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The Soy Connection

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HEALTH AND NUTRITION NEWS ABOUT SOY

Research Updates

By Mark Messina, Ph.D.

Hypoglycemic Effects of Isoflavones

Researchers from the National Taiwan University Hospital in Taipei, Taiwan, compared the effects of isoflavone supplements to conventional (0.625 mg conjugated estrogen) hormone replacement therapy on glucose and insulin levels in postmenopausal women over a six-month period. Thirty women were randomly assigned to each group. Fasting levels of glucose and insulin significantly declined in both groups. When compared to baseline, glucose and insulin levels declined by about 85 percent and 60 percent, respectively. These results suggest that isoflavones may help to prevent or treat diabetes, but the lack of a placebo group limits the potential implications of these findings.

J Womens Health 2004; 13:1080-6

Soy & Cognitive Function

Several previously-published studies have found that isoflavone supplements improve various aspects of cognitive function. In the most recent study to examine this topic, cognitive function before and six weeks after consuming either a placebo or an isoflavone supplement

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In This Issue:

Putting the Coronary Effects of Soy into Perspective

By Mark Messina, Ph.D. and John W. Erdman, Jr., Ph.D.

Introduction

In 1999, based on soy protein's cholesterol-lowering effects, the U.S. Food and Drug Administration (FDA) approved a health claim for soy protein and coronary heart disease (CHD).[1] One year later, the American Heart Association, in a paper written by Erdman (a co-author of this article), endorsed the use of soyfoods for people with elevated cholesterol.[2] And in 2002, a health claim for soy protein similar to the U.S. claim was approved in the United Kingdom. Not surprisingly, consumer awareness of the heart-healthy benefits exceeds that of any other attribute of soy protein.[3]

In spite of all the formal recognition, however, two recently published editorials by well-respected researchers have challenged the notion that soy protein exerts coronary benefits.[4, 5] Therefore, the purpose of this article is to provide dietitians and nutritionists with an updated perspective on the relationship between soy intake and risk of CHD. This article covers the topic in two parts: cholesterol reduction and coronary effects independent of cholesterol reduction.

Part I: Cholesterol Reduction

Historical Perspective

The first human study demonstrating reduced cholesterol levels in response to soy protein was published in 1967.[6] Beginning in 1977, Italian researchers working primarily with very hypercholesterolemic patients published several reports describing dramatic (approximately 25 percent) soy protein-induced reductions in cholesterol.[7, 8] Still, as late as 1993, the American Heart Association concluded that soy protein lowered cholesterol in animals, but not in humans.[9] Perspective quickly changed two years later, however, when Anderson *et al.* published a meta-analysis in the *New England Journal of Medicine*; they found that of 38 trials, soy protein lowered cholesterol in 34, and that the average overall reduction in low density lipoprotein cholesterol (LDLC) was 12.9 percent.[10] Over a period of years, such a reduction could be expected to lower risk of CHD as much as 25-50 percent.[11, 12]

Trials included in this meta-analysis formed the bulk of the research upon which, four years later, the FDA based its decision to award a health claim for the cholesterol-lowering effects of soy protein. The 14 clinical studies with the best experimental designs were given the highest priority.[1]

Upon what basis then – given all of this research – can the coronary benefits and cholesterol-lowering properties of soy be challenged? In regard to the latter, it is quite apparent that since the publication of the meta-analysis by Anderson *et al.* not all studies have found that soy protein lowers blood cholesterol levels in comparison to the control protein,[13-16] which is most often casein. Of course, some inconsistency in the literature is expected, as many of the cholesterol-lowering trials involve relatively small sample sizes, and ±20 percent of individuals whose cholesterol levels are elevated do not respond to dietary changes in general.[17] Nevertheless, the failure of these trials to find reductions in cholesterol appear to

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stand in marked contrast to the very consistent hypocholesterolemic effects noted by Anderson *et al.*

Rarely pointed out, however, is that 77 percent of the studies in the 1995 meta-analysis had 95 percent confidence intervals that encompassed zero.[18] That is, the results from most trials were not statistically significant. Furthermore, several of the trials included subjects who had extremely (>300 mg/dl) elevated cholesterol levels; results from these studies contributed significantly to the large (12.9 percent) overall average reduction in LDLC. The inconsistent literature likely played a key role in the decision by the Adult Treatment Panel III of the National Cholesterol Education Program in 2001 not to endorse the hypocholesterolemic effects of soy protein – unlike their decisions regarding soluble fiber and phytosterols/phytostanols.[19]

