL-C (+2%, +8%), and TG (-12%, -16%) following the high-carbohydrate and hazelnut diets, respectively, were not significantly different when compared to baseline.

In a recent study 15 hypercholesterolemic men consumed either a control diet or the control diet supplemented with 40 g/d of hazelnuts, providing 11.6% of the total energy content of the diet.[14] Compared with baseline, the hazelnut-enriched diet decreased the concentrations of TG and apolipoprotein B and increased HDL-C ($P < 0.05$). In addition there was a trend for a decrease in TC (5.2%) and LDL-C (3.3%).

Incorporating Nuts into a Healthy Eating Plan

There is a strong body of evidence that nut consumption is associated with a decrease in CVD risk, a result due in part to the beneficial effects their fatty acid profiles have on plasma lipids and lipoproteins. However, it is important to appreciate that nuts are a calorically dense food. The concern in recommending nut consumption lies in the appropriate incorporation of this food within the diet to prevent overconsumption of calories and weight gain. The clinical research summarized demonstrates that the incorporation of nuts into the diet elicits a favorable response on multiple CVD risk factors without causing weight gain in an experimental setting. What is important is whether weight control can be achieved when individuals are making self-selected food choices that include nuts. It is reassuring that epidemiologic studies show that individuals who consume nuts do not have a greater BMI than individuals who do not eat nuts.[15] In fact, the epidemiologic studies show an inverse association between frequency of nut consumption and BMI.[15]

Data from the Continuing Survey of Food Intake by Individuals and Diet and Health Knowledge Survey from 1994 to 1996 were used to test for differences between peanut users and non-users for total energy and nutrient intakes, diet quality as measured by Health Eating Index (HEI) scores, and BMI.[16] The HEI was significantly greater for peanut users (men 61.4, women 65.1, children 66.8) compared to non-users (men 59.9, women 64.1, children 64.7) for men ($P < 0.01$) and children ($P < 0.001$). Although total energy intake (over a two-day period) was significantly higher in all population groups

of peanut users, mean BMI for peanut users was lower for all gender/age categories. These results demonstrated improved diet quality of peanut users, indicated specifically by the higher intakes of the micronutrients vitamin A, vitamin E, folate, calcium, magnesium, zinc, iron, and dietary fiber, and by the lower intake of saturated fat and cholesterol. In addition, despite a higher energy intake over a two-day period, peanut consumption was not associated with a higher BMI.

In a 24-week free-living weight-loss clinical study, Wien and colleagues evaluated the effect of incorporating 84 g/d of almonds into a formula-based low-calorie diet (LCD, 39% total fat, 3% SFA, 25% MUFA, and 11% PUFA) compared to a complex-carbohydrate formula-based LCD (18% total fat, 3% SFA, 5% MUFA, and 10% PUFA).[17] Improvements were observed in the lipid profile following both the almond-enriched diet and the complex carbohydrate diet. While both groups did lose weight, the loss was greater ($P < 0.0001$) for the almond-enriched diet (18%), compared to the complex-carbohydrate diet (11%). Overall, the almond-enriched LCD produced a sustained and greater weight loss in comparison to the complex carbohydrate LCD, accompanied by similar improvements in lipid profile.

Maximal Cholesterol Lowering Achievable with a Portfolio Diet

Numerous clinical studies have demonstrated cholesterol-lowering effects of diets that contain nuts without an increase in body weight. For the maximal reduction of TC and LDL-C by diet, it is now evident that a total diet approach is necessary that not only emphasizes the lowest amount of saturated fat and cholesterol achievable, but also the incorporation of high levels of viscous fiber and plant sterols.

A study conducted by Jenkins et al showed that a vegetarian diet that was very low in saturated fat and cholesterol and high in plant sterols (1 g/1,000 calories), soy protein (21.4 g/1,000 calories), viscous fiber (9.8 g/1,000 calories), and almonds (14 g/1,000 calories) decreased LDL-C by approximately 30%, similar to that observed with low-dose statin therapy (20 mg/d).[18,19] While this study used almonds, based on studies conducted to date, it would be predicted that other nuts could be substituted to achieve the same blood cholesterol-lowering outcome. The portfolio diet and low-dose statin therapy both significantly reduce C-reactive protein, now a recognized CVD risk factor, by 28% and 33%, respectively. Thus, tree nuts can be an important part of a blood cholesterol-lowering diet that elicits a maximal effect attainable by diet that is comparable to low-dose statin therapy without an increase in body weight.

