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The Soy Connection

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HEALTH AND NUTRITION NEWS ABOUT SOY

CDS Examines Soy, Human Health

The Fifth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease was held last fall in Orlando, Florida. The first such symposium was held in 1994. For a decade this symposium has been the seminal gathering place for investigators and health professionals to discuss the latest research on the health effects of soyfoods and soybean constituents. The 2003 meeting attracted nearly 300 participants from 20 different countries. In total there were approximately 200 oral and poster presentations – that's a lot of new data. But as is often the case, it is the discussion following the oral presentations and during the poster sessions that some of the most important information is shared. In this issue of *The Soy Connection* the chairman of the symposium, Mark Messina, Ph.D., summarizes some of the central findings from the event.

Findings covered in this issue:

- Bone health
- Breast cancer
- Calcium excretion
- Cholesterol reduction
- Cognitive function
- Eye health
- Hot flashes
- Isoflavone content
- Phytoestrogens
- Prostate cancer
- Renal function
- Soy allergy
- Weight loss

Findings and Perspectives from the Fifth International Chronic Disease Symposium

By Mark Messina, Ph.D.

This issue briefly reviews some of the findings from The Fifth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Two areas – bone health and cognitive function – are discussed in detail. The findings presented at the meeting in these two areas are placed in the context of the existing literature. But first, one perspective relevant to understanding soy research in general is presented. This spring, *The Journal of Nutrition* will publish several full manuscripts and all of the abstracts from the meeting.

Isoflavones Do Not Equal Estrogen

Arguably, the popularity of soyfoods has been aided by the understanding that isoflavones are phytoestrogens. The notion that isoflavones might have some of the same postulated benefits as estrogen but not the disadvantages certainly led many postmenopausal women and health professionals to embrace soyfoods. However, as the potentially harmful effects of estrogen have become more apparent and as concerns about the possible adverse “estrogenic” effects of isoflavones in some subsets (such as young children) of the population have been raised it has become especially important to clearly articulate that isoflavones are dissimilar from estrogen in many ways.

Isoflavones are referred to as phytoestrogens because they bind to estrogen receptors and exert *estrogen-like* effects under some experimental

conditions. However, the ability of a chemical to bind to hormone receptors, such as the estrogen receptor, in and of itself, says little about potency and likely biological activity. There are many other factors that are critically important. Most important, is the conformational change in the ligand-receptor complex. The resulting confirmation change in the ligand (any compound that binds to a receptor)-receptor complex varies greatly among ligands independent of the affinity they have for a receptor. This partly explains why although both the breast cancer drug tamoxifen and the hormone estrogen bind to estrogen receptors, the former exerts an antiestrogenic, and the latter an estrogenic effect, on breast tissue.

Furthermore, in comparison to estrogen, isoflavones have a higher binding affinity for estrogen receptor beta (ER β) than for estrogen receptor alpha (ER α) and when bound to ER β , more potently triggers transcriptional activity (exert effects on cells) than when bound to ER α .^{1,2} The higher binding affinity of isoflavones for ER β and the different

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tissue distributions of ER α and ER β suggest isoflavones have tissue-selective effects. This is why isoflavones are sometimes classified as selective estrogen receptor modulators (SERMs), as are the breast cancer drug tamoxifen and the osteoporosis drug raloxifene.³

Unlike estrogen, SERMs are tissue selective, having estrogen-like effects in some tissues but either no effects or antiestrogenic effects in other tissues. The ideal SERM would seemingly have estrogen-like effects on the coronary vessels, skeletal system and brain, but antiestrogenic effects on the breast and endometrium. Support for the SERM-like qualities of isoflavones include the observations that estrogen increases endometrial cell proliferation (and consequently endometrial cancer risk) and serum triglyceride levels, whereas isoflavone-rich soy protein and isolated isoflavones have no effect on endometrial cell proliferation^{4,5} and either have no effect or slightly decrease serum triglyceride levels.⁶ In view of these observations, it is arguably more accurate to refer to isoflavones as having *estrogen-like* effects rather than *estrogenic* effects. That said, applying the term phytoestrogens to isoflavones is arguably misleading since it neither fully nor accurately characterizes isoflavones.