Revised Estimates

Since the publication of the meta-analysis by Anderson *et al.*, two research teams have published meta-analyses on the cholesterol-lowering effects of soy protein. Both of these included only research published since 1995, and both found the reduction to be much lower than the 1995 estimate. In one, which involved 10 trials and 959 subjects, Dutch researchers found the reduction was only 4 percent,[20] and in the other, which involved 33 comparisons and almost 2000 subjects, Chinese investigators found the reduction was 5.25 percent.[21]

Obviously, these estimates are only averages and the response of any given individual, depending upon a number of factors, might vary considerably. For example, the Chinese investigators found men responded better than women, pre- and peri-menopausal women better than post-menopausal women, and those with elevated cholesterol better than those with normal cholesterol or whose cholesterol was only mildly elevated.[21] Soy protein containing greater amounts of isoflavones was also more hypocholesterolemic than protein relatively low in these soybean constituents.

Even within these broad subject categories there likely will be significant variation among individuals, perhaps for example, as a result of differences in the metabolism of isoflavones.[22-24] And aside from isoflavone content, speculation has arisen that the processing of soy protein affects efficacy.[25]

But even in the best-case scenario, the hypocholesterolemic effect of soy protein pales in comparison to the potent effects of the second-generation statins, which lower cholesterol as much as 50 percent,[26] and the effect of soy protein is likely even smaller than the response to phytosterols/phytostanols, which typically lower LDLC 5-10 percent.[27] Conversely, soy protein is on par with the cholesterol-lowering effects of soluble fiber and oats, both of which have been awarded FDA health claims.[28]

The Portfolio Approach

Soy protein was never justifiably positioned as the sole dietary means of lowering cholesterol, but was only properly viewed as one part of an overall heart-healthy diet. Thus, despite the downward estimates of the cholesterol-lowering effects of soy protein, there is no reason for this view to be altered. In this regard, Jenkins *et al.* have demonstrated marked (30 percent decreases) reductions in LDLC by using a combination of dietary approaches – what they refer to as the portfolio diet.[29-31] The portfolio diet includes soy protein, soluble fiber, nuts, phytosterols, lots of fruits and vegetables, and is low in saturated fat.

Of course, adopting such a diet represents a major dietary challenge for most people, and the reduction in cholesterol in response to the portfolio diet is likely to be somewhat less than that found under the research conditions employed by Jenkins *et al.*[32] Nevertheless, the portfolio diet reflects the proper approach toward lowering cholesterol by non-pharmacological means.

Statins plus Diet

Even those who choose the pharmaceutical route – which, given the current discussions about the ideal cholesterol level, is likely to represent an increasing proportion of the population – would do well to incorporate soy protein in their diet as statin-users are well advised to eat heart-healthy diets.[33] In fact, doubling the statin dose to achieve target LDLC levels results in only about an additional 6 percent reduction in cholesterol, but increases the rate of side effects.[34] Adopting a heart-healthy diet that includes soy protein may avoid the need for such a step. Furthermore, many soyfoods directly help to displace higher saturated fat foods in the diet.

Part II: Other Effects

Arguably, the most compelling argument in support of the use of soyfoods for reducing risk of CHD may be evidence suggesting they have coronary benefits independent of cholesterol reduction. Although the effect of soy on any individual CHD risk factor may be modest, the collective effects are likely impressive.

Several epidemiologic studies, although not all, have found that soy and/or isoflavone intake is inversely related to coronary events – in two cases non-fatal myocardial infarction and in one case fatal CHD. In these studies the reduction in risk ranged

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from 32-86 percent.[35-37] Since these marked protective effects are not likely due to the modest LDLC-lowering effects of soy protein alone, these findings suggest several CHD risk factors are favorably affected by soy. Interestingly, in the study that found risk was reduced by 86 percent (a prospective study from Shanghai involving approximately 65,000 women) soy protein intake in the fourth quartile was approximately only 16 g/day, much less than the 25 g/day set by the FDA as the amount needed for cholesterol reduction.

