Metabolic Syndrome: Soybean Foods and Serum Lipids

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Metabolic syndrome is a cluster of coronary heart disease (CHD) risk factors of which central obesity, insulin resistance, increased triglycerides/decreased HDL cholesterol, and hypertension are major cardiovascular risk factors. The educational objectives of this review are to describe hypocholesteromic effects from soybean foods. Early Italian observations indicated that isolated soy protein lowered total cholesterol, especially the LDL component, in humans with elevated serum lipids. Whole soybeans, with their major phytoestrogen inflavones (genistein, daidzein, and glycetin) intact, are known to decrease both total and LDL cholesterol. Major early reviews, meta-analyses, and clinical trials in hyperlipidemic humans indicate a predictable range of decreases in serum lipids: total cholesterol (10–19%), LDL cholesterol (14–20%), and triglycerides (8–14%). Recent, large, randomized trials in postmenopausal women indicated that a soy protein component induces significant increases in HDL cholesterol. Therapy for metabolic syndrome must first be patient education, especially for predominant U.S. minority groups (Afro-, Latino-, and Native Americans). The four major preventive health educational facts necessary to reduce CHD/metabolic syndrome must now recognize that whole soybeans are abundant sources of: 1) vegetable protein, 2) high soluble fiber content, 3) virtual absence of saturated fat, though high in polyunsaturated fats, and 4) major phytoestrogens.

Key words: metabolic syndrome ■ obesity ■ hypertension ■ coronary heart disease ■ hypercholesterolemia ■ HDL cholesterol ■ LDL cholesterol ■ triglycerides ■ Kupperman menopausal index ■ postmenopausal women ■ soybeans ■ isolated soy protein ■ isoflavones ■ genistein ■ daidzein ■ glycetin ■ Afro Americans

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African Americans have the highest overall mortality rate and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Recent guidelines from the National Cholesterol Education Program (NCEP): Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) indicate that lowering of LDL cholesterol become the primary target in reducing coronary heart disease (CHD). Mounting evidence indicate that elevated LDL cholesterol is a major risk factor in developing CHD, and that the hypercholesterolemia tends to cluster with other cardiovascular risk factors.[1]

This clinical cluster, commonly known as metabolic syndrome, has been defined by the ATPIII as: 1) abdominal obesity (waist circumference >102 cm in men and >88 cm in women), 2) triglycerides >150 mg/dL, 3) HDL cholesterol <40 mg/dL in men and <50 mg/dL in women, 4) fasting glucose >110 mg/dL, 5) hypertension (systolic blood pressure [SBP] >130 mmHg or diastolic blood pressure [DBP] >85 mmHg. The prevalence of metabolic syndrome, as estimated 10 years ago from the noninstitutionized U.S. population, was 22.8% (men) and 22.6% (women). Major findings in the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) indicate that metabolic syndrome was present in 4.6%, 22.4%, and 59.6% of normal-weight, overweight, and obese U.S. adults.[2]

George Washington Carver, who postulated 70 years ago numerous health benefits from soybeans, peanuts, and sweet potatoes,[3] may have suggested that the increased LDL cholesterol, especially in high-risk minorities, may well be helped with the soybean foods. Soybeans contain high-quality protein (as assessed by the FDA's "Protein Digestibility Corrected Amino Acid Score"), soluble fiber, the "good" unsaturated fat, and several classes of anticarcinogens (protease inhibitors, phytosterols, saponins, and isoflavones). The isoflavones are heterocyclic phenols structurally similar to the estrogenic steroids—frequently termed phytoestrogens because of their abili-

ty to exert estrogen-like effects. Major isoflavones include genistein, daidzein, and glycetin. These compounds are usually identified in mg/g of soy protein. Isoflavones, which are excellent antioxidants, have more affinity for the estrogen receptor beta (ERB) than the estrogen receptor alpha (ERA). This helps to explain their selective tissue effects.

To reduce one risk factor for CHD within metabolic syndrome (i.e., increased LDL cholesterol), the cholesterol-lowering properties of soy foods should be further investigated in populations at high risk for metabolic syndrome. The ATPIII specifically recommends a multifaceted approach that emphasizes low-saturated fat diets combined with plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10–25 g/day), weight reduction, and increased physical activity.