Finally, research published last year shows just how different isoflavones are from estrogen. In this study, the gene expression of female rats was examined after the animals were subcutaneously injected with genistein, the main isoflavone in soybeans, estradiol, or bisphenol A (BPA), an estrogen-like substance present in plastics. Genistein led to a statistically significant change in 227 genes, whereas the expression of only 26 and 35 genes was significantly changed by estrogen and BPA, respectively.⁷ These types of results along with the other kinds of observations noted above clearly show that no conclusions about the health effects of isoflavones or soyfoods for that matter – good or bad – can be made on the basis of what estrogen does or doesn't do.

Bone Health

Results from the Women's

Health Initiative (WHI) demonstrated that the harm of conventional hormone replacement therapy (HRT, the combination of estrogen and progesterone) outweighs the benefits.⁸ This is why the WHI was terminated prematurely. However, the WHI also demonstrated that HRT reduces risk of fracture. There is considerable speculation about, and intriguing experimental support for, the potential skeletal benefits of isoflavones – in part because of their estrogen-like effects. Several but not all trials have found that isoflavone-rich (compared to isoflavone poor) soy protein and isolated isoflavones reduce bone loss in perimenopausal and postmenopausal women.⁹⁻¹¹

A study presented at the symposium by Dr. Suzanne Ho from the Chinese University of Hong Kong arguably provides the strongest data to date that isoflavones do have skeletal benefits. This is because there were nearly 70 subjects per group, which makes this study more than twice as large as any previously conducted bone study involving soy. In this one-year study postmenopausal Chinese women consumed a placebo or an isoflavone supplement each day that provided either 40 mg or 80 mg/day.¹² Women in the highest isoflavone group experienced a statistically significant increase in hip bone mineral content (BMC) in comparison to women not consuming isoflavones. There were no improvements in BMC in the low isoflavone group.

The high dose isoflavone group consumed an amount of isoflavones found in about three cups of soymilk; this not an excessive amount but is about twice the average Japanese

adult intake. Perhaps it is the case that relatively high amounts of isoflavones are needed for skeletal benefits as this study and other intervention trials suggest, although few dose-response trials have been conducted. However, the epidemiologic data suggest otherwise.¹³⁻¹⁵ In fact, at the meeting, Dr. Ho and colleagues also reported the results of an epidemiologic study involving 454 postmenopausal Chinese women. Among women at least four years menopausal, soy intake was associated with a statistically significant increase in BMC at several bone sites. Importantly, average isoflavone intake among all women in the study was only about 11 mg/day and even in the fourth quartile, average isoflavone intake was only about 60 mg/day.

Of course, epidemiologic studies only show associations and can not demonstrate causal relationships. But the epidemiologic findings suggest that the isoflavone dose needed to demonstrate benefits in short-term clinical trials may be higher than the amount needed when consumed throughout life. That said, Anderson et al previously showed that in a one year study isoflavones did not increase bone mass in premenopausal women.¹⁶

There were two other particularly noteworthy studies in the bone area presented at the symposium. One examined the effect of isoflavone supplements on bone health in 87 postmenopausal Chinese women. Women received no isoflavones, 84, or 126 mg per day for 24 weeks. There was also a small group of women who received an estrogen-like

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Ten Specific Findings on Soy and Human Health

By Mark Messina, Ph.D.

Prostate Cancer

FINDING: *Daidzein and equol (a bacterially derived metabolite of daidzein) levels in the prostate of men after consuming soyfoods were found to be approximately 6 and 13 fold higher than serum levels whereas genistein levels were approximately 50 percent lower.*

These findings indicate that serum levels don't necessarily reflect tissue levels, and that in the case of two of the major isoflavones, levels in the prostate are actually much higher. Interestingly, previous animal work demonstrated that genistein exerted anticancer effects on prostate tissue at levels that were much lower than what was anticipated to be necessary based on the in vitro data.¹ Collectively, these findings emphasize the need for doing human research before making definitive conclusions.

