

## Soy Protein and Cardiovascular Disease A Statement for Healthcare Professionals From the Nutrition Committee of the AHA

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Cardiovascular disease (CVD) is the leading cause of death in the United States.<sup>1</sup> Diet has a major impact on several modifiable risk factors for heart disease: hypercholesterolemia, hypertriglyceridemia, elevated LDL cholesterol, low HDL cholesterol, hypertension, obesity, and diabetes. The recommended low-saturated-fat, low-cholesterol diet<sup>1</sup> does help lower risk of CVD.<sup>2,3</sup> However, other dietary factors may offer additional benefits.

There is increasing evidence that consumption of soy protein in place of animal protein lowers blood cholesterol levels and may provide other cardiovascular benefits. Epidemiologists have long noted that Asian populations who consume soy foods as a dietary staple have a lower incidence of CVD than those who consume a typical Western diet.<sup>4</sup> Soy protein consumption in Japan is reported to be as much as 55 g/d,<sup>5</sup> compared with <5 g/d in the United States.<sup>6</sup> In 1998, deaths from CVD per 100 000 people between the ages of 35 and 74 years were as follows: 401 for US men, 201 for Japanese men, 197 for US women, and 99 for Japanese women.<sup>1</sup> There are many differences in dietary patterns and lifestyle factors that could account for differences in disease patterns among countries.

The American Heart Association (AHA) Dietary Guidelines for Healthy American Adults<sup>2</sup> stated that although there was some evidence that when soy protein was substituted for animal protein, total and LDL cholesterol could be reduced, the findings were inconclusive. The AHA Nutrition Committee concluded that the use of soy foods was consistent with the AHA Dietary Guidelines, but no recommendation was made to include soy protein in the diet. More research on the mechanisms explaining the effects of soy protein and related phytochemicals on blood lipids was recommended. This AHA Science Advisory provides an update on recent research reports.

The following description is from the Food and Drug Administration (FDA).<sup>7</sup>

Soy protein is an edible component of the soybean, *Glycine max*. Soy protein is produced from raw whole soybeans by a multistep process that removes the lipid and indigestible components to concentrate the protein and

increase its availability. Depending on the particular steps used during processing, soy protein ingredients may take the form of isolated soy protein (ISP), soy protein concentrate, or soy flour. Each ingredient may be further processed into texturized soy protein or texturized vegetable protein (TVP) used in the manufacture of meat and poultry analogues by thermoplastic extrusion or steam texturization to impart structure and shape. In addition to protein, these soy protein ingredients contain other naturally occurring soy constituents, such as isoflavones, fiber, and saponins. The specific processing steps that are used determine the extent of retention of naturally occurring components in the final product.

Soy protein is also consumed as a component of traditional fermented and nonfermented soy foods, such as tofu, tempeh, and miso, as well as whole soybeans, soynuts, soymilk, soy yogurt, and soy cheese. These products contain variable amounts of soy protein and other naturally occurring soy constituents depending on the specific technologies used in these products. Soy protein ingredients and soy protein-containing foods may partially replace or be used in addition to animal or other vegetable protein sources in the human diet.

### Clinical Studies

In 1995, a meta-analysis of 38 controlled clinical studies<sup>8</sup> concluded that substituting soy protein for animal protein significantly lowered total cholesterol, LDL cholesterol, and triglycerides without affecting HDL cholesterol. These effects were greater in subjects with higher baseline cholesterol values. Daily soy protein consumption resulted in a 9.3% decrease in total serum cholesterol, a 12.9% decrease in LDL cholesterol, and a 10.5% decrease in triglycerides.<sup>8</sup> The cholesterol-lowering effect of soy was in addition to the effect seen with a diet low in saturated fat and cholesterol (NCEP [National Cholesterol Education Program] Step I diet).