The medical educational objectives are first to educate physicians as to the cholesterol-lowering properties of soybean foods and to provide a chronologic review of published mechanisms of action. The first suggestion that soy protein lowered serum cholesterol came from six Iowa male prison inmates in 1967 with an ensuing lapse of 15 years[4-9] before meaningful human trials were again reported (Table 1).

REVIEWS (1991–1998)

In 1991, Sanchez[10] tried to explain these documented hypocholesterolemic effects of soy protein by suggesting that soy protein contains higher amounts of arginine and glycine than casein (animal protein) and that these amino acids induce a low postprandial insulin/glucagon ratio in both hypercholesterolemic and normocholesterolemic subjects. (Casein is known to produce a high postprandial insulin/glucagon ratio, an effect that augments atherogenesis.) Their data suggest that control of cholesterol by insulin and glucagon may be regulated by these dietary plasma amino acids. Later that year, Carroll reviewed a small number of clinical trials and numerous laboratory studies on soy and its cholesterol-lowering properties. Brief clinical observations indicated that soy protein (either alone or when added to the diets) lowered both total and LDL cholesterol by approximately 20% and that hypertriglyceridemia subjects experienced a decrease in serum triglycerides.[11]

Concomitant clinical observations spanning 20 years involving over 1,000 Italians with raised serum cholesterol indicates that textured vegetable protein (soy-based) induces a significant hypocholesterolemia, especially evident in Fredrickson type IIA.[12] Anderson[13] reported a meta-analysis of 38 controlled clinical trials to examine the relationship between soy protein consumption and serum lipid concentrations in humans. In most studies, the intake of energy, fat, saturated fat, and cholesterol was similar in subjects that ingested control and soy-containing diets. Soy protein intake averaged 47 g per day. Soy protein produced the following net changes in serum lipid concentration when compared to control diets:

1) Soy protein decreased total cholesterol 23.2 mg/dl (0.6 mmol/l) = 9.3%

2) Soy protein decreased LDL cholesterol 21.7 mg/dl (0.5 mmol/l) = 12.9%

3) Soy protein decreased triglycerides 13.3 mg/dl (0.15 mmol/l) = 10.5%

4) Soy protein ingestion was accompanied by a nonsignificant increase in HDL cholesterol of 2.4%

5) Changes in serum cholesterol and LDL concentrations were directly related to initial serum cholesterol ($p<0.001$)

Table 2 summarizes studies (University of Illinois, 1993–1998) using soy foods in humans with elevated serum lipids.[14-17]

A small (French) study involving male smokers (n=12) with normal lipid profiles was entered into an eight-week trial of soybean oil (mixed with butter) and normal butter.[18] The phytosterols were purified from soybean oil unsaponificable matter and mixed in butter during processing to final concentrations of 1.07 g/100 g butter. Subjects were then randomized to four weeks of either soybean butter or normal butter in traditional French diets then crossed over to the other diet. Their results indicated the soy butter decreased both the total and LDL cholesterol ($p<0.001$) even in normal males.

Kurowska,[19] in a family practice setting in London, Ontario, studied 17 men and 17 women who had increased total and LDL cholesterol (but were healthy otherwise). A three-treatment crossover trial determined the effects of substituting soybean products for cows' milk. Subjects were randomized to one of the following three diets for four weeks each and washed out for two weeks between each diet. The treatments were: 1) normal diet with cows' milk products, 2) normal diet with soybean products, and 3) combination of skim milk/soy oil. Each diet contained 31 g protein and 18 g fat in each diet group. Their results suggest that the diets had no effect on body weight, body mass index, or levels of apolipoproteins B and A. However, HDL cholesterol was increased (mean 9%), and the LDL/HDL cholesterol ratios decreased (mean 14%) during soybean diets. Significant decreases in total cholesterol results primarily from a decrease in LDL cholesterol. In 24 subjects with the highest baseline values, the soybean diet reduced LDL cholesterol (mean 11%),

decreased LDL/HDL ratio (mean 19%), increased HDL cholesterol (mean 9%), but did not significantly alter triglycerides. Investigators found that soybean foods reduced both the DBPs and SBPs in men but not in women.