Taking the Next Step: Cellular Mechanisms of Nuts and Their Components

Current dietary guidelines recommend inclusion of unsaturated fatty acids within the context of a nutritionally adequate diet that provides 20-35% of calories from total fat, with 5-10% recommended for PUFA.[20] Nuts are a powerful tool in achieving the above fatty acid profile for the reduction of lipids and lipoproteins due in large part to their fatty acid profile. Recent research findings have demonstrated how PUFA exert their regulatory and metabolic effects on a host of biological systems including decreasing TG and fatty acid synthesis and increasing mitochondrial β-oxidation, as well as peroxisome β-oxidation.[21] There is also keen interest in understanding the role of PUFA in oxidative stress and inflammation, key physiological processes in the development of atherosclerosis. Relative to the latter, the mechanisms by which linoleic acid (LA) and α-linolenic acid (ALA) affect inflammation need to be better understood. There is recent evidence that LA and ALA, as well as docosahexaenoic acid, decrease IL-6, IL-1β, and TNF-α gene expression, and nuclear factor-κB activation, whereas peroxisome proliferator-activated receptor-γ DNA binding activity was increased.[22] These findings reinforce the need to learn more about the signal pathways that mediate the effects of PUFA on gene transcription in a variety of biological systems. Moreover, it will be important to clarify how individual PUFAs, including omega-6 and omega-3 fatty acids, regulate a variety of biological systems that affect chronic disease risk.

Qualified Health Claims for Tree Nuts and Walnuts

As a result of the scientific literature demonstrating cholesterol-lowering effects of diets that contain tree nuts and walnuts, the Food and Drug Administration has approved qualified health claims for tree nuts and walnuts. The qualified health claims are as follows:

For tree nuts: "Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts [, such as name of specific nut,] as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease." These health claims will help consumers make wise food choices that can reduce risk of CVD.

For walnuts: "Supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease. See nutrition information for fat [and calorie] content."

Brazil nuts, macadamia nuts, cashews, and some types of pine nuts are excluded from the qualified health claim due to their saturated fat content.

Table

Energy and nutrient profile of nuts (per 1 ounce serving)

Nut	# nuts/ 1 oz serving	Energy (kcal)	SFA (g)	MUFA (g)	PUFA (g)	LA (g)	ALA (g)	Cholesterol (mg)	Fiber (g)	Phytosterols (mg)
Walnuts	14 halves	190	1.5	2.5	13	10.8	2.6	0	1.9	20
Almonds	20-24	160	1	9	3	3.6	0	0	3.3	33
Macadamia nuts	10-12	200	3	17	0.5	0.4	0.06	0	2.3	32
Peanuts	28	170	2	7	4	4.4	0	0	2.3	0
Pecans	18-20 halves	200	2	12	6	5.6	0.3	0	2.7	24
Pistachios	45-47	160	1.5	7	4	3.9	0.07	0	2.9	61
Hazelnuts	18-20	180	1.5	13	2	2.4	0.02	0	2.7	31
Brazil nuts	6-8	190	5	7	7	5.8	0.01	0	2.1	0
Cashews	16-18	160	3	8	2	2.2	0.05	0	0.9	45
Pine nuts	150-157	160	2	5	6	9.4	0.05	0	1.0	40

Note: All of the nuts are dry roasted with no added salt; SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; LA = linoleic acid; ALA = α-linolenic acid.

Source: The International Tree Nut Council Research and Education Foundation, U.S. Department of Agriculture Database for Standard Reference; Release Aug. 15, 2002.

Conclusion

Epidemiologic evidence clearly demonstrates that nut consumption reduces the risk of CVD, Type 2 diabetes, and gallstone disease. Clinical studies consistently have demonstrated beneficial effects on lipids and lipoproteins, primarily a reduction in LDL-C, which reduces CHD risk. This effect has been demonstrated in different population groups, utilizing various study designs and methods without any increase in body weight. Thus, when nuts are incorporated into a healthy diet, there is an improvement in the lipoprotein profile and a subsequent decrease in CVD risk.

