Role of Soy Protein in Cholesterol-Lowering
How Good Is It?

Paul Nestel

In 1999, the Food and Drug Administration authorized a health claim for the cholesterol-lowering potential of modest intakes of soy protein. This has been controversial partly because much of the evidence was based on a meta-analysis published in 19951 that some nutritionists regarded as inadequate. About half of the quoted studies showed minor or no cholesterol-lowering effects and three of every four trials included in the meta-analysis had such wide confidence limits that an alternative conclusion might have been reached with equal validity. The meta-analysis certainly predicted the variability in results that would follow. Nevertheless, there have been sufficient well designed and executed studies to indicate a likely, although quite modest, effect on plasma lipids that seems to be confounded by as yet unidentified variables.

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Subsequent clinical trials have approached the problem in several ways. Soy protein containing defined amounts of isoflavones has been compared against another source of protein, mostly casein or whole milk. In some studies, the soy protein has been largely depleted of its isoflavone content through ethanolic extraction. Finally, several trials have focused on purified isoflavones, mostly from red clover. The precise constituent in soy protein responsible for LDL cholesterol (LDL-C) lowering is uncertain. The isoflavone content has been a strong candidate since some trials had shown that isoflavone-depleted protein was ineffective.2,3 In a statement on behalf of the American Heart Association Nutrition Committee, Dr John Erdman suggested that there might be a synergy between the components of soy protein since no single constituent appeared capable of lowering LDL-C in isolation.4 The absence of a clear dose-response effect even in those studies that have shown lowering of LDL-C or of non-HDL cholesterol is of concern.5–7

The bioavailability of soy isoflavones varies substantially for reasons that are only partly understood.8 Absorption depends on bowel microbial activity, conjugation to biologically inactive (or less active) entities occurs rapidly, the pharmacokinetics of individual isoflavones are dissimilar, and finally, knowledge about the conversion to potentially active metabolites is fragmentary.9,10 Furthermore, the isoflavone content and composition within different regions of the plant can vary substantially. Within that context, it is not surprising to find inconsistent results from simple comparisons of soy protein isolates and animal protein.

In this issue, Lichtenstein and colleagues,11 mostly from Tufts University’s Human Nutrition Center, have provided further evidence of the limitations to the health claim for soy protein. Diets containing similar amounts of protein from soy or animal sources, each containing either trace or 50 mg of isoflavones, thus providing four separate diets, were compared in 42 subjects for six weeks. Despite providing soy protein at levels that were more than twice the intake on which the health claim is based, there was not a significant difference in the final LDL-C concentration between the diets at least in normocholesterolemic subjects (LDL-C <4.14 mmol/L). However, in subjects with higher LDL-C levels, the soy protein diets, irrespective of the isoflavone content, led to a significant, albeit modest, fall in LDL-C (5%). Crouse et al2 had previously also demonstrated a benefit only in hypercholesterolemic subjects in whom soy protein containing 62 mg isoflavone reduced LDL-C by 6%.

Several recent studies have also shown modest lowering of either LDL-C or non-HDL cholesterol that has varied from as little as 2.6%5 to 6.5%.3,6 In several of these studies, total cholesterol was not lowered, although HDL cholesterol changed little with one exception,4 underscoring the modest efficacy of soy protein. Others such as Gardner et al12 found similar falls in LDL-C with soy protein and milk protein, an observation also evident in other comparisons. Wiseman et al13 reported similar LDL-C values with isoflavone depleted and intact soy protein, although interestingly, the plasma concentration of an F2-isoprostane, a robust biomarker of oxidant status, declined significantly with the isoflavone enriched soy protein, suggesting another function for isoflavones.

Trials of purified isoflavones have been disappointing to date. Nestel et al14,15 found no effects with isoflavones derived from either soy or red clover. Similar negative findings have been published by others.16–18 As reviewed above, the effect of isoflavones is in doubt even within soy protein with some studies showing a clear difference between isoflavone depleted and intact soy protein2,3 that was not observed by others including Lichtenstein et al.11 A mixture of isoflavones characterizes both soy and red clover, suggesting the possibility that not all isoflavones are effective. A preliminary report supports this possibility with significant (9%) lowering of LDL-C with biochanin but not with formononetin,19 the two major isoflavones in red clover. It has also been postulated recently that only the one quarter or so of the population that converts one of the soy isoflavones

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© 2002 American Heart Association, Inc.
Arterioscler Thromb Vase Biol. is available at http://www.atvbaha.org
DOI: 10.1161/01.ATV.0000035520.25551.97

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Isoflavones may play a greater role in improving vascular functions than in reducing cholesterol. Isoflavones resemble estradiol structurally but bind preferentially to the ERβ receptor that is present in the vasculature and may resemble the behavior of selective estrogen receptor modulators. There have been several recent reports of improved arterial function in response to purified isoflavones. Walker et al infused genistein into the brachial artery and demonstrated an increase in blood flow within the microcirculation of the forearm. Nestel et al showed that systemic arterial compliance (increased distensibility of large arteries) was improved with consumption of isoflavones, and Squadrito et al reported improved flow-mediated dilation in the brachial artery in women taking genistein for six months.

In recent years, with the encouragement of nutritionists and industry, the Food and Drug Administration has complied to permit health claims based on less rigorous evidence than in the past. As Lichtenstein et al conclude on the role of soy intake to healthy men.

References

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doi: 10.1161/01.ATV.0000035520.25551.97
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/22/11/1743

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