Soy Supplements: Studies in Normal and Perimenopausal Women

Crouse[20] studied 156 healthy subjects (males and females) to compare the effects of casein and soy protein containing various amounts of isoflavones on plasma concentrations of lipids and lipoproteins. This nine-week randomized trial compared casein 25 g per day to 25 g/day of isolated soy protein (ISP). The ISP contained isoflavones at four different levels (27 mg; 37 mg; 62 mg; or ethanol-extracted soy proteins, which contained only 3 mg). All isoflavones quantities were expressed as their aglycone equivalent. The study needed 30 participants per group to have 95% power to detect a 6% relative change in LDL cholesterol levels among groups. Therefore, there were 5 groups with 31 subjects per group. Investigators stated that baseline entry LDL levels ranged from 3.62 mmol/L (140mg/dL) to 5.17 mmol/L (200 mg/dL) while on a National Cholesterol Education Program Step-1 diet for one month prior to randomization. Diets were equivalent with respect to percentage of daily energy: 15% protein; 56% carbohydrates; and 32% fat, which contained 9% saturated, 12% monounsaturated, and 12% polyunsaturated fats. The results indicated that:

1) There was a 3-mmHg decrease in DBP in women receiving ISP-62 mg isoflavones ($p<0.04$), but there was no change in blood pressure in men.

2) ISP-62 mg isoflavone decreased total cholesterol by 4% (241.2 to 231.7 mg/dL).

3) ISP-62 mg isoflavone decreased LDL cholesterol by 6% (164.7 to 154.5 mg/dL) in both men and women.

4) There were no significant effects on either triglycerides or HDL cholesterol.

Subjects were thereafter subdivided in two groups depending on entry LDL levels. There were 70 subjects with high-LDL cholesterol; dose-dependent changes of ISP-62 and ISP-37 isoflavone were: ISP-62 mg isoflavones had the following effects: 1) total cholesterol decreased by 9% (261–237 mg/dL), 2) LDL cholesterol decreased by 10% (260–240 mg/dL), and 3) no effect on HDL cholesterol.

Table 1. Early Clinical

Source	Study Population
Hodges, RE, et al. *Am J Clin Nutr.* 1967;20:198-208.	Six male Iowa prison inmates had a 14-day metabolic baseline period prior to study.
Goldberg AP, et al. *Atherosclerosis.* 1982;43:355-368.	Twelve type-IIA hypercholesterolemic and four normals stabilized on NIH low-fat diet x six weeks.
Fumagalli R, et al. *Atherosclerosis.* 1982;43:341-353.	Seven type-II Italian hyperlipoproteinemic subjects studied as inpatients.
Kolb S. & Sailer D. *Nutr Report Internat.* 1984;30:719-724.	Fourteen German inpatients (11 type-IIA and three type-IIB) had 10 females and four males.
Verrillo A, et al. *Atherosclerosis.* 1985;54:321-331.	Italian outpatients (45 type-IIA and 21 type-IIB enrolled for four-month study.
Shorey RL, et al. *Am Diet Assoc.* 1985;85:1461-1465.	Twenty-two male and nine female outpatients with mild hypercholesterolemia were studied.

The ISP-37 mg isoflavone had similar effects: 1) total cholesterol decreased by 8% (260–240 mg/dL), 2) LDL cholesterol decreased by 8% (182–165 mg/dL), and 3) no effect on HDL cholesterol.

There was a small decrease in LDL cholesterol even from the 3-mg isoflavones.

When a gender subset of postmenopausal women was considered, those that received 62-mg isoflavones had reductions of total cholesterol (7%) and LDL cholesterol (8%) when compared to casein but no change in HDL cholesterol or triglycerides.

Washburn[21] entered 51 perimenopausal women as outpatients (ages 45–55 years) into a randomized, double-blind crossover trial for 18 weeks. Subjects were randomized to one of three treatment groups, then crossed over to the other therapies (six weeks per treatment). Soy protein supplements (not food) were supplied in powder form as follows: group 1—20 g complex carbohydrates containing no phytoestrogens, group 2—20 g soy protein supplement containing 34 mg phytoestrogens once daily, and group 3—20 g soy protein supplement containing 34 mg phytoestrogen in split doses.

All the diets were isocaloric, and women were given the supplemental powder, which was to be mixed with their food. The results in this short-term study indicated that:

1) Significantly lower levels of serum total cholesterol (decrease of 6%) were observed in both soy diets when compared to the carbohydrate diet.

