Background

The major cause of death in the United States and most other developed countries is coronary heart disease (CHD).(2)Modifiable risk factors for CHD include poor serum lipid profile, cigarette smoking, hypertension, obesity, physical inactivity and diabetes mellitus; nonmodifiable risk factors include age, male sex and family history of premature CHD.(36) Perhaps the single most important risk factor is an elevated serum low-density lipoprotein (LDL) cholesterol. LDL cholesterol is almost certain to be the primary agent involved in the development of blood vessel-occluding atherosclerosis.(12) A negative lipid risk factor is an elevated serum high-density lipoprotein (HDL) cholesterol, which appears to have a protective effect and may in fact act to promote the removal of cholesterol that accumulates on the walls of the macrovasculature.(44) With so much attention paid to cholesterol and saturated fat intake, it has been easy to overlook the known fact that the type of protein one consumes also has a major impact on cardiovascular health. It was demonstrated more than half a century ago that animal protein is more atherogenic than plant protein.(26)

The soybean has been receiving increasing attention in recent years from health care providers, biomedical researchers and the lay public alike because of its potential role in the prevention and treatment of a number of chronic diseases, most notably cancer, osteoporosis and CHD.(20,24,28,30) A member of the legume family and a staple of most Asian diets, the soybean has a storied history originating in the northern plains of China several thousand years ago. It reached the New World as ballast in trading ships returning from Asia in the early 19(th) century, and a century would pass before there would be any real interest in producing the soybean as a commercial crop.(46) Today, American farmers account for over half of the world's soybean production, although most of it is used as animal livestock feed here in the U.S. or exported to the rest of the world for human consumption.(46)

What makes the soybean entirely unique is its amazing nutrient profile. Without peer in the plant kingdom, it contains all three macronutrients (protein, carbohydrate and lipid) and a full complement of vitamins and minerals. It is the only vegetable to possess complete protein, with significant essential amino acid content and a high digestibility score.(30) Although relatively high in fat (18% content(46)) as compared to other vegetables, it is easily lower in total fat content than meats and cheese. The unsaturated fat:saturated fat ratio of 85:15(46) and relatively high levels (8% of soy oil) of the w_3 fatty acid linolenic acid(41) give the soybean a superior fat and lipid profile. The soybean is an excellent source of complex carbohydrates and dietary fiber (both soluble and insoluble) as well as vitamins and minerals.(30) The soybean's amino acid profile, lipid profile and carbohydrate component may potentially be responsible for its apparent protective effects on cardiovascular health.

For a long time, the biologically-active compounds found in the soybean were actually cause for avoidance of the legume, many citing anti-nutritive or toxic properties.(4) However, the last fifteen or so years has seen a reversal of earlier convictions and resulted in renewed interest in the non-nutritive component of soybeans as having a positive impact on human health. Soybean phytochemicals of interest include the protease inhibitors, phytic acid and the phytosterols and saponins.(29) Perhaps the most interesting compounds found in the soybean are the isoflavones and lignins, so-called phytoestrogens and unique to the soybean. A large part of the ongoing investigation of the pharmacodynamics and pharmacokinetics of the soybean phytoestrogens is

directed towards elucidating a possible role for them in the prevention and management of CHD. Estrogens have been shown to prevent heart disease in women and may do so by acting at several steps in the atherogenic process.(35)

Animal studies

Experiments conducted in various animal models have shown that consumption of diets containing soy protein result in lower serum total cholesterol as compared to baseline and to diets containing the milk protein casein.(5,6,7,15,32,34,38,49) The cholesterol-lowering effect of soy may be targeted at the LDL fraction.(7,11) Sakono and colleagues found the degree of exogenously induced atherosclerotic lesions of the thoracic aorta to be markedly decreased in hypercholesterolemic rats fed dietary soy protein compared with that in hypercholesterolemic rats fed casein.(42)

