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Got soy?[1,2]

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Data supporting the benefits of soy protein and soy-derived isoflavones in the dietary management of risk factors for cardiovascular disease (CVD) have woven on and off the straight and narrow path over the past few years. The data presented by Gardner et al (1) in the current issue of the Journal add another twist to this tortuous path.

A meta-analysis published in 1995 concluded that the consumption of 25–50 g soy protein, compared with animal protein, resulted in a significant decrease in LDL-cholesterol concentrations of 7% in persons with initial total cholesterol concentrations between 3.31 and 6.59 mmol/L (128 and 255 mg/dL, respectively), 10% in persons with initial total cholesterol concentrations between 6.69 and 8.60 mmol/L (259 and 333 mg/dL, respectively), and 24% in persons with initial total cholesterol concentrations >8.66 mmol/L (335 mg/dL) (2). Changes in HDL-cholesterol concentrations were not significant. Whether the effect was attributable to the soy protein per se or to other soybean-associated factors, the most likely of which is the constitutive isoflavones, was yet to be determined. Notably, 77% of the studies included in the meta-analysis had 95% CIs that included zero.

Since then, several well-controlled studies have reexamined the effect of soy protein and isoflavones on blood lipid concentrations. The results of more recent studies are variable. Changes in LDL-cholesterol concentrations attributable to the substitution of 25–50 g soy protein for animal protein range from a null effect (3) to a 3–6% decline in LDL-cholesterol concentrations (4–6) in persons with total cholesterol concentrations ranging from a mean of 4.88 to 6.05 mmol/L (190 to 235 mg/dL, respectively). Soy-protein preparations that resulted in a decrease in LDL-cholesterol concentrations had varying amounts of isoflavones (4–6). Changes in HDL-cholesterol concentrations ranged from –15% to 7% (3–6).

The effect of soy-derived isoflavones on blood cholesterol concentrations appears to be somewhat dependent on whether the isoflavones are ingested in isolation or as an enriched preparation of those endogenously present in soy. Fifty-five to 80 mg isolated soy-derived isoflavones given in pill form was reported to have no significant effect on blood lipid concentrations in persons with total mean cholesterol concentrations between 5.07 and 5.86 mmol/L (196 and 227 mg/dL, respectively) (7–9). In contrast, soy protein enriched in isoflavones (>60 mg isoflavones/d, but not lower doses) were reported to decrease LDL-cholesterol concentrations by ≈6% relative to casein or soy protein depleted of isoflavones in persons with a mean total cholesterol concentration of 6.3 mmol/L (244 mg/dL) (3–5). Additional benefit at a higher dose of soy-derived isoflavones was not observed (4). In one study in which both soy protein and isoflavone intake was varied from 20 g soy protein/38 mg isoflavones through 50 g soy protein/95 mg isoflavones, relative to casein, a maximal decline in non-HDL-cholesterol concentrations of 2.6% was observed at the lowest dose and did not increase with higher doses (6).

In the study of Gardner et al (1), postmenopausal, moderately hypercholesterolemic women [mean LDL cholesterol, 4.1 mmol/L (159 mg/dL)] were given, in random order, a milk protein supplement (42 g protein/d), a soy-protein supplement devoid of isoflavones (42 g protein/d), and a soy-protein supplement enriched in isoflavones (42 g protein/d and 80 mg isoflavones/d). At the end of the 12-wk study, there was no significant effect of either soy-protein preparation relative to the milk protein on LDL-cholesterol concentrations. Relative to the soy protein devoid of isoflavones, the soy protein with isoflavones resulted in an 8% decline in LDL-cholesterol concentrations. No significant effect of type of protein or isoflavones on HDL-cholesterol concentrations was observed. In light of these and the other recent data on the effect of soy protein and soy-derived isoflavones on blood cholesterol concentrations, how should we focus dietary recommendations aimed at decreasing the risk of CVD? To answer this question, we first need to put what we know about diet and CVD risk factors into perspective.

The relation between diet and CVD was recognized early in the 20th century. Although cholesterol and saturated fat were the first to be identified as major pieces of the diet-CVD puzzle, it was also clear that, although these represented relatively large pieces, they were by no means the only pieces. Other dietary components, such as soy protein, isoflavones, fiber, n−3 fatty acids, *trans* fatty acids, and plant sterols, to name a few, as well as energy balance, have since been investigated as potential pieces of the puzzle. When public health recommendations are being refined, it is important not only to identify all the pieces of the puzzle, but also to determine how big each of the pieces is. Taking a step back, it appears that, at least for persons with LDL-cholesterol concentrations representative of ≈95% of the US population, the consumption of soy protein per se, devoid of isoflavones, may not have as beneficial an effect on LDL- and HDL-cholesterol concentrations as first suggested. It also appears that the consumption of isolated isoflavones may not have a

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beneficial effect on LDL- and HDL-cholesterol concentrations. However, it does appear that soy protein containing the constitutive isoflavones or perhaps enriched in constitutive isoflavones has a modest LDL-cholesterol-lowering effect, most likely realized in persons with LDL-cholesterol concentrations in the borderline-high-risk or high-risk range. Why there is a discrepancy between the effects observed between the isolated and constitutive isoflavone is unclear at this time. The discrepancy might be related to the relative proportions of each of the individual isoflavones, the efficiency of absorption, the synergistic action of the soy protein with the isoflavones, or a yet to be determined factor. Can soy protein or soy-derived isoflavones have cardioprotective effects beyond altering blood cholesterol concentrations? The results of one study (7), although by no means conclusive (8), indicate that the answer may be yes. It is likely that we have not heard the final word on this issue.

The question still remains: How do we best advise the American public on the use of diet to reduce the risk of developing CVD? The single largest dietary determinants are most likely body weight and saturated fat intake. As a nation, we are not particularly successful at avoiding excess weight gain at various stages of the life cycle. Also, we still have not met our target saturated fat intake of $<10\%$ of energy. We have come a long way in enabling people to decrease their saturated fat intake through the introduction and widespread availability of low-fat and fat-free dairy products, leaner cuts of meat, and reduced-fat meat products. Potentially, an additional way for individuals to displace saturated fat from the diet is to exchange soy-based products for animal-based products. However, at the soy-protein intakes likely to arise from this strategy, additional beneficial effects will likely be modest and dependent on the presence of isoflavones.

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