Current dietary guidelines for reducing risk of chronic diseases recommend inclusion of unsaturated fatty acids within the context of a nutritionally adequate diet that provides 20-35% of calories from total fat, with 5-10% recommended for PUFA.[20] The Third Adult Treatment Panel of the National Cholesterol Education Program recommends a diet that provides 25-35% of calories from total fat with up to 10% coming from PUFA.[23] All current dietary guidelines recommend a diet low in SFA (< 10% of calories)[20] and less than 7% of calories.[23-25] Nuts are a food source that can be used to achieve these dietary recommendations. Because nuts are a rich source of unsaturated fats and are low in saturated fats, they are an important tool for achieving the recommended fatty acid profile for lowering blood cholesterol levels, and favorably affecting TG and HDL-C to reduce CVD risk. There is emerging evidence that nut consumption beneficially affects markers of inflammation and LDL particle size thereby further decreasing CVD risk beyond that due to changes in lipids and lipoproteins. It is likely that future research will identify other bioactive compounds in nuts that confer additional health benefits.

Recommendation

The recommendation to consume 4-5 servings (1 ounce servings) per week will markedly reduce risk of CVD. Patients should be advised to substitute 1 ounce of nuts for 2 ounces of meat and/or 2 teaspoons of vegetable oil. In addition, patients should be encouraged to refer to the dietary recommendations at www.mypyramid.gov, which provide information about how to include nuts in a heart healthy diet. In the table above, the number of different nuts per 1 ounce serving is provided.

The effects on LDL-C likely will be small (up to 5% decrease) based on the change in the fatty acid profile (and maybe the decrease in dietary cholesterol) of the habitual diet due to substitution of nuts for food sources high in saturated fat. The decrease in LDL-C would be expected to occur within a two-week period.

The effects of nut consumption (30 g/d; ~ 1 ounce) on the primary prevention of CVD is being studied in a randomized controlled clinical trial by the PREDIMED Study Investigators. The beneficial effects of a Mediterranean diet with nuts (and with olive oil vs. a low-fat group) on CVD risk factors have been reported.[26] The results of this first intervention study with nuts on CVD endpoints will be important to determine the extent to which nut consumption can reduce CVD morbidity and mortality. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Male and Frail: Androgen Supplementation?

Source: Muller M, et al. Effects of dehydroepiandrosterone and atamestane supplementation on frailty in elderly men. *J Clin Endocrinol Metab* 2006;91:3988-3991. Epub 2006 Jun 27.

Goal: To determine whether hormone replacement therapy with dehydroepiandrosterone (DHEA) and/or atamestane improves age-related frailty (ARF) in elderly men.

Design: Double-blind, randomized, controlled trial completed over 36 weeks.

Subjects: Independently living Dutch men older than age 70 years with low strength test scores (n = 100 selected from 400 who had participated in a prior study, complete data available for 83).

Methods: Following completion of fasting baseline assessments, including blood samples and measures of strength/frailty and cognition, participants were randomized to one of four different groups: atamestane 100 mg/d and placebo; DHEA 50 mg/d and placebo; combined atamestane 100 mg/d and DHEA 50 mg/d; two placebo tablets daily (all were to be taken at breakfast). Subjects had a total of seven clinic visits, with the last visit being 24 weeks after the last tablet was ingested. Outcome measures included muscle strength, physical frailty, functional performance, cognition, general well-being, bone mineral density, and body composition.

Results: DHEAS levels increased in the DHEA groups, while total testosterone levels increased in all three intervention groups. No differences were noted in any of the outcome measures studied between the placebo group and the groups that received various interventions.

Conclusion: Hormone replacement therapy with atamestane 100 mg/d and/or DHEA 50 mg/d does not improve the course of ARF in men.

Study strengths: Outcome measures chosen; intention-to-treat analysis; duration of trial.

Study weaknesses: Participants had normal testosterone levels at baseline; dropout rate of 17% (but no difference in rate among the groups); compliance measured by pill count, and with a liberal cutoff for noncompliance (< 80%).

Of note: Studies suggest that age-related declines in male hormones may play a role in ARF; results of research employing DHEA for the treatment of ARF have been contradictory, with some showing benefits in muscle strength and body composition, and others showing no benefit; studies employing testosterone supplementation have reported improvements in cognition and bone mineral density, as well as muscle mass and strength, but at the expense of increased prostate size; subjects with a history of prostate cancer were excluded from the trial; IGF-1 levels increased only in the atamestane/DHEA group; body mass index measurements increased in both the atamestane and DHEA groups.

We knew that: ARF is characterized by generalized weakness, decreased endurance, poor mobility, limited flexibility, and impaired balance, which is associated with an increased incidence of disability; atamestane is an aromatase inhibitor that has been shown to increase testosterone levels in elderly men by 30-50% while simultaneously decreasing estradiol levels.

