The Dilemma With the Soy Protein Health Claim

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The foundation of nutrition education is to help individuals make healthy food choices that are consistent with current dietary guidelines. A major advance in our education efforts was the passage of The Nutrition Labeling and Education Act of 1990, which provided regulatory authority to the US Food and Drug Administration (FDA) to revise the food label for purposes of reducing consumer confusion, helping consumers make better food choices, and incentivizing food manufacturers to provide more healthful food choices in the marketplace.[1] A core component of The Nutrition Labeling and Education Act of 1990 is that the FDA is authorized to create health claims, which focus on a relationship between a risk of disease and a food, food component, or dietary ingredient.

In 1999, the FDA authorized a health claim for soy protein and risk of coronary heart disease (CHD) on the basis of significant scientific agreement.[2] Products that contain at least 6.25 g of soy protein per reference amount customary consumed may carry the following health claims:

> A total of 25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies __ g of soy protein.
>
> Diets low in saturated fat and cholesterol that include 25 g of soy protein a day may reduce the risk of heart disease. One serving of [name of food] provides __ g of soy protein.

In 2007, the FDA announced an intention to reevaluate the scientific evidence for the soy protein health claim. After this, in 2017, a proposal to revoke the authorized health claim for soy protein and CHD was announced on the basis of the evidence reevaluation and tentative conclusion that significant scientific agreement is lacking.[3] A period of public comment ended in April 2018.

The FDA stated that published studies evaluating the effect of soy protein on CHD or surrogate end points since the 1999 ruling were inconsistent and inconclusive. On the basis of the totality of the evidence, consisting of studies conducted before the 1999 authorization and subsequent publications, the FDA concluded that significant scientific agreement has not been reached to support the health claim. In alignment, an American Heart Association Science Advisory from the Nutrition Committee, published in 2006, stated that the effect of soy protein is small relative to the dose needed to consume to confer clinical benefit and concluded that the evidence base does not confirm the clinical importance of soy protein.[4]

In this issue of the *Journal of the American Heart Association* (*JAHA*), a cumulative chronological meta-analysis, by Jenkins and colleagues, aims to establish whether at any time since 1999, the effect of soy protein on total cholesterol and low-density lipoprotein (LDL)-cholesterol becomes statistically nonsignificant.[5] This meta-analysis includes the same 46 intervention studies, of high or moderate quality, that the FDA reviewed as part of its scientific reevaluation of the evidence base. However, the FDA only examined the studies for consistency in the reported effect and found that 19 studies showed that soy protein reduced CHD risk and the remaining 27 studies did not support reduced risk of CHD with soy protein consumption. The FDA summary also highlighted the substantial heterogeneity present among the 46 studies with regard to study design, dose of soy protein, and sample size.[3]

The analysis of the evidence base by Jenkins et al[5] differed from the FDA's evaluation because the magnitude of the effect of soy protein on total cholesterol and LDL-cholesterol was what was of specific interest.[5] On the basis of the data reported by Jenkins and colleagues,[5] in 1999, the available evidence showed soy protein lowered total cholesterol and

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LDL-cholesterol by 4.53 mg/dL (95% CI, −8.08 to −0.99 mg/dL; P=0.01) and 6.33 mg/dL (95% CI, −8.74 to −3.92 mg/dL; P<0.00001), respectively. The addition of evidence through 2013 showed that at no point did the effect of soy protein on total cholesterol or LDL-cholesterol become statistically nonsignificant. However, the magnitude of the effect of soy protein on LDL-cholesterol was somewhat attenuated with the inclusion of studies published through 2013; the mean difference between soy and the comparator was −4.76 mg/dL (95% CI, −6.71 to −2.80 mg/dL; P<0.00001). In the case of total cholesterol, in 2013, the reduction observed with soy protein was slightly higher at 6.41 mg/dL (95% CI, −9.30 to −3.52 mg/dL; P<0.00001). Based on these small differences, the authors concluded that there has been no deviation in the magnitude of total cholesterol and LDL-cholesterol lowering with soy protein since 1999, and the effect evident in 1999 has persisted over time.

In this meta-analysis, the cumulative effect of the addition of each published study to the overall effect size was evaluated; however, the FDA's concern about the inconsistency of the evidence base was not addressed by this analysis. This group of authors published another meta-analysis of the same 46 studies in the *Journal of Nutrition* earlier this year[6] that showed significant heterogeneity for both total cholesterol (I^2=74%) and LDL-cholesterol (I^2=55%), which could not be explained by numerous factors, including the study design, baseline cholesterol levels, dose of soy protein, soy protein food source, the comparator treatment, and other hypothesized moderating factors. This suggests that the moderate to high heterogeneity observed is caused by variance in the true effect,[7] which is in alignment with the FDA's conclusion about the inconsistency of the evidence base.

Furthermore, the clinical significance of the effect of soy protein on total cholesterol and LDL-cholesterol observed in the cumulative meta-analysis must be considered. In the included studies, the median soy protein dose was 25 g/d, and the food-based choices, described by the authors,[5] that an individual would need to consume to ingest the amount of soy protein associated with lipid lowering are unlikely to be feasible for most Americans. Furthermore, when considering this in the context of the health claim, which is authorized for products that contain 6.25 g of soy protein (one quarter of the median amount tested), a clinically nonsignificant effect on total or LDL-cholesterol is probable if only one product carrying a health claim is consumed per day. In addition to the amount of soy protein included in products, it is pertinent to also consider how products that may carry a health claim for soy protein may fit into a healthy dietary pattern.

