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Subjects with elevated LDL cholesterol and metabolic syndrome benefit from supplementation with soy protein, phytosterols, hops *rho* iso-alpha acids, and *Acacia nilotica* proanthocyanidins

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BACKGROUND: Metabolic syndrome is associated with increased cardiovascular disease (CVD) risk, a risk that is significantly increased when accompanied by elevated low-density lipoprotein cholesterol (LDL-C). Whereas lifestyle therapies are the initial intervention of choice for both of these risk factors, it has not been clearly determined that this approach is efficacious when they occur concomitantly.

OBJECTIVE: To evaluate effects of supplementing a lifestyle program with a medical food and nutraceutical in individuals with metabolic syndrome and elevated LDL-C.

METHODS: We conducted a subgroup analysis of a 12-week, randomized trial in adults with metabolic syndrome; data from those with LDL-C $\geq$ 160 mg/dL were analyzed. Control-arm subjects were instructed to consume a modified Mediterranean-style, low-glycemic-load diet (MED, n = 12). Treatment-arm subjects received a phytochemical-enhanced diet (PED, n = 12) consisting of the same low-glycemic-load diet plus a medical food containing soy protein and plant sterols and a nutraceutical containing hops *rho* iso-alpha acids and acacia proanthocyanidins. All subjects received identical aerobic exercise counseling.

RESULTS: At 12 weeks, mean weight loss did not differ between arms. However, the PED arm exhibited greater improvement than the MED arm ($P < .05$) in total cholesterol, LDL-C, non−high-density lipoprotein cholesterol (non-HDL-C), cholesterol/HDL-C, triglyceride/HDL-C, apolipoprotein (apo) B, apo B/apo A-1, homocysteine, total LDL particle number, and large HDL particle number. All individuals in the PED arm but only one third in the MED arm achieved LDL-C levels < 160 mg/dL.

CONCLUSION: Individuals at high CVD risk benefit from a soy/phytosterol containing medical food and phytochemical supplemented lifestyle program.

Metabolic syndrome is characterized by visceral adiposity (high waist circumference), insulin resistance (elevated fasting glucose), atherogenic dyslipidemia (low high-density lipoprotein cholesterol [HDL-C] and high triglyceride [TG] levels), and blood pressure (BP) elevation.[1,2] It is associated with a proinflammatory and prothrombotic state and confers a substantial increase in risk for cardiovascular disease (CVD) that is independent of other common risk factors, including age, sex, serum cholesterol levels, and smoking.[3]

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Elevated low-density lipoprotein cholesterol (LDL-C) is a major independent risk factor for CVD that carries a relative risk comparable with that associated with isolated metabolic syndrome.[3] The coexistence of metabolic syndrome and elevated LDL-C magnifies the risk of CVD. Campbell et al[4] reported that men without metabolic syndrome with LDL-C ≥160 mg/dL had more than double the risk of coronary artery calcification than those without metabolic syndrome with LDL < 160 mg/dL (odds ratio = 2.29); men with metabolic syndrome and LDL-C ≥160 mg/dL had a more than 4-fold increased risk (odds ratio = 4.21). Similarly, menopausal women with metabolic syndrome and elevated LDL-C had approximately six times greater risk of atherosclerosis (as measured by carotid intima-media thickness) than those with normal LDL-C.[5] Comparable results have been reported for Japanese subjects with elevated LDL-C.[6] In a population-based study in Denmark, the risk of events such as cardiovascular death, ischemic heart disease, and stroke was shown to be approximately the sum of the risks conferred by metabolic syndrome and elevated LDL-C.[3]

Given the rapid increase in the prevalence of metabolic syndrome and the growing burden it places on health-care resources, intensive lifestyle modification has become a major focus in efforts to prevent CVD associated with metabolic syndrome. Accordingly, the National Cholesterol Education Program and the American Heart Association recommend modification of diet and exercise as first-line therapy for metabolic syndrome. Adoption of a Mediterranean-style diet, which is high in plant-based foods and monounsaturated fatty acids, has been shown to reduce CVD risk and inflammation associated with metabolic syndrome.[7-9] Such a diet provides relatively high levels of phytochemicals often in short supply in typical American diets.