Cholesterol Reduction

FINDING: *A "non-denatured" isolated soy protein was found to decrease LDL-cholesterol levels to an approximately twofold greater extent than a commercially available isolate.*

These results should be considered quite preliminary but they clearly have potentially important implications. Certainly, they offer a potential explanation for the substantial variation in response to the cholesterol lowering effects of soy protein observed among studies.

Hot Flashes

FINDING: *Preliminary results from a meta-analysis indicate soy and isoflavones exert modest beneficial effects on hot flashes but primarily only in women with very frequent hot flashes.*

These results are consistent with a recently published review which found that soy and isoflavone supplements decreased the frequency of hot flashes by approximately 5 percent above the placebo response for each hot flash a woman has above 5/day.² In theory, a woman who has 8 hot flashes per day would experience a 15 percent reduction in frequency above the placebo response which is typically about 25 percent. Thus, the total response would be a 40 percent reduction; hot flashes would decrease from 8/day to about 4-5/day.

The authors of this published analysis concluded that the evidence is sufficiently suggestive to recommend that women try soy and isoflavone supplements for alleviation of hot flashes but not sufficiently strong to definitely conclude that soy is efficacious. The authors felt the possible coronary and skeletal benefits of soy in combination with the placebo effect that would result by virtue of women using soy for relief of hot flashes provided additional justification for recommending soy despite the tentative data.

Soy Allergy

FINDING: *Only one out of 3,000 adults is estimated to be allergic to soy protein.*

This estimate is much lower than is commonly perceived. However, the incidence of true food allergy among adults is quite low and soy is much less allergenic than many commonly consumed foods, thus this low estimate appears reasonable. Also, the reaction to soy protein is typically less severe than is the case for many other foods.

Breast Cancer

FINDING: *Isoflavone-rich isolated soy protein inhibited the proliferative effect of estrogen on breast tissue in ovariectomized monkeys and reduced breast tissue inflammation in women.*

However, overall, it is not clear from the existing literature that soy exerts antiestrogenic effects on breast tissue in women and a recent study failed to conclusively show that soy inhibits the hyperplastic effects of estrogen on the endometrial tissue.³

Calcium Excretion

FINDING: *Soy protein did not decrease urinary calcium excretion in comparison to meat protein in postmenopausal women.*

The metabolism of the sulfur amino acids in protein leads to the production of acid which in turn causes bone resorption so that the buffering agents in the skeletal system can be utilized to maintain pH within the appropriate range. However, the relationship between protein intake and bone health is complex and recent work suggests higher protein diets may reduce the risk of osteoporosis. Nevertheless, several human studies conducted over the past 15 years demonstrated that soy protein decreases calcium excretion in comparison to animal protein.^{4,5} This is not surprising since soy protein is lower in sulfur amino acids than animal protein.

Thus, these new findings presented at the symposium contrast with the existing literature. However, this study was well designed and therefore the results should not be discounted. Worth noting, is that in the meat-soy study the calcium content of the diets was only about

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Ten Specific Findings *(Continued from Page 3)*

700 mg whereas in a recent study showing markedly lower urinary calcium in response to soy protein compared to a casein-whey mixture calcium intake was about 1500 mg.⁶ Perhaps, the low calcium intake in the soy-meat study prevented the hypocalciuric effect of soy protein observed in other studies from having an impact on calcium excretion. Of course, this must be demonstrated experimentally. Obviously, more research is needed to clarify the relationship among various proteins and calcium excretion.

Eye Health

FINDING: *The isoflavone genistein protected against x-ray induced cataract formation in rats.*

This is a new area of research. Genistein was found to be present in the crystalline lens and was effective against x-rays whether given in the form of soy protein or as a supplement. The antioxidant effects of genistein may have been responsible for protection against cataract formation