Clinical import: A segment of the medical community now concerns itself with "anti-aging" therapies, including means of addressing andropause, the gradual age-related decrease in male hormones that may be associated with changes in body composition and functionality. In parallel to the previously long-favored approach to menopause, the idea of hormone replacement therapy for men garnered significant interest. Results of some studies created a buzz with data suggesting improved energy, stamina, and strength, but concerns about the potential risks associated with long-term androgen administration, notably fears over the possibility of an increased risk of prostate cancer, tempered initial enthusiasm. The present study at hand revealed no improvements in frailty with either DHEA or an agent that indirectly increases testosterone levels. Some will argue that higher doses should have been employed, or that subjects with low levels of DHEA or testosterone should have been the focus of the trial. Regardless, using hormone replacement therapy to try to stave off the effects of aging may be fraught with problems, if not frank dangers. Until there is clear evidence of benefit and definitive data regarding lack of increased risk for prostate cancer, androgen supplementation to prevent the effects of aging should be avoided. The goal for us all is to safely get older without growing older. Thankfully, many lifestyle and dietary interventions alone may help us achieve that goal.

What to do with this article: Keep a copy of the abstract on your computer. ❖

"Coffee, No Sugar"—Coffee and IGT

Source: Smith B, et al. Does coffee consumption reduce the risk of type 2 diabetes in individuals with impaired glucose? *Diabetes Care* 2006;29:2385-2390.

Goal: To compare the coffee habits of people with impaired glucose control (IGT) to those with normal baseline

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

12. Which of the following is not related to *Panax ginseng*?
a. American ginseng
b. Asian ginseng
c. Korean ginseng
d. Siberian ginseng

13. Which of the following statements is true?
a. CVT-E002 appears to decrease the number of recurrent colds if introduced early in the cold season.
b. CVT-E002 seems to decrease the duration of cold symptoms if introduced early in the cold season.
c. Controlled trials of CVT-E002 have been industry-sponsored.
d. All of the above

14. Epidemiologic studies show an inverse association between frequency of nut consumption and BMI.
a. True
b. False

15. Which of the following nuts is included in the FDA's qualified health claim for nuts?
a. Brazil nuts
b. Walnuts
c. Macadamia nuts
d. Cashews

16. To achieve a 5% reduction in LDL-C, how many 1 ounce servings of tree nuts or walnuts should be consumed each week?
a. 1-2 servings
b. 3-4 servings
c. 4-5 servings
d. 6 or more servings

Answers: 12. d, 13. d, 14. a, 15. b, 16. c.

glucose levels, and examine the relationship between coffee intake and incident diabetes mellitus (DM).

Study design: Prospective.

Subjects: Adults from Southern California older than age 50 years (n = 910, average age 65.9) who had previously participated in the Rancho Bernardo Study (RBS) in the 1970s and were without DM at baseline; 317 had impaired baseline glucose levels.

Methods: Between 1980 and 1984, 80% of the survivors of the RBS completed a baseline DM evaluation, and then a subsequent follow-up evaluation in 1992-1996 (74% of survivors). At each visit, anthropometric measures were obtained together with a complete history and blood tests. An oral 75 g glucose load was administered in the morning following an overnight fast, with blood drawn both before the glucose load and two hours thereafter. Subjects were followed for an average of eight years (up to 11 years). In 1992, a mailed survey was completed that included information on current and lifetime drinking of coffee, both caffeinated and decaffeinated (to be analyzed separately). Logistic regression models were employed and adjusted for multiple potential confounders including gender, age, physical activity, body mass index, smoking, alcohol, and hypertension.

Results: At baseline only 97 subjects reported never drinking coffee, while 153 were past drinkers, and 660 were current coffee drinkers (average of 2.8 cups/d). The number of cups of coffee imbibed each day, coffee consumption after age 45, and number of cup-years were not associated with risk of DM. Subjects who regularly drank coffee, either in the past or currently, had a reduced risk of incident DM (odds ratio [OR] = 0.38 and 0.36, respectively) compared with those who never drank coffee. Subjects who had impaired glucose at baseline and who were past or current coffee drinkers also were at reduced risk for development of DM (OR = 0.31 and 0.36, respectively).

Conclusion: Caffeinated coffee provides a significant protective effect against development of DM independent of multiple potential confounders. In contrast to the findings of some other trials, the quantity of coffee ingested daily does not predict impact on later risk of developing DM.