Lipid Effects

In both of the previously-cited post-1995 meta-analyses, soy protein was found to raise high-density lipoprotein cholesterol (HDLC) 3 percent.[20, 21] Although a 3 percent increase may not be noticed at the individual level, at the population level it is quite clinically relevant. Each 1 mg/dl increase in HDLC may reduce CHD risk 2-4 percent.[38] Furthermore, in the meta-analysis by Zhan and Ho, soy protein lowered serum triglyceride levels a statistically significant 7 percent.[21] There is debate among experts, but many consider elevated triglycerides to be an independent CHD risk factor.[39] Anderson *et al.*[10] also noted a reduction in triglycerides, but this finding was based on only four comparisons, versus 33 in the more recent meta-analysis.[21]

Finally, recent work from Tufts University showed that soy protein increased LDLC particle size.[40] There are a wide variety of mechanisms by which large LDLC particles decrease risk of atherosclerosis relative to smaller particles.[41] The increase in LDLC particle size observed in the Tufts' study may represent as much as a 5 percent decrease in the five-year risk of ischemic heart disease.[42]

Coronary Effects of Isoflavones

The soybean is essentially the only commonly consumed food to contain nutritionally relevant amounts of isoflavones – a class of chemical compounds that may possess both hormonal and non-hormonal properties possibly relevant to protection against CHD. In this regard, rodent studies have demonstrated that isoflavones reduce atherosclerosis independent of effects on lipid levels.[43-45] Parenthetically, as noted previously, there is debate about the extent, if any, to which the isoflavone content of soy protein affects cholesterol reduction.

Human studies have not consistently demonstrated coronary benefits of isoflavones, but the results from several trials are intriguing. For example, in postmenopausal women, Italian researchers found that the isoflavone genistein significantly increased forearm vessel diameter in comparison to the placebo; the increase was similar to the effect of conventional hormone replacement therapy.[46, 47] This particular assay measures the health of the endothelium – the thin layer of cells that line the blood vessels. Endothelium function is considered to be a global indicator of CHD risk.[48] Similarly, Australian researchers have shown that in postmenopausal women, isoflavones enhance systemic arterial compliance to the same extent as estrogen.[49, 50] Systemic arterial compliance is a measure of arterial flexibility and is also viewed as an indicator of CHD risk.[51]

Despite these findings and others by several research groups, the literature regarding the coronary effects of isoflavones is very conflicting, as many studies have failed to show isoflavones exert coronary benefits. Thus, further research is required to determine the direct effects of isoflavones on blood vessel health.

Blood Pressure and LDLC Oxidation

Several studies have demonstrated that soy protein inhibits LDLC oxidation and that isoflavone-rich soy protein inhibits LDLC oxidation in comparison to soy protein nearly devoid of isoflavones.[52, 53] Oxidized LDLC is taken up by scavenger receptors along the vessel wall, and so is thought to be more atherogenic than non-oxidized LDLC.[54] However, many studies have not shown soy protein inhibits LDLC oxidation. Furthermore, the atherogenic effects of oxidized LDLC have been challenged as a result of recent clinical trials failing to demonstrate the coronary benefits of vitamin E.[55]

Finally, several studies have shown soy protein lowers blood pressure, in some cases quite markedly.[56] A recent review concluded that in hypertensive patients, soy protein is quite efficacious.[57] Nevertheless, the very inconsistent data prevent broad conclusions from being made. Note, however, that even small decreases in blood pressure are associated with marked decreases in both stroke and CHD.[58]

Conclusions

The cholesterol-lowering effects of soy protein are certainly not as large as initially proposed, but the reductions are still clinically relevant. For this reason alone, and because they can help to displace higher saturated fat foods, soyfoods warrant a role in a heart-healthy diet. Furthermore, soy protein and possibly isoflavones appear to exert multiple coronary benefits that collectively may very significantly contribute to protection against CHD. Finally, although not discussed, full-fat soyfoods are good sources of the omega-3 fatty acid and alpha-linolenic acid, which may have its own coronary benefits.[59] Thus, despite the downward estimates of the hypocholesterolemic effects of soy protein, there are ample reasons for including soyfoods in diets designed to prevent and treat CHD.

In regard to recommended intakes, there are intriguing data suggesting less than 25 g/day (the FDA target intake) soy protein is required for cholesterol reduction.[60] Clinical trials suggest approximately 50 mg isoflavones may exert coronary benefits, although this remains speculative. Each gram of soy protein in traditional (tofu, miso, soybeans) soyfoods provides approximately 3.5 mg isoflavones, whereas in more processed soy products, each gram provides approximately 1-2 mg isoflavones. The soy protein content of soy products also varies markedly. Thus, the

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Demystifying Soy Protein

By Suzanne Vieira, M.S., R.D., L.D.N.

F.Y.D. From Your Dietitian

When a practitioner mentions words like "soy" or "tofu" to clients of the Baby Boomer generation, they sometimes are confronted with a pursed look and a response like, "I don't eat that." Remember the days of textured vegetable protein in the 70s? The School Lunch program experience left a lasting negative image in the minds and on the palates of many older consumers. The younger generation of 20- to 30-year-olds has a better understanding of nutrition, as well as the benefit of better tasting soy products in restaurants and schools.