Studies included in the meta-analysis<sup>8</sup> used soy protein in the form of either TVP or ISP. No difference in efficacy was noted between these sources of soy protein, although the compositions of these soy products were quite differ-

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ent. TVP is usually made from a combination of soy flour and soy protein concentrate. Soy flour is  $\approx 50\%$  protein and contains  $\approx 5\%$  fiber. Soy concentrate is  $\approx 65\%$  to  $70\%$  protein and contains a small amount of fiber. ISP is  $\approx 90\%$  protein with no fiber.<sup>9</sup> Soy protein contains all of the essential amino acids in sufficient quantities to support human life and is therefore a complete protein.<sup>9</sup> Several components associated with soy protein have been implicated in the hypocholesterolemic benefits: trypsin inhibitors, phytic acid, saponins, isoflavones, and fiber. One major difference in soy concentrates and isolates is whether the manufacturer chooses to use water or ethanol washing to concentrate the protein. Ethanol washing removes most of the isoflavones and saponins. Unfortunately, at the time some of the earlier human studies were conducted, the exact processing conditions and composition information were not reported.

### Studies in Adults With Normal Cholesterol Levels

It is important to note that consumption of soy protein does not appear to have a hypocholesterolemic effect in adults with low or normal cholesterol levels. Therefore, there is no need for concern that soy could cause dangerously low cholesterol levels. In a study of 12 adults with a mean total cholesterol level of 145 mg/dL at baseline, the incorporation of 66 to 80 g soy protein (meat replaced by soy analogues and milk replaced by soy beverage) resulted in no significant changes in serum lipids.<sup>10</sup> Other investigators who studied the effect of soy protein as part of a hypocaloric diet found significantly lower total and LDL cholesterol compared with a conventional hypocaloric diet.<sup>11,12</sup> Sacks et al<sup>13</sup> found no significant change in serum lipids in 13 strict vegetarians whose baseline cholesterol was 129 mg/dL. Wong et al<sup>14</sup> found no significant change in 13 normocholesterolemic men 20 to 50 years of age (mean baseline total cholesterol, 169 mg/dL) who consumed 50 g soy protein in addition to a diet low in saturated fat and cholesterol. In the meta-analysis of the effect of soy protein on serum cholesterol levels by Anderson et al,<sup>8</sup> no significant effect of soy protein was found for those with a cholesterol  $< 200$  mg/dL.

### Studies in Adults With Elevated Cholesterol Levels

Although there have been some conflicting results in studies in adults with elevated serum cholesterol levels, most studies report total and LDL cholesterol reductions after the addition of soy protein to a diet that is low in saturated fat and cholesterol. In a recent study, postmenopausal women on a diet low in saturated fat and cholesterol (NCEP Step I diet) consumed 40 g/d of soy protein with either 56 or 90 mg of isoflavones daily or casein for 6 months. Both soy groups had significantly better blood lipid profiles (average change from baseline, 8.2% decrease in non-HDL cholesterol and a 4.4% increase in HDL cholesterol) than the casein group. However, no differences in lipids were seen between the 2 isoflavone levels.<sup>15</sup> HDL significantly increased 7% from baseline with

consumption of 32 g soy protein as soymilk in both women and men with hypercholesterolemia.<sup>16</sup> Crouse et al<sup>17</sup> reported reductions of 4% and 6% in total and LDL cholesterol, respectively, in hypercholesterolemic individuals consuming 25 g soy protein with isoflavones (see below) as part of a diet low in saturated fat and cholesterol.

A 9-week human study comparing the effects of soy protein (25 g/d) containing varying levels of isoflavones with those of casein found that consumption of the highest isoflavone level (62 mg/d) resulted in significantly lower total and LDL-cholesterol values than those of the casein group. Subjects with the highest LDL-cholesterol levels (top 50%) also experienced significant decreases in total and LDL cholesterol with 37 mg/d of isoflavones. However, those consuming soy protein with lower isoflavone levels ( $\leq 27$  mg/d) did not have any significant cholesterol-lowering effect.<sup>17</sup>

Researchers have also addressed the question of the threshold of dietary soy protein needed to reduce cholesterol. A dose-response study in hypercholesterolemic men on an NCEP Step I diet used 20, 30, 40, or 50 g/d of soy protein compared with casein. After 6 weeks, all levels of soy consumption led to significantly greater reductions in non-HDL cholesterol (1.5% to 4.5%) than did the casein, with higher levels being more effective.<sup>18</sup> An earlier study by Bakhit et al<sup>19</sup> showed cholesterol lowering with as little as 25 g/d of ISP in hypercholesterolemic but not normocholesterolemic men. Thus, 20 to 50 g soy protein/d improved blood lipid levels (1.5% to 4.5%) in mildly hypercholesterolemic persons. The FDA recently published its final ruling on a food-labeling health claim for soy protein and cholesterol reduction stating that 25 g/d of soy protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.<sup>7</sup>

### Mechanisms of Cholesterol Reduction by Soy

Several components associated with soy protein have been implicated in lowering cholesterol: trypsin inhibitors, phytic acid, saponins, isoflavins, and fiber.

