Soybeans or soymilk: does it make a difference for cardiovascular protection? Does it even matter?\textsuperscript{1,2}

Francene M Steinberg

The effect of dietary soy on cardiovascular disease risk factors has been a topic of intense scientific and public interest over the past 10 or more years—a topic that was brought to the forefront by Anderson’s 1995 meta-analysis that highlighted clinical studies from the previous 20 y (1). The originally reported magnitude of the hypocholesterolemic effect of soy protein (9.3% decrease in total cholesterol and 12.9% decrease in LDL cholesterol) was criticized as being overstated because of the inclusion criteria used in the analysis, and it is difficult to reconcile with the current results of metabolic studies. Of interest, changes in serum cholesterol concentrations from the first and second quartiles of initial cholesterol values representing normo- and modest hypercholesterolemia are closer in magnitude to the changes reported in recent investigations, which suggests that the large response to soy is not driven by the amount of dietary soy but rather by the initial blood cholesterol concentration (2). Subsequently, the Food and Drug Administration (FDA) approved a health claim in 1999 that food products containing soy protein protect against heart disease (3). The American Heart Association published a statement on soy in 2000 in which it was deemed “prudent” to recommend inclusion of soy protein in the diet for cardiovascular disease protection (4). On consideration of current research, this position was recently revised to state that soy protein and isoflavones do not appear to have clinically significant effects that are superior to those of other proteins for heart health, but that soy products in general are beneficial because of their overall nutrient profile (5).

The soy hypothesis for lipid lowering and cardiovascular disease risk reduction has focused mainly on the isoflavone content of soy, but uncertainty still exists regarding the bioactive component responsible for the physiologic response to soy. Techniques for processing soy food can alter the isoflavone content and many other naturally occurring components. The use of different products in clinical trials and different study designs has contributed to much of the variability in study results. In an effort to make sense of the large body of research on soy and cholesterol lowering, a number of recent meta-analyses have examined study results since 1995 and reported a modest cholesterol lowering potential of soy. Weggemans and Trautwein (6) analyzed 10 studies (1995–2002) that compared soy protein with control protein (often casein) and found an average decrease of 4% in LDL cholesterol associated with the daily consumption of 36 g soy protein and 52 mg isoflavones but found no independent effect of soy-associated isoflavones. Zhuo et al (7) analyzed 8 studies that compared the effects of high with low isoflavones in subjects with identical soy-protein intakes. They found that soy-associated isoflavones have LDL cholesterol–lowering effects independent of soy protein, yet no linear relation exists in relation to the intakes of soy protein or isoflavones. Zhan and Ho (8) likewise concluded from a meta-analysis of 23 studies that soy protein containing isoflavones was associated with a 3.77% decrease in serum total cholesterol and a 5.25% decrease in LDL cholesterol, but no dose-response relation was observed. A 2006 comprehensive analysis of 41 trials conducted since 1966 concluded that a slight dose-response relation exists between soy protein, isoflavones, and net reductions in serum lipids (9). Lipid lowering is not the only proposed cardiovascular benefit of dietary soy, and results are limited and equivocal with regard to promoting vascular endothelial function and antioxidant protection and inhibiting platelet reactivity.

Taken together, the meta-analyses and recent critical reviews of the field agree that soy protein and associated isoflavones have modest hypocholesterolemic effects, ie, are associated with reductions in LDL cholesterol of 3–5% (2, 10). A realistic assessment of the efficacy of soy is that it is not a “magic bullet” and that its effects are small relative to those associated with pharmacologic management with statins but still useful in promoting healthy eating patterns for cardiovascular health. Interest in elucidating protective mechanisms at the cellular and organism level with the goal of maximizing the utility of dietary soy either in food product formulations, in specific patient populations, or in individuals who may respond differently to soy (such as equol producers) remains high. Actively being pursued are a number of research avenues that address the putative active components in soy, the mechanisms by which they act, and the effect that food matrices may have on the bioavailability and clinical effectiveness of such components.

The article in this issue of the journal by Matthan et al (11) addressed this latter issue in a well-controlled randomized trial that compared the effects of soy proteins from differently processed products and relative to animal protein on a variety of cardiovascular disease risk factors (lipids, lipoproteins, apolipoproteins, C-reactive protein, blood pressure, and endothelial function). A strength of this

\textsuperscript{1}From the Department of Nutrition, University of California, Davis, Davis, CA.
\textsuperscript{2}Reprints not available. Address correspondence to FM Steinberg, Department of Nutrition, University of California, Davis, Davis, CA 95616. E-mail: fmsteinberg@ucdavis.edu.
addressed the issue of whether different clinically significant biomarkers and surrogate markers for cardiovascular disease needed to investigate clinically relevant sensitive and specific clinically significant differences in atherosclerosis. An area of soymilk diet and from the other soy-product diets would result in necessarily mean that clinical significance was achieved. It is doubt-
lipids, is unknown.
foods and resulted in the significantly different change in blood
based diet contained soymilk, yogurt, tofu, and other mixed
nomenon occurred in the present study, in which the soymilk-
plied food matrix or compositional effects. Whether this phe-
plasma isoflavone concentrations and total areas under the curve,
recently compared the pharmacokinetics of isoflavones from
be determined from the study design, particularly because blood
function. The reason for the difference in serum lipids could not
in LDL cholesterol), but had no significant change on vascular
protein, which will result in reductions in total fat, saturated fat,
and cholesterol. Soy consumption is one of a variety of dietary
tools that can reduce the risk of cardiovascular disease and that
may be a useful adjunct to pharmacologic strategies. As more
research expands our knowledge of the bioactive components of
soy and its efficacy with regard to cardiovascular disease pro-
tection and other aspects of health, such as protection against
osteoarthritis, we will be able to make more specific recommenda-
tions about dietary soy.

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