2) LDL cholesterol was decreased by 7.5% in both soy diets, but there was no change in HDL cholesterol.

3) The DBP was significantly lower (decrease of 4.9 mmHg) in the split soy diet, when compared to the carbohydrate diet. Night sweats and hot flash severity (not frequency) were decreased in the split dosage group.

A major primate study helps to identify possible mechanisms of action.[22] Young, male cynomolgus macaques monkeys were fed moderately atherogenic diets for three months—thereafter, randomly assigned to one of three groups. The source of protein in each dietary treatment was: 1) casein/lactalbumin, n=27; 2) Supro 670-HG (soy + therapy which contained genistein 1.10 mg and daidzein 0.37 mg per gram of isolate, n=27; and 3) Supro-670-IF (containing genistein 0.12 mg and daidzein 0.05 mg per gram of isolate, n=28. Amounts of calcium and phosphorus were equal in all the diets. After the three-month baseline period, the diets were fed for 14 months during which

Observations (1967–1985)

	Study Design	**Clinical Results**
	No animal protein in diets; only vegetable sources in form of isolated soy protein (ISP). Time of trial was 24 weeks.	ISP decreased serum cholesterol despite source of carbohydrates (refined sugars or starch). Refined sugars increased triglycerides while complex CHO's decreased triglycerides.
	Subjects were randomly assigned to diets containing 90% soy protein or diets with animal protein.	ISP decreased cholesterol an additional 4–10% in hypercholesterolemia; TC decreased 3.5%, LDL-C decreased 6.0%, and apoprotein B decreased 9.8%. Soy protein (n=12) lowered LDL-C better than animal protein.
	Subjects were given either textured soy protein (three weeks) or low-fat diet (three weeks).	Six subjects had decreased TC by 10–28%, most evident in LDL-C. The hypocholesterolemic effects could not be explained by fecal excretion of bile acids or neutral steroids.
	After a four-week baseline period, five-to-seven slices of crispbread, which contained 50–60 g. Soy protein was added to diet.	At 30 days the crispbread decreased TC 27 mg/dl (8%) and LDL-C 46 mg/dl (16%).
	Subjects given diets with soy protein alone (85%) or diets augmented with soy protein added to low fat/cholesterol diet.	In type-IIA (n=39), the soy protein alone decreased TC 31.5%, LDL-C 43.4% and in type-IIB (n=20), the soy protein decreased TC 30.3% and LDL-C 31.7%
	Subjects given 25 g soybean polysaccharide (75% CHO, 12% protein, 2% fat, 74% fiber) or placebo starch in their diets.	During this eight-week, crossover, blind study, the soybean polysaccharide diet decreased TC 28 mg/dl (11%) with no change in HDL-C in the 31 subjects.

blood samples were collected at assigned intervals. At the end of 14 months, the youngest 11 monkeys were necropsied (according to Federal Government Guidelines), and atherosclerosis evaluations and testicular weights were analyzed. The results indicated that: 1) The soy+ group had significantly lower total and LDL/VLDL cholesterol when compared to the other two groups ($p<0.001$); 2) The soy+ group had increased HDL cholesterol when compared to the other two groups ($p<0.001$); 3) Morphometric and angiochemical studies were done to quantify atherosclerosis. Coronary artery atherosclerotic lesions were smallest in the soy+ group (90% less than the casein group and 50% less than the soy- group; 4) Data on intimal area (lesion size) for coronary arteries, abdominal aorta and left carotid bifurcation, left common carotid, and left common iliac arteries indicated that the average intimal area (atheromatous lesion size) was smallest in the soy+ group; 5) Testicular weights were unaffected by the phytoestrogens.

An Australian study (placebo-controlled, crossover trial) in healthy women (perimenopausal and menopausal) employed isoflavone tablets (80 mg isoflavone, of which 45 mg was genistein) and placebo to measured systemic arterial compliance within the main conduit arteries.[23] Investigators estimated arterial elasticity by frequent automated arterial pressure measurements at five- and 10-week intervals. Isoflavones (80-mg tablets) improved systemic arterial compliance, and the mean difference (placebo = 0.81 ± 0.4 and isoflavone = 0.99 ± 0.54) was highly significant (paired t-test analysis, $p=0.011$). Placebo had no effect on systemic arterial compliance, while the isoflavone group experienced a 26% improvement in arterial compliance. The authors speculated that the smooth muscle layer within the vessel wall may be under influence of endothelial cell events, and that soybean isoflavones stimulate endothelial-related arteriolar relaxation.