#### Trypsin Inhibitors

Trypsin inhibitors are ubiquitous in foods. All soy products are heat-treated, which destroys most of the activity of trypsin inhibitors. Small amounts of the heat-stable Bowman-Birk inhibitor may exert a hypocholesterolemic effect by increasing the secretion of cholecystokinin. This would then stimulate bile acid synthesis from cholesterol and thus help to eliminate cholesterol through the gastrointestinal tract. However, animal studies have not demonstrated a hypocholesterolemic effect when trypsin inhibitor was added to the diet.<sup>20</sup>

#### Phytic Acid

Phytic acid, myoinositol hexaphosphate, is found in all nonfermented soy protein products and is very stable during heating. Phytic acid chelates zinc strongly in the intestinal tract, thus decreasing its absorption.<sup>21</sup> A copper deficiency or a high ratio of zinc to copper results in a rise in blood cholesterol.<sup>22</sup> The hypothesis advanced is that soy foods

contain both copper and phytic acid and therefore may lower cholesterol levels by decreasing the ratio of zinc to copper.

### Saponins

Saponins are heat-stable and are present in all of the soy protein products except those that are extracted with alcohol. These compounds may contribute to cholesterol lowering by increasing bile excretion.<sup>23</sup>

### Fiber

Some researchers have reported that soy fiber lowers cholesterol levels in humans with hypercholesterolemia.<sup>24</sup> Others have found that soy fiber has a hypocholesterolemic effect when added to other foods but that when added to soy protein it does not further enhance the hypocholesterolemic effect of the protein.<sup>19,25</sup> The soy protein products used in most published trials have contained little or no fiber. Thus, soy fiber does not appear to be a major factor in the lipid-lowering effects of soy foods.

### Direct Protein Effects on Hormones

Early researchers noted in animal studies that the amino acids lysine and methionine tend to raise cholesterol levels, whereas arginine has the opposite effect.<sup>26</sup> Soy protein, compared with animal protein sources, has a higher ratio of arginine to lysine and methionine. Interestingly, 2 animal studies found that a mixture of L-amino acids equivalent to the pattern of soy protein had an intermediate cholesterol-lowering effect that was not as pronounced as that of hydrolyzed whole soy protein.<sup>27,28</sup> Thus, some other component in the whole soy protein may have a beneficial effect beyond that of the protein alone. The higher arginine-to-lysine ratio of soy protein may decrease insulin and glucagon secretion, which would then inhibit lipogenesis.<sup>29</sup> These soy protein effects on insulin and glucagon levels have been reported in hypercholesterolemic humans.<sup>30</sup> In animal studies, thyroxine levels increased with consumption of soy protein.<sup>31,32</sup> High thyroxine levels were theorized to decrease cholesterol levels, but human studies have been inconsistent.<sup>32,33</sup>

### Protein Effects on LDL Receptors

Soybeans contain 2 types of storage proteins, the globulins 11S and 7S. Cell culture studies suggest that these globulins stimulate LDL receptor activity.<sup>34</sup> On the basis of several clinical studies, Sirtori et al<sup>35</sup> suggest that consumption of soy protein upregulates LDL receptors in humans. LDL receptor mRNA levels in mononuclear cells were much higher in subjects fed soy protein than in those fed casein.<sup>15</sup>

### Soy Peptides and Bile Acids

Soy protein treated with proteases forms 2 distinct fractions: an insoluble high-molecular-weight fraction and a soluble lower-molecular-weight fraction. The insoluble fraction, when fed to rats, lowered blood cholesterol levels by increasing fecal excretion of sterols.<sup>36</sup> The theory that soy protein lowers cholesterol by enhanced bile excretion has been explored extensively. Cholesterol lost from the body in the form of bile shifts the liver toward providing more cholesterol for increased bile acid synthesis and increases LDL receptor activity. Thus, the end result is increased LDL

removal from the blood. However, human studies with soy have not shown an increase in fecal bile acid excretion.<sup>37,38</sup>