Investigations conducted at the Wake Forest University School of Medicine in monkeys have offered a closer look at the effects of soy in animals closely related to humans. One study with crossover design showed that phytoestrogen-intact soy protein (as compared with alcohol-extracted soy protein) significantly reduced LDL cholesterol in both males and females (~30-40% lower), increased HDL cholesterol for females (~15% higher) and lowered total cholesterol:HDL cholesterol ratios (~20% for males and ~5% for females).(6) Another study, in addition to showing lower serum total and LDL cholesterol levels and higher HDL cholesterol levels, also found significant differences in atherosclerotic lesion size in the coronary and peripheral vessels.(5) In artificially-induced (ovariectomized) menopausal monkeys, soy protein compared with casein consumption resulted in favorable plasma lipid and lipoprotein profiles for the former and a decrease in arterial lipid peroxidation.(49)

Human studies

Does soy's beneficial effects on cardiovascular health extend to humans? Several investigations using crossover designs have shown that this question can be answered with an emphatic yes. In hypercholesterolemic individuals, soy protein diets consistently decrease serum total and LDL cholesterol levels when compared with baseline values (before administration of the soy-containing diet) and with diets containing casein.(27,40,45,52) Some studies have shown that soy protein may also increase HDL cholesterol levels.(47,48) Anderson and colleagues, in a widely read meta-analysis of 38 controlled clinical trials, summarized the relation between soy protein consumption and serum lipid concentrations in humans. With an average soy protein intake of 47 g/day, the following net changes were seen in serum lipid concentrations from concentrations reached with a control diet: decrease in total cholesterol of 23.2 mg/dL (9.3%); decrease in LDL cholesterol of 21.7 mg/dL (12.9%); and a decrease in triglycerides of 13.3 mg/dL (10.5%).(3) There was also a nonsignificant 2.4% increase in HDL cholesterol.(3) Data is less consistent for treatment of patients with marginal hypercholesterolemia or hypercholesterolemia already corrected by standard diets before administration of soy products.(45) In fact, changes in serum lipids are highly correlated with initial levels; i.e., the higher the total serum cholesterol at baseline xor achieved with a control diet, the greater the decrease observed upon consumption of a soy-based diet.(3,11)

Possible mechanisms

Certain amino acids (lysine and methionine) are known to be hypercholesterolemic.(11,25,32) The amino acids arginine and glycine, which are found in high levels in the soybean, appear to counteract the hypercholesterolemic effects of lysine and methionine.(11) Animal studies also suggest the presence of other factors in soy protein that may help counteract the effects of hypercholesterolemic amino acids.(11,32)

Consumption of soy protein appears to result in impaired absorption of cholesterol and reabsorption of bile acids.(37) Nagaoka and colleagues found that the fecal excretion of total steroids was significantly greater in rats fed a soy protein peptic hydrolyzate compared with those fed a casein tryptic hydrolyzate.(34) Another study reported similar results as well as a significant inverse correlation between serum total cholesterol and fecal total steroid excretion.(32)

Alteration of endocrine status (insulin:glucagon ratio and serum thyroxine) has also been proposed as a possible mechanism of action.(39,43) A decreased circulating insulin level, due to the actions of the amino acids arginine and glycine, is hypocholesterolemic by preventing the liver from producing cholesterol. Increased plasma thyroxine is associated with decreased plasma cholesterol, and studies have shown that feeding soy protein to laboratory animals results in elevated plasma thyroxine with subsequent decreased plasma cholesterol levels.(11,14,37)

The lipid and carbohydrate components of the soybean likely contribute to its overall hypocholesterolemic and anti-atherogenic effects. Kurowska and colleagues attribute some of the improvement in plasma lipid profile seen in their study of hypocholesterolemic individuals to soy oil.(27) The compounds in the lipid fraction possibly helping to mediate this improvement include the ω_3 fatty acids(13,22,50) and the cholesterol-binding phytosterols and saponins.(29) Dietary fiber has been shown to have moderate hypocholesterolemic effects(21), and the antioxidant phytic acid (inositol-1,2,3,4,5,6-hexaphosphate), found in relatively high concentrations in the soybean, has been proposed as responsible for fiber's multiple health benefits.(18,19)