We postulate that enhancement of a Mediterranean-style diet with specific phytochemicals would lead to further improvements in outcome. We reported that compared with the American Heart Association Step 1 diet, a Mediterranean-style, low-glycemic-load diet supplemented with soy protein and phytosterols led to greater improvements in lipid markers (cholesterol/HDL-C and TG/HDL-C), BP, and the Framingham 10-year CVD risk score among overweight and obese postmenopausal women with hypercholesterolemia.[10]

Subsequently, we found that specific phytochemicals, including *rho* iso-alpha acids from hops (*Humulus lupulus* L.) and proanthocyanidins from acacia (*Acacia nilotica*), increased insulin sensitivity in 3T3-L1 adipocytes (manuscript in press). Further studies in *db*/*db* mice revealed that at a ratio of 5:1, the combined phytochemicals reduced both glucose and insulin levels by a similar level of magnitude as metformin and rosiglitazone (manuscript in preparation).

Recently, we reported results of a randomized trial comparing a modified Mediterranean-style low-glycemic-load diet to the same diet enhanced with phytochemicals by provision of a medical food containing soy protein and phytosterols and a nutraceutical containing a 5:1 ratio of hops *rho* iso-alpha acids and acacia proanthocyanidins.[11] Individuals who received the enhanced diet had significantly greater improvements in lipid markers of CVD risk than those who received the diet alone. Additionally, nearly twice as many individuals on the enhanced diet had net resolution of metabolic syndrome by study end.[11] Given the dramatically increased risk of CVD among individuals with both metabolic syndrome and elevated LDL-C, we conducted a post-hoc subgroup analysis of this trial, by using the Adult Treatment Panel (ATP)-III criterion for high LDL-C (≥160 mg/dL), to identify high-risk individuals.

Methods

Subjects

Subjects presented here were a subset of individuals with LDL-C ≥160 mg/dL who participated in a previous study.[11] The parent study was open to men and women from 25 to 80 years of age with metabolic syndrome and hypercholesterolemia. Eligibility criteria included body mass index (BMI) ≥27 kg/m^2, TG ≥150 and <400 mg/dL, LDL-C ≥130 mg/dL, and at least two of the following four criteria: (1) waist circumference >35 inches (women) or >40 inches (men), (2) HDL-C <50 mg/dL (women) or <40 mg/dL (men), (3) BP ≥130/85 mm Hg and <155/95 mm Hg or currently receiving medication for diagnosed hypertension, and (4) fasting glucose ≥100 mg/dL and ≤126 mg/dL. Key exclusion criteria included involvement in a weight-loss program leading to ≥10% body weight loss within the previous 6 weeks, nonsteroidal anti-inflammatory drug use ≥3 days/week in the previous 4 weeks, use of blood glucose or cholesterol-lowering agents or corticosteroids in the previous 12 weeks, or a history of chronic illness. The Copernicus Group Independent Review Board approved the study and informed consent was obtained from all participants prior to study initiation.

Study design

This was a randomized, 12-week, open-label, 2-arm trial. All participants were instructed to follow a modified Mediterranean-style, low-glycemic-load diet (MED) and to engage in 150 minutes of aerobic exercise each week. The diet was not caloric restricted because it was not designed to be a weight-loss program. Participants were randomized to one of two arms (stratified by sex): individuals in the MED arm consumed the modified Mediterranean diet only and those in the phytochemical-enhanced diet (PED) arm additionally received a combination of soy protein and plant sterols in a powdered beverage form of a medical food and a nutraceutical tablet containing a 5:1 ratio of *rho* iso-alpha acids and acacia proanthocyanidins, each taken twice daily. Ingredients and main nutrient core of the