Study strengths: Use of oral glucose tolerance test (OGTT); duration of follow-up.

Study weaknesses: Self-reporting (potential recall bias); inability to assess impact of caffeine; not easily generalizable (subjects were mainly middle-class Caucasians); no information on additives other than milk; conclusions based on a single follow-up OGTT.

Of note: Only 12 subjects drank decaffeinated coffee exclusively, so separate analysis was not possible; the prevalence of DM in the United States increased three-fold between 1990 and 1999 (almost 7% of the U.S. population is believed to have DM), and global prevalence of DM is expected to almost double by 2030; based on 1999 WHO criteria, subjects in the trial were classified as having Type 2 DM if results of their OGTT were fasting glucose level ≥ 7.0 mmol/L, if post-challenge glucose was ≥ 11.1. mmol/L, if a clinical diagnosis of DM had been made, or if the subject was being treated for DM; 85% of participants reported physical activity three times a week, 44% were hypertensive at baseline, while more than half drank 1-2 alcoholic beverages per day; current coffee drinkers were significantly more likely to report they were also current smokers; in this study, those who were obese or hypertensive, as well as those who either did not drink alcohol or who had three or more alcoholic beverages/d, were more likely to develop DM; most U.S. coffee is made using arabica beans, which contain about 50% of the caffeine found in the robusta coffee beans that are primarily used in Europe.

We knew that: More than half of all U.S. adults drink coffee daily; cohort studies suggest that coffee drinking, whether caffeinated or decaffeinated, confers a protective effect against subsequent development of DM; results of small, placebo-controlled trials suggest that coffee can contribute to insulin resistance and increase blood glucose levels; diterpene content (reportedly associated with increased serum cholesterol levels and higher risk of cardiovascular disease) is significantly lower in drip-filtered coffee; besides caffeine, coffee also contains chlorogenic acid, quinides, and trigonelline.

Comments: It's been easy for this reviewer to comment on articles suggesting possible downsides to drinking coffee—I prefer tea. Of late, however, a spate of articles touting the health benefits of coffee have appeared, including potential improvements in memory and the relief of muscle pain after exercise. Add the current article to the list—but this study should be kept in mind if for no other reason than the benefit suggested by the results for people who already have IGT. Data are beginning to accumulate that compounds within coffee, apart from caffeine, appear to offer a preventive action against development of DM. Is the answer to preventing DM simply to get more of our patients to drink coffee regularly? Obviously not, just as drinking green tea by itself is unlikely to impact cancer incidence in those of us who eat unhealthily and forget to exercise. But the results are intriguing, even to a tea drinker.

What to do with this article: Keep a hard copy in your file cabinet. ❖

In Future Issues:

Vitamin E: An Update

CAM Treatments for Migraine Headache

Supplement to *Alternative Medicine Alert*
March 2007

ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

Patient Handout: Heart Disease Is the No. 1 Cause of Death

HEART DISEASE IS THE LEADING CAUSE OF DEATH IN THE UNITED STATES AND IS A MAJOR cause of disability. Almost 700,000 people die of heart disease in the United States annually. That's about 29% of all U.S. deaths. Heart disease is a term that includes several specific heart conditions. The most common heart disease in the United States is coronary heart disease, which often appears as a heart attack.

The chance of developing coronary heart disease can be reduced by taking steps to prevent and control factors that put people at greater risk. Additionally, knowing the signs and symptoms of heart attack are crucial to the most positive outcomes after having a heart attack. People who have survived a heart attack can also work to reduce their risk of another heart attack or a stroke in the future.

Diseases and conditions that put your heart at risk

Other conditions that affect your heart or increase your risk of death or disability include arrhythmia, heart failure, and peripheral artery disease. High cholesterol, high blood pressure, obesity, diabetes, tobacco, and secondhand smoke are also risk factors associated with heart disease. For a full list of disease and conditions along with risk factors and other health information associated with heart disease, visit the American Heart Association (www.americanheart.org).

Know your signs and symptoms

Some heart attacks are sudden and intense; however, most heart attacks start slowly, with mild pain or discomfort. Often people affected aren't sure what's wrong and wait too long before getting help. Here are signs that can mean a heart attack is happening:

Chest discomfort. Most heart attacks involve discomfort in the center of the chest that lasts more than a few minutes, or that goes away and comes back. It can feel like uncomfortable pressure, squeezing, fullness, or pain.