Cassidy,[24] in studying 15 healthy (inpatient) nonvegetarian premenopausal women, provided evidence that soybean protein may have both agonist (stimulation) or antagonist (inhibitory) effects on estradiol 17 Beta receptors. Subjects were assigned to one of three groups receiving: 1) 60 g textured soybean protein (TSP) containing 45 mg conjugated isoflavones, n=6); 2) 28 g textured soybean protein containing 23 mg conjugated isoflavones, n=6); and 3) 50 g miso (fermented soybean paste) which contains 25 mg unconjugated isoflavones, n=3). Methodological limitations exist in these small numbers, as no diet significantly affected transit time

Table 2. Illinois Clinical Trials:

Investigator/Year	Method/Material
Potter SM, et al. *Am J Clin Nutr.* 1993;58:501-506.	Thirty-nine males (inpatients VA Hospital) control on NCEP Step-1 diet. Randomization: four weeks each of following: 1) soy flour with 50% protein and 2 g fiber 2) soy protein/soy cotyledon fiber 3) nonfat dry milk/casein 4) ISP/cellulose
Bakhit RM, et al. *J Nutr.* 1994;124:213-222.	Twenty-one male outpatients were controlled on two weeks of NCEP Step-1 diet; then randomized to one of four RX for four weeks each: 1) ISP/cellulose 2) ISP/soybean cotyledon fiber 3) Casein/soybean cotyledon fiber 4) Casein/cellulose
Baum JA, et al. *Am J Clin Nutr.* 1998;68:545-551.	Sixty-six postmenopausal females (BMI range 26.7–29.1) were entered into a six-month study. There were 24 with increased baseline TC. Subjects were stabilized and maintained on NCEP Step-1 diet during trials of: 1) ISP56 mg total (1.39 mg) isoflavone/40 g protein 2) ISP90 mg total (2.25 mg) isoflavone/40 g protein 3) Casein+nonfat dry milk/no isoflavone (control)
Potter SM, et al. *Am J Clin Nutr.* 1998;68(Suppl):S1375-S1379.	Bone mineral content and density of lumbar spine (L1-4), femur and total body measured by dual-energy x-ray absorptiometry at entry and 24 weeks.

ISP: isolated soy protein, TC: total cholesterol, HDL-C:

over complete menstrual cycle. The menstrual transit time during the follicular phase was longer in the miso group (miso= 45.8 ± 5.3 hours; control = 35.1 ± 4.7 hours). These normal premenopausal females exhibited a decrease in total cholesterol in the group receiving with TSP-60 g with 45 mg isoflavones. In addition, the group receiving the higher (TSP-60 g with 45 mg isoflavones) exhibited increased follicular phase length and peak progesterone concentrations delayed ($p<0.01$). Mid-cycle peaks in luteinizing hormone (LH) and follicle stimulating hormone (FSH) were suppressed with 45 mg isoflavonoids. ($p<0.05$). The menstrual cycle effects of soybean protein with intact isoflavones must be evaluated.

CLINICAL RANDOMIZED TRIALS (2000–2003)

Dose responses for varying concentrations of soybean protein were determined in 81 hypercholesterolemic males (ages 23–74, free-living outpatients, Champaign-Urbana, IL) while being maintained on National Cholesterol Education Program Step-1 diet. (<30% energy from fat, <10% saturated fat, and <300 mg cholesterol).[25] Pertinent baseline data included mild hypercholesterolemia (220–300 mg/dL) and the body mass index range 26.4–27.8. After a three-week lead-in period, subjects were randomly assigned to one of five experimental groups. For six weeks, each group received 50 g/day, which included isolated soy protein (ISP; Supro Plus 675 HG with 1.9 mg total isoflavone aglycone units/g protein, Protein Technologies International, St. Louis, MO) and casein (calcium caseinate, Alanate 391; New Zealand Milk Products, Wellington). The five groups received 50-, 40-, 30-, 20-, and 0 g (control) ISP and 0-, 10-, 20-, 30-, and 50 g casein, respectively. Test proteins were given through baked foods and ready-to-mix beverages, and the consumption of foods was monitored five times per week. Primary outcome measurement was change from baseline for each subject, and there were 15–18 males per group. At six weeks, non-HDL cholesterol was reduced in all groups that received ISP. The reduction in total cholesterol was significant at six weeks for the groups that 20-, 30-, and 50-g ISP. The 40-g ISP reduced total cholesterol 0.053 mmol/L (statistically not significant). At week six, no significant changes were found for concentrations of HDL cholesterol, triacylglycerol, apo A-I, or lipoprotein(a) or TC:HDL cholesterol in any group that received ISP. This trial therefore identifies a cholesterol lowering effect with doses as low as 20 g of soy protein/day in this normal-weight, mildly hypercholesterolemic male population.