To increase older clients' acceptance of the new generation of soy products, create a bridge to higher-quality protein and an expanded low-cost menu. Stress that protein is crucial to health (tissue repair of bone and muscle, enzyme and hormone regulation, infection resistance and metabolism). The Recommended Dietary Allowance is 0.8 gram of protein per kilogram of body weight (or 0.37 gram of protein per pound of body weight). For example, a 150 lb. adult should consume approximately 56 g protein/day.

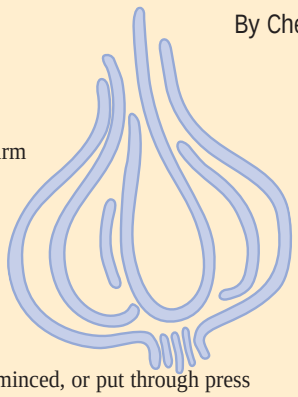
The mainstreaming of soyfoods should complement the recipe, not segregate the products. Soyfoods can be incorporated to complement meals containing foods from the meat/bean group, resulting in lower saturated fat, interesting texture and improved health.

Easy Soy Tips

- Substitute puréed silken tofu for eggs in baked dishes, pancakes and waffles.
- Whip up an easy ranch dip: mix unsweetened soymilk or puréed silken tofu (to replace sour cream) with one package of ranch dressing mix.
- Use soymilk in place of milk in soups, custards, puddings and oatmeal. Simmer; do not boil, as the protein coagulates quickly.
- Add canned soybeans, also known as "sweet beans," to any recipe in place of or in addition to other beans.
- Rinse "sweet beans," sprinkle with a spice blend and roast for 10-15 minutes at 350° for an easy snack.
- Try edamame (green soybeans in the shell), which are typically sold in the frozen state. Blanched and frozen within six hours, they are a great vegetable addition.
- Substitute soy cream cheese for cream cheese and sour cream in basic recipes.
- Slice tofu thinly, dry between paper towels, marinate and broil or grill to use with chicken, pork or beef.

Soba Noodle Salad

By Chef Elaine R. Cwynar, M.Ed.



***Yield**: Eight 6 oz. servings*

Ingredients:
1/2 lb. tofu, Chinese-style firm
1/2 lb. chicken breast

Marinade:
1/3 cup hoisin sauce
2 tsp. dark sesame oil
1/3 cup red wine (mirin)
3 Tb. tamari
1 1/2 Tb. dark brown sugar
3 cloves garlic, peeled and minced, or put through press
1 Tb. minced ginger
2 pinches red pepper flakes

Noodles:
2 red bell peppers, halved lengthwise, seeded, brushed with oil
1 12-oz. package soba (buckwheat) noodles
2 Tb. sesame oil
1 bunch scallions, thinly sliced, including a little of the greens
2 Tb. cilantro, washed and chopped
2 Tb. sesame seeds, black or white, toasted

Preparation:
1. Cut the tofu into slabs about 1/8-inch thick and drain briefly on paper towels. Whisk the marinade ingredients together in a pie plate. Add the tofu and turn the pieces so that all are covered with the marinade.
2. Slice chicken breast into 1/4-inch strips and add to marinade. Cover and refrigerate until ready to use.
3. Prepare the grill or heat the broiler. Remove the tofu and chicken from the marinade. Grill and hold.
4. Grill or broil the pepper until the skin blisters, then peel and slice into narrow strips. Boil the noodles in a large pot of salted water for 2 or 3 minutes. Drain and rinse under cold water to stop the cooking, and shake off excess water.
5. Toss the noodles with the sesame oil, scallions, cilantro, peppers, tofu and chicken. Sprinkle the sesame seeds over the noodles. Toss again and serve.

Nutrition Facts per Serving: **Calories** 272, **Total Fat** 6 g, **Saturated Fat** 1 g, **Carbohydrates** 42 g, **Protein** 14 g, **Cholesterol** 16 mg, **Fiber** 1 g, **Sodium** 946 mg.

Nutritional Analysis was performed with The Food Processor Program, Version 9.2.0, 2003 ESHA Research, Inc.

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number of servings needed for the proposed coronary benefits of soyfoods will vary, but in general, two to four servings per day is likely to be sufficient. Examples of one serving include 1 cup soymilk, 3-4 oz. tofu, 1/2 cup soybeans or 1/4 cup soynuts.

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Complete references for this article can be found on pages 7 and 8 of this pdf version.