Perhaps it is the soybean phytoestrogens that are the ultimate source of soy's cardiovascular protective effects, and the work with monkeys comparing the effects of soy protein with and without the soybean phytoestrogens are supportive of such an assertion.(5,6) Nathan and Chaudhuri, in their review of the relationship between estrogens and atherosclerosis, ascribe the benefits of estrogens in cardiovascular health 1) to their ability to favorably alter the lipoprotein profile; 2) to their ability to prevent oxidative modification of low-density lipoprotein; 3) to their direct actions on the vascular endothelium and vascular smooth muscle; and 4) to their ability to alter the reactivity of atherosclerotic vessels and thereby promote vasodilation.(35) The soybean phytoestrogens are diphenolic compounds structurally similar to the hormone estrogen, and as such, have been extensively studied as both estrogen receptor agonists *and* antagonists as well as for their antioxidative properties and ability to affect key enzymes in the signal transduction machinery.(1,8,9,31,51) Kanazawa and colleagues, working with lipoproteins isolated from stroke patients and healthy patients, found that soy protein had protective effects on the peroxidizability of lipoproteins.(23) Considering this ability to prevent LDL oxidation(12,53) and their ability to disrupt important signaling pathways involved in pathophysiological processes (e.g. smooth muscle cell proliferation, platelet aggregation and thrombus formation,

etc.), it is not hard to believe that the soybean phytoestrogens may be able to prevent plaque formation. If considering only their estrogen receptor-dependent actions, the soybean phytoestrogens may be thought of as naturally occurring selective estrogen receptor modulators (SERM), a class of new therapeutic agents that may potentially challenge the supremacy of hormone replacement therapy (HRT) in the prevention and management of various women's health problems.(8,10) In the case of the cardiovascular system, the soybean phytoestrogens are presumed to play an agonist role.

Conclusion

The soybean and soy food products have been demonstrated to have a positive impact on human health and may be dietary preventive/protective factors for a number of chronic diseases with multifactorial etiology, including cancer, osteoporosis and CHD. The evidence for soy's cardiovascular protective effects is convincing; however, there will always be questions that remain to be answered. A study done in rats found that consumption of soy protein (compared with casein consumption) resulted in hypercholesterolemia and actually potentiated lipoprotein susceptibility to peroxidation, and these effects were attributed to amino acid imbalances.(33) Gooderham and colleagues found in their randomized trial comparing men consuming either a soy protein isolate beverage powder or a casein supplement dramatic elevation of plasma isoflavone concentrations upon supplementation in the soy group but absence of significant changes in plasma total and HDL cholesterol.(17) These and other "unexpected" results should remind us that just as the chronic diseases we are trying to understand are multifactorial in etiology and that complex interactions between organism and environment are involved, the nutrient and non-nutrient components of foods we consume do not act in isolation and may have *both* adverse and beneficial effects. Synergistic and perhaps even antagonistic interactions occur among various components, and responses may vary between individuals, or even in the same individual at different times. The bioavailability and pharmacokinetics of biologically active agents of interest are just as important as pharmacodynamical considerations in ultimately determining how the body is affected upon consumption. While traditional Asian soyfoods are derived in large part from the entire soybean, the legume's penetration into the American diet thus far has largely been in the form of isolated components. Future basic and clinical research should take into consideration this fundamental difference between the types of soy food products being consumed by traditional Asian populations and the American public. It is the opinion of this author that the soybean promotes cardiovascular health as well as having protective effects for cancer, osteoporosis and other chronic diseases and that attempts be made to incorporate soy food products into the American diet. Facilitation of this course of action will occur with more publication of articles in mainstream medical journals detailing the benefits of soy consumption and increased accessibility to readily available packaged products, recipes and cookbooks.(16)

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