Studies on Serum Lipids (1993–1998)	
	Result In subjects with hypercholesterolemia (n=26), the three treatments with soy decreased TC at 16 weeks. The ISP/cotyledon fiber group had the most marked decrease in both TC and LDL. The ISP groups lowered apolipoprotein B, but there was no effect on HDU-I HDL-C.
	A repeated ANOVA performed on all (n=21) subjects indicated that dietary RX did not influence serum lipids. In subjects with elevated initial TC (n=11), both ISP protein RXs lowered TC when compared to the two casein groups ($p<0.05$).
	Non-HDL-C in both ISP56 and ISP90 groups was reduced compared to control ($p<0.05$), but the TC was not significantly changed. HDL-C was increased in both ISP56 and ISP90 groups ($p<0.05$). Ratio of TC to HDL-C was decreased in ISP56 and ISP90 when compared to control. Mononuclear cell LDL receptor mRNA was increased in subjects receiving ISP56 and ISP90.
	Within the ISP90 group, there was a significant increase in both bone mineral content and density at 24 weeks.
high-density cholesterol, LDL-C: low-density cholesterol	

Another randomized, double-blind, placebo-controlled study from Brazil[26] examined the change in menopausal symptoms and cardiovascular risk factors in 80 postmenopausal women (ages 45–55). These subjects all had to be in menopause at least 12 months, and no subject had been treated with hormonal or lipid lowering therapies within the previous 12 months. Subjects were randomized to either:

1) Isoflavone group (n=40)—Each capsule was 83.3 mg and was composed of soy protein 50.3 mg (60%) and isoflavone 33.3 mg (40%), which consisted of genistein (23.3 mg), daidzein (6.2 mg), and glycetin (3.8 mg).

2) Placebo group (n=40)—Each capsule was 83.3 mg and was composed of purified soy protein 50.3 mg (without any kind of isoflavone) and glucose 33.3 mg.

The 80 women completed the five-month study, which included screening, baseline, and four months of treatment. At the end of the study, menopausal symptoms were assessed; BMI, blood pressure, lipids, hormone levels, and transvaginal sonography were determined; and these data compared to baseline. The Kupperman index was used to evaluate 11 menopausal symptoms: 1) hot flashes (vasomotor), 2) paresthesia, 3) insomnia, 4) nervousness, 5) melancholia, 6) vertigo, 7) weakness, 8) arthralgia/myalgia, 9) headache, 10) palpitation, 11) formication (the sense of feeling ants or insects on the skin). To calculate the index, each symptom is graded (0–3) for no, slight/moderate, or severe complaints. Symptoms are rated as follows: hot flashes (x4) paresthesia (x2), insomnia (x2), nervousness (x2), and all others (x1). Therefore, the highest potential score is 51. The score of hot flashes was based on number of complaints per day: slight (<5), moderate (5–10) or severe (>10).

Evaluations of cardiovascular disease risk indicated that both total and LDL cholesterol were significantly decreased in the isoflavone group compared with baseline or placebo group. The HDL cholesterol and triglycerides increased in both groups. (control n=40, isoflavone (n=40). Isoflavones decreased total cholesterol (mean ± SEM) by 26.8 ± 5.8 ($p<0.001$) and LDL cholesterol by 13.3 ± 4.6 ($p<0.001$). HDL cholesterol increased in both groups by 4 ± 1.5 ($p<0.001$ paired t-test, two-tailed.) Triglycerides were modestly elevated in both control (10.3 ± 6.2) and isoflavone groups (6.5 ± 15). During the four-month treatment period, the menopausal symptoms in the isoflavone group were significantly less than placebo group. The Kupperman menopausal index, decreased approximately 20 points within the isoflavone group, was accompanied by marked improvements in climacteric signs and symptoms.