### Isoflavones

Isoflavones are present in all soy flours and in concentrates and isolates produced by a water extraction process. Isoflavones are phytoestrogens and are bioactive in humans. Soy is the major food source of isoflavones, which include genistein, daidzein, and glycitein. Isoflavones have been the subject of an intensive research effort evaluating their possible hypocholesterolemic effects,<sup>17,39,40</sup> antioxidant effects,<sup>41</sup> and estrogen-like effects on blood vessels.<sup>42,43</sup>

Isoflavones have weak estrogenic effects in both animals and humans. The beneficial effects of estrogen include lower LDL cholesterol and increased HDL cholesterol. Phytoestrogens presumably work in a similar, although less potent, manner. Soy protein containing isoflavones lowered cholesterol significantly more than soy protein without isoflavones in humans.<sup>17,39,40</sup> Crouse et al<sup>17</sup> concluded that the cholesterol-lowering effect of soy protein is entirely due to isoflavones. However, Nestel et al<sup>42</sup> found no changes in plasma lipid levels in women consuming extracted soy isoflavones (without soy protein), although there was improved systemic arterial compliance. Therefore, both soy protein and isoflavones may be needed for the maximal cholesterol-lowering effect of soy.

Soy protein (20% of diet) with isoflavones also inhibits formation of atherosclerotic lesions in primates.<sup>44</sup> Soy protein without isoflavones had an intermediate effect in the primate study. Genistein is known to inhibit tyrosine kinase, an enzyme involved in the cascade of events leading to formation of thrombi and lesions.<sup>45</sup> Isoflavones also act as antioxidants and can inhibit LDL oxidation.<sup>41</sup> In another study, isoflavones enhanced vascular reactivity in female macaques.<sup>43</sup> As noted above, an isoflavone extract from soy improved systemic arterial elasticity in women without effects on blood lipid levels.<sup>42</sup> These studies indicate that isoflavones and/or other ethanol-soluble soy phytochemicals may have direct effects on the vascular system, independent of lipid metabolism.

### Availability of Soy Foods

Soy foods have been consumed in Asian countries for hundreds of years but are fairly new to the Western dietary regimen. In the past 10 years, the variety of soy foods available in US stores has increased, yet food manufacturers still need to provide more acceptable soy-based foods for the consumer.<sup>46</sup> The traditional Asian soybean curd, tofu, is becoming popular because it can be used in many dishes. It has a relatively bland flavor and can easily take the place of eggs or dairy products in many recipes. TVP is commonly used as a meat extender or replacement. Soy flour and ISP can be added to baked products to improve their nutritional quality without affecting their taste. New soy products are appearing that are replacements for common foods, such as soymilk and soy cheeses. Health-conscious Americans now have additional dietary choices that are low in saturated fat and contain virtually no cholesterol to assist in the control and/or reduction of total and LDL cholesterol.

## Summary

Considering the totality of research, daily consumption of  $\geq 25$  g of soy protein with its associated phytochemicals intact can improve lipid profiles in hypercholesterolemic humans. This effect was observed in clinical trials to be additional to the benefits of an NCEP Step I diet and is greater in more-hypercholesterolemic subjects. The mechanisms by which soy modulates blood cholesterol and lipoprotein levels need further research. Soy protein without the isoflavones appears to be less effective. Consuming isoflavones without soy protein does not lower cholesterol but may provide other cardiovascular benefits. The effects of using soy extracts of isoflavones as dietary supplements are largely unknown and cannot be recommended.

Apparently there is a synergy among the components of intact soy protein, which provides the maximum hypocholesterolemic benefit. A variety of clinical trials have demonstrated that consuming 25 to 50 g/d of soy protein is both safe and effective in reducing LDL cholesterol by  $\approx 4\%$  to 8%. The beneficial effects of soy are proportionally greater in people with hypercholesterolemia. Lichtenstein<sup>47</sup> has noted that the judicious substitution of soy for animal protein can result in lower saturated fat and cholesterol intakes, thereby indirectly resulting in a more favorable blood cholesterol level and potentially reducing coronary heart disease risk.

In conclusion, it is prudent to recommend including soy protein foods in a diet low in saturated fat and cholesterol to promote heart health.

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