Soy protein with or without isoflavones: in search of a cardioprotective mechanism of action$^1,2$

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In an article published in this issue of the Journal, Vega-López et al (1) report on a carefully controlled feeding study that they conducted to evaluate the independent effects of soy protein or soy-derived isoflavones on plasma antioxidant capacity and biomarkers of oxidative stress. Prevention of lipid oxidation and, specifically, LDL oxidation is thought to be potentially important for the prevention of atherosclerosis and ischemic heart disease (2). Because no one marker of oxidative stress can provide an accurate picture of either antioxidant status or oxidative stress in an organism (3), the authors measured plasma antioxidant concentrations and a variety of markers of oxidative stress. Despite the finding that plasma total antioxidant performance was modestly increased (by 10%) at the end of the soy-protein phases and that the isoflavones studied had in vitro antioxidant properties, the authors reported no significant effects of the soy diets on the biomarkers of oxidative stress measured. These findings, in conjunction with those of clinical studies showing that soy protein has a substantive effect on blood cholesterol concentrations only in persons with markedly elevated blood cholesterol concentrations (4) and results in clinically meaningful reductions in blood pressure mainly in hypertensive persons (5), temper enthusiasm about the role of soy in reducing the risk of cardiovascular disease (CVD).

Oxidative processes are thought to be important in the initiation and progression of atherosclerosis. The oxidative hypothesis of atherosclerosis is based on the oxidative modification of LDL and phospholipids, which leads to foam cell formation and proliferation, which create an inflammatory state. Current thinking is that antioxidants inhibit lipid peroxidation and, thus, protect against CVD (6). Although this has been the focus of much research, it is possible that other oxidative systems are involved that have not been studied or identified. Recently, interesting data have emerged that may provide clarity about the antioxidant hypothesis. Zheng et al (7) have shown that apolipoprotein A-I (apo A-I), the primary protein constituent of HDL, is a target for myeloperoxidase-catalyzed nitrification and chlorination in vivo and that the myeloperoxidase-catalyzed oxidation of HDL and apo A-I inhibits cholesterol efflux from macrophages. Interestingly, these authors showed that apo A-I enriched in nitrotyrosine and chlorotyrosine was present in human atherosclerotic lesions. Additional studies may provide mechanistic evidence that fulfills the oxidative hypothesis theory by a novel system involving HDL.

It is also possible that antioxidants may exert beneficial effects on other mechanisms important for heart health. For example, antioxidants may enhance endothelial nitric oxide synthase activity. An increase in endothelial nitric oxide synthase coupled with an increase in nitric oxide production in hypercholesterolemic vessels may enhance endothelial function. Evidence indicating that soy protein improves endothelial function, as measured by flow-mediated dilation of the brachial artery (5, 8, 9), supports this possibility.

Historically, epidemiologic observations of diet and CVD in Japan have linked soy-product consumption with a decreased risk of CVD (10). More recently, the Shanghai Women’s Health Study reported that soy-food consumption was associated with a reduced risk of coronary heart disease, especially nonfatal myocardial infarction, in women (11). However, large-scale randomized controlled trials have not consistently shown a beneficial effect of antioxidant supplements on CVD morbidity and mortality endpoints (12). Although these negative results refute the oxidation hypothesis, it is possible that other antioxidants not tested could be involved.

For example, α-tocopherol does not inhibit many of the oxidation pathways in human atheroma, including those mediated by myeloperoxidase-catalyzed halogenation and nitric oxide–derived oxidants. In addition, α-tocopherol and ascorbate do not affect systemic measures of oxidant stress. Thus, soy protein may exert effects via changes in endothelial health or by affecting other oxidative systems. Clearly, additional studies are needed to resolve this issue.

In summary, the benefits of soy—if any—require further investigation to determine the mechanisms responsible for these effects. Until then, it remains prudent to recommend soy products in a heart healthy diet because of their nutritional value and as a healthy substitute for protein sources that are higher in saturated fat and cholesterol.

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REFERENCES


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