Research Updates *(Continued from Page 1)*

(60 mg/day) was examined in 50 postmenopausal women age 51-66 years. Tests included those assessing attention, memory and frontal lobe function. After six weeks of treatment, there was a significant ($P < 0.02$) reduction in somatic menopausal symptoms in the group taking soy supplements, but there were no other significant effects of soy on menopausal symptoms or mood. On the test of nonverbal short-term memory, the soy group showed greater improvement than the placebo group ($P < 0.03$), but there were no effects of soy on long-term memory, category generation or sustained attention. However, the soy treatment produced significantly better performance on the two tests of frontal lobe function, those of mental flexibility (simple rule reversal, $P < 0.05$; complex rule reversal, $P < 0.03$) and of planning ability ($P < 0.05$). These results suggest that the main improvement after six weeks of soy supplementation was in frontal lobe function. These findings are consistent with findings from a previously published 12-week study involving postmenopausal women. Despite the encouraging data, longer-term studies are needed before firm conclusions can be made.

Menopause 2005; 12:193-201

Calcium, Isoflavones and Soy Protein

The estrogen-like effects of isoflavones have led to considerable investigation of their possible skeletal benefits. In addition, previous research has suggested that soy protein is less hypercalciuric than animal protein. In a recent study from the laboratory of Connie Weaver, Ph.D. of Purdue University, the effects of both soy and animal protein on calcium metabolism were examined in a three-week study involving postmenopausal women. In random order, subjects consumed each of three diets that were supplemented with 40 g/day of a casein/whey mixture, isoflavone-rich soy protein, or isoflavone-poor soy protein. Protein type did not affect calcium absorption, but urinary calcium was significantly ($P < 0.01$) reduced by about one-third when women were consuming the soy diets in comparison to the non-soy diet. However, endogenous fecal calcium was increased while on the soy diets. Consequently, overall calcium retention was not significantly affected by the type of dietary protein.

On the basis of these findings, the authors suggest that it is unlikely that either soy protein or isoflavones favorably affect the skeletal system in the long-term. However, an editorial *(Am J Clin Nutr 2005; 81: 733-735)* in response to this article questioned the ability of this study to predict long-term effects. In support of this contention are the results from a recently presented two-year study involving postmenopausal women that found not only that soy markedly reduced bone loss at the spine and hip (results were not quite statistically significant at this site), but that the results at two years were more pronounced than at one. This suggests that long-term studies are needed to predict long-term results. Currently, the U.S. government is funding three large, long-term studies examining the effects of isoflavone supplements on bone health in postmenopausal women.

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Soybean Oil May Reduce Risk of Heart Disease

Several recent studies have shed light on the potential for alpha-linolenic acid (ALA) to reduce heart disease risk. Soybean oil is an excellent source of ALA, as are flax and walnuts.

Recent research has shown that ALA decreases C-reactive protein (CRP), a marker of inflammation strongly associated with heart disease. In one study, Zhao *et al*. studied the effects of three experimental diets: the average American diet (7.7 percent energy from LA; 0.8 percent from ALA), a linoleic acid (LA) diet (12.6 percent energy from LA; 3.6 percent from ALA) and an ALA diet (10.5 percent energy from LA; 6.5 percent from ALA). After six weeks, the researchers found that CRP declined after both the LA and ALA diets, but much more significantly in the ALA diet.[1] The study chose 23 participants who represented the typical individual at risk for cardiovascular disease, selecting 20 men and three women who were overweight, about 50 years old on average, and had moderately elevated total cholesterol and LDL cholesterol.

In a second study, Albert *et al.* examined the diets of women taking part in the Nurses Health Study.[2] They found a protective association between ALA intake and coronary heart disease among the women observed in the study. The Nurses Health Study has monitored 76,000 women's lifestyles and health over a 16-year time period. Albert presented the research at a November 2004

Soybean Oil

meeting of the American Heart Association.

Two other recent, noteworthy studies point to soybean oil's heart healthy benefits. First, in a meta-analysis by Brouwer *et al.* published last year in the *Journal of Nutrition*, high ALA intake was associated with reduced risk of fatal heart disease.[3] Second, results from a study published earlier this year by Djoussé *et al.* suggest that dietary linolenic acid is protective against hypertension.[4] Among participants in the National Heart, Lung, and Blood Institute Family Heart Study, risk of hypertension was reduced by approximately one-third when comparing the first (mean intake, 0.44 g/day) versus the fourth (mean intake, 1.28 g/day) linolenic acid intake quartile. The difference of 0.84 g linolenic acid between the first and fourth quartiles is approximately the amount of ALA present in 1/4 cup soynuts.

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