Phytoestrogens have recently been linked to improved bone health in postmenopausal women in anecdotal, lay press, and agromedical literature. Estrogen consumed in foods of postmenopausal females has long been suggested as playing a role in the decreased osteoporosis in Chinese, Japan, and other Asian countries.[27] Recent reports (Women's Health Initiative Investigators) in postmenopausal women of serious HRT-induced, adverse side effects from especially the oral estrogen/progesterone combinations[28] have resulted in decreased prescriptions for Prempro (66%) and Premarin (33%) during the six months January–June 2003 when compared to January–June 2002.[29]

A large study (n=650) of Hong Kong southern Chinese females has correlated soy food intake using food frequency tertiles and documents these effects on bone health.[30] There were nine major sources of soy foods evaluated by low, medium, and high daily intake. Bone mineral density (BMD) was measured at lumbar spine (L2–4), femoral neck, trochanter, Ward's triangle, and total hip using dual-energy x-ray absorptiometry in 293 premenopausal and 357 postmenopausal women. BMD measurements of the three groups of phytoestrogen intakes were evaluated after controlling for age, weight, height, and years since menopause, smoking, alcohol, calcium intake, and previous hormonal replacement therapy (only 4.5% within postmenopausal women group had previous HRT). Their data indicate that postmenopausal females consuming higher daily intake of soy foods had increases in bone mineral density at three characteristics locations: Lumbar spines 2–4, total hip, and femoral head (Ward's triangle). Ward's triangle, an area of radiolucency between primary trabecular patterns within the femoral neck, is a particularly prone to osteoporosis in menopausal women. Though soybean foods appear to increase BMD within these three anatomic areas in postmenopausal Chinese women, there were no detectable effects in premenopausal women presumably because there was still enough circulating endogenous estrogen. Evidence exists that soybean sources of estrogen in postmenopausal women induce positive effects in bone physiology. This results in a decreased loss of bone because soybean foods slow the resorption of bone. Women with the highest intake of isoflavones had significantly lower levels of serum PTH, osteocalcin, and urinary NTx excretion when compared to the low isoflavone intake group.

Two Canadian studies involving unique populations of hyperlipidemic Caucasians reported the

effects of soy foods on elevated serum lipoproteins. The first[31] involves 41 subjects, whose mean age was 62 and mean BMI=25.3. No subject had clinical or biochemical evidences of diabetes, liver, or renal disease. All subjects had elevated LDL cholesterol (>4.1 mmol/L). The three diet phases included: 1) Control phase—low fat dairy, egg substitution, low fat cheeses, and protein foods of the NCHEP Step-II diet (<7% energy from saturated fats and <200 mg/d of dietary cholesterol) 2) Low isoflavone phase, and 3) High isoflavone phase. The major isoflavones were genistein, daidzein, and glycetin, and the approximate amounts obtained in the low phase were 10 mg/d and 73 mg/d in the high phase. Sources of soy protein and isoflavones were soy milk (low fat 0.1% fat), soy hot dogs, breakfast links, cold cuts, and tofu burgers and nuggets made from soybeans. Their results indicated that there was over 96% compliance to the diets in all three phases. There was no significant difference in blood lipid responses between the low- and high-phase isoflavone groups, but both exhibited significantly more effects than the control phase. More specifically, there were significant decreases in total cholesterol (7%) and LDL cholesterol (7.1%). Both soy isoflavone phases decreased the oxidized LDL levels and homocysteine levels (6%). The high isoflavone group experienced a 8% decrease in SBP in men but not women.