The 2015 to 2020 Dietary Guidelines for Americans recommend 3 healthy dietary patterns.[8] In the Healthy US Style and the Healthy Mediterranean Style Eating Patterns, 5 oz eq/wk of nuts, seeds, and soy products (at the 2000-kcal level) is recommended. In the Healthy Vegetarian Eating Pattern, 14 oz eq/wk is recommended because less protein is consumed from animal sources. Furthermore, soy beverage (soy milk) or yogurt may be consumed to meet dairy recommendations (2–3 cup eq/d at the 2000-kcal level). Therefore, if the Healthy Vegetarian Eating pattern was followed, it is likely that 25 g of soy protein would be consumed per day, and lipid and lipoprotein benefits would be conferred. However, regardless of the dietary pattern followed, replacement of animal protein with plant protein confers cardiovascular benefit[9] and should be encouraged from both a health perspective and an environmental perspective.[10]

What is problematic is when highly processed foods that do not align with recommended healthy dietary patterns contain ≥6.25 g of soy protein per reference amount and, therefore, qualify for the health claim. Although meeting the health claim criteria, this is not consistent with the spirit of the Nutrition Labeling and Education Act, specifically to help consumers make healthy food choices. Examples of such products include protein snack bars, protein powders, and other protein enriched foods. Health claims can lead to positivity bias or health halo effects,[11] so this issue should be considered. In the case of the soy protein health claim, Moon et al[12] demonstrated that nonsoy users and infrequent soy users exposed to the soy protein health claim were more likely to state they would eat the soy-containing product versus those not exposed to the health claim; no difference was detected between the conditions for regular soy consumers.

Soy protein is widely used in the production of ultraprocessed foods in the United States.[13] Epidemiologic research shows intake of ultraprocessed food is positively associated with overweight, obesity, and metabolic syndrome.[14] Moreover, 2 recent studies of cohorts from Spain and France reported ultraprocessed foods are adversely associated with mortality and cardiovascular end points.[15,16] The study conducted in Spain showed that consumption of >4 servings/day of ultraprocessed foods increased risk of early mortality by 62%.[15] In the French cohort, compared with the first quartile of ultraprocessed food intake, the fourth quartile had a 12% increase in cardiovascular disease, an 11% increase in cerebrovascular disease, and a 13% increase in CHD.[16] Furthermore, recent evidence from a randomized, crossover, inpatient feeding study demonstrated that provision of isocaloric, macronutrient matched diets comprising either ultraprocessed foods or unprocessed foods resulted in higher ad libitum consumption of calories (≈500 kcal/d) after the ultraprocessed diet versus the unprocessed diet.[17] After 2 weeks of the ultraprocessed diet, body weight (0.9 kg) and fat mass (0.4 kg) increased, whereas a reduction was observed after the unprocessed diet (−0.9 and −0.3 kg, respectively).

In the United States, ≈58% of calories consumed are from ultraprocessed foods, 29% of calories are from unprocessed or minimally processed foods, 10% of calories are from processed foods, and 3% of calories are from processed culinary ingredients.[18] Thus, although soy products, such as unsweetened soy beverages, soy yogurts, tofu, and some fermented soy products, are part of healthy dietary patterns, consumption of ultraprocessed products containing soy protein should not be encouraged.

Although the intrinsic, or the direct, effect of soy protein on total cholesterol and LDL-cholesterol appears modest, the addition of the extrinsic, or displacement, effect to the overall cholesterol-lowering effect is more tangible. A meta-analysis by Jenkins et al[19] in 2010 showed soy protein lowered LDL-cholesterol by 4.3%; however, displacement analyses showed replacement of 13 or 50 g of animal protein with soy protein would be expected to lower LDL-cholesterol by 3.6% and 6.0%, respectively. Therefore, the combined intrinsic and extrinsic effect of soy protein on LDL-cholesterol was projected to range from −7.9% to −10.3%. This analysis is more aligned with optimal implementation of the soy protein health claim, whereby soy proteins are incorporated into a healthy dietary pattern and displace some animal protein to increase overall diet quality.

Nutrition science is continually evolving, and it has become evident that reductionist policies that focus on single nutrients or components of whole foods may not completely align with the goal of chronic disease prevention.[20] Whole food– and dietary pattern–based approaches are likely to have greater public health impact. Thus, although Jenkins et al[5] state that the proposed revoke of the soy protein health claim may lead to reevaluation and revoke of the remaining heart health claims, this may be a necessary evolution to address the current applications of some food substances with approved health claims that are used as ingredients in ultraprocessed foods or other applications not consistent with dietary recommendations. To reduce the burden of chronic disease, particularly cardiovascular diseases, shifts to healthier dietary patterns are needed and a key element to achieve this is supportive public health policy.

Dietary risk factors are attributable to ≈18% of deaths and 11% of disability-adjusted life years in North America.[21] Cardiovascular diseases are the leading cause of diet-related death and disability, and estimates suggest that improvements in diet quality from the current US diet to a healthy dietary pattern would reduce total deaths in the United States by ≈26% to 28%.[22] Sources of plant protein, including soy products, are an integral component of healthy dietary patterns and consumption should be promoted; however, ultraprocessed foods, for the most part, do not align with the principles of a healthy dietary pattern and, therefore, should not be encouraged.

In the FDA's evaluation of the evidence, of the 46 articles cited for soy protein and LDL-cholesterol, only 8 evaluated soy foods; most evaluated soy protein isolate.[3] Thus, to be consistent with the intent of health claims, further research focused on the replacement of animal products with soy foods is needed to provide a more substantive evidence base on which to base a healthy soy protein food health claim. Such a health claim would better serve the consumer and promote public health.

Disclosures

None.

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