Discomfort in other areas of the upper body. Symptoms can include pain or discomfort in one or both arms, the back, neck, jaw, or stomach.

Shortness of breath. May occur with or without chest discomfort.

Other signs. These may include breaking out in a cold sweat, nausea, or lightheadedness.

The American Heart Association and the National Heart, Lung, and Blood Institute (www.nhlbi.nih.gov/actintime/index.htm) have launched a new "Act in Time" campaign to increase people's awareness of heart attack and the importance of calling 9-1-1 immediately at the onset of heart attack symptoms.

Healthy diet and nutrition

A healthy diet and lifestyle are the best weapons you have to fight heart disease. Many people make it harder than it is. It is important to remember that it is the overall pattern of the choices you make that counts. As you make daily food choices, base your eating pattern on

these American Heart Association recommendations:

- Choose lean meats and poultry without skin and prepare them without added saturated and trans fat.
- Select fat-free, 1% fat, and low-fat dairy products.
- Cut back on foods containing partially hydrogenated vegetable oils to reduce trans fat in your diet.
- Cut back on foods high in dietary cholesterol. Aim to eat less than 300 mg of cholesterol each day.
- Cut back on beverages and foods with added sugars.
- Choose and prepare foods with little or no salt. Aim to eat less than 2,300 mg of sodium per day (or less than 1,500 mg if you are in a higher risk group for high blood pressure).
- If you drink alcohol, drink in moderation. That means no more than one drink per day if you're a woman and two drinks per day if you're a man.
- Follow the American Heart Association recommendations when you eat out, and keep an eye on your portion sizes.

Heart disease in men

In 2002, 340,933 men died from heart disease, the leading cause of death for men in the United States. Major risk factors for heart disease include high blood pressure, high blood cholesterol, tobacco use, diabetes, physical inactivity, and poor nutrition.

- The age-adjusted death rate for heart disease in men was 297 per 100,000 population in 2002.
- About 8.9% of all white men, 7.4% of black men, and 5.6% of Mexican American men live with coronary heart disease.
- The average age of a first heart attack for men is 66 years.
- Almost half of men who have a heart attack before age 65 die within eight years.
- Results from the Framingham Heart Study suggest that men have a 49% lifetime risk of developing coronary heart disease after the age of 40.
- Between 70% and 89% of sudden cardiac events occur in men.
- Studies suggest that a 10% decrease in total cholesterol levels may reduce the development of coronary heart disease by as much as 30%.

Women and heart disease

Although heart disease is sometimes thought of as a "man's disease," it is the leading cause of death for both women and men in the United States and women account for 51% of the total heart disease deaths. Of the 1,244,123 deaths among women in 2002, 28.6% were due to diseases of the heart.

Heart disease is often perceived as an "older woman's disease," and it is the leading cause of death among women aged 65 years and older. However, heart disease is the third leading cause of death among women aged 25-44 years and the second leading cause of death among women aged 45-64 years.

According to surveys by the American Heart Association, the percentage of women who spontaneously identified heart disease as the number one killer of women increased from 30% in 1997 to 46% in 2003. Unfortunately, only 13% of the women in the 2003 survey perceived heart disease as their greatest health problem. Although this is an increase from the 7% level in 1997, it still reflects an attitude that heart disease is "not my problem."

There is a range of risk for heart disease depending on family and personal health history and the treatment recommendations from a physician will depend on a woman's level of risk. Regardless of the risk level, these lifestyle modifications are recommended for all women:

- Cigarette smoking cessation
- 30 minutes physical activity most days
- Heart-healthy diet
- Weight maintenance/reduction
- Evaluation and treatment of depression

CDC's Wisewoman program

The mission of CDC's Wisewoman program is to provide low-income, under- or uninsured 40- to 64-year-old women with the knowledge, skills, and opportunities to improve diet, physical activity, and other lifestyle behaviors to prevent or delay cardiovascular and other chronic diseases.

WISEWOMAN provides these additional services:

- Screening for chronic disease risk factors
- Dietary, physical activity, and smoking cessation interventions
- Referral and follow-up as appropriate

For more information on how you can take advantage of these services, visit www.cdc.gov/wisewoman/index.htm.

Source: Centers for Disease Control and Prevention. Available at: www.cdc.gov/dhdsp/announcements/american_heart_month.htm. Accessed Feb. 15, 2007.