A follow-up outpatient (three-month) study from the same Toronto center has been completed in 46 subjects. The randomized, clinical trial was designed to compare low-fat foods and lovastatin 20 mg/day in hyperlipidemic Caucasians.[32] There were 25 males and 21 postmenopausal women and only one black female. The mean age was 59 (range 36–85 years), mean body mass index (BMI) was 27.6 ± 0.5 (range 20.5–35.5). Mean LDL cholesterol was >158 mg/dL or >4.1 mmol/L. No subject had a history of heart disease, diabetes, renal or liver disease, and no subject was receiving lipid-lowering agents. (Twenty-one subjects had been treated with oral statins, but all had discontinued these medications two weeks prior to study and five subjects received antihypertensive medications throughout the study.) There was only one cigarette smoker. All subjects received the NCHEP Step-II diet for one month prior to study entry. Subjects were randomized to either: 1) a diet very low in saturated fat, based on milled whole-wheat cereals and low-fat dairy foods (n=16; control) 2) same diet plus lovastatin, 20 mg/d (n=14), or 3) diet high in plant sterols (dietary portfolio) derived from enriched margarines (1.0 g/1,000 kcal), soy protein (21.4 g/1,000 kcal), viscous fibers (9.8 g/1,000 kcal), and almonds (14 g/1,000 kcal; n=16). The control, statin, and dietary portfolio groups had mean (SE) decreases in LDL cholesterol of 8.0 ± 2.1% (P=0.002), 30.9 ± 3.6% (P<0.001), and 28.6 ± 3.2% (P<0.001), respectively. The reductions in C-reactive protein were 10 ± 8.6% (control), 33.3 ± 8.3% (statin group) and 28.2 ± 10.8% (dietary portfolio). Hence, there was no significant difference in efficacy between the statin group and dietary portfolio group, yet both diets were superior to the control diet. Both Canadian studies confirm soybean foods, often-reported serum-cholesterol-lowering effects, even within in this unique Caucasian population (no biochemical or clinical indicators of diabetes, liver or renal disease). Preventive primary care must now mandate that soy foods, which are known to lower the bad LDL cholesterol, become a primary intervention for elevated cholesterol before our polypharmacy approach.[33]

Call-to-Action: Community Coordination to Reduce Metabolic Syndrome

The full preventive potentials of soybeans and their derivatives can be maximized by including them in comprehensive lifestyle behavior changes. The Food and Drug Administration (October 1999) recognized the benefits of soy foods on cardiovascular diseases in its statement that daily consumptions of 25 g of soy protein combined with other lifestyle modulations (i.e., exercise) helps prevent heart disease.[34] The American Heart Association statement on the known modifiable risk factors in heart disease suggests that physicians and healthcare provide encouragement for the incorporation of soy foods into primary preventive therapy for elevations in total and LDL cholesterol.[35] The most frequently documented soybean effect has been the decrease in the total and bad LDL cholesterols, yet soybeans are also an excellent source of dietary soluble fiber which also is known to decrease serum cholesterol.[36]

Metabolic syndrome mandates that each of its five components be approached with diet/exercise as primary preventive therapy. Low-fat, high vegetable/fruits diets (Dietary Approaches to STOP Hypertension—DASH diet) have been shown to reduce both SBP and DBP in Afro-Americans as well as single-drug therapy. Hypertensive black subjects (n=133) within the DASH trial had decreases of 11.4 mmHg in SBP and 5.5 mmHg in DBP.[37] Further restriction of sodium intake within the DASH diet indicated additive hypotensive effect on blood pressure. Blacks exhibited a 12.6 mmHg decrease SBP, yet only a 9.5-mmHg decrease was documented within other ethnic groups. Subjects most responsive to sodium restriction were those with established hypertension, blacks, and women.[38] Comprehensive lifestyle modification (reduced weight, improved fitness, and sodium restriction) on blood

pressure control (PREMIER clinical trial)[39] has also indicated that an additional 4.3-mmHg decrease in SBP occurs within DASH-type food therapy. Hence, physician education must now include pertinent heart-healthy properties of soy foods.

The surgeon general's warning (overweight/obesity) and its Call-to-Action must now incorporate community resources with known dietary therapies that may reduce metabolic syndrome, especially within high-risk minority populations.[40] Governmental surveys (NHANES 2000 and BRFSS 2001) have emphasized our nations' obesity epidemic in the U.S. adult population, but there are dramatic increases in prevalence within the three major minority groups (African-, Mexican/Latino-, and Native Indian Americans.[41-44] The major challenge facing physicians and healthcare providers hinges on our ability to disseminate the known preventive health education to high-risk minority groups in culturally sensitive educational models. Only after recognized ethnic/cultural barriers to diet and exercise lifestyle changes have been identified can we begin to reduce long-term effects of metabolic syndrome. There are no quick fixes to this pandemic, and soy supplements do not offer the solution because they do not possess the same heart-healthy properties as whole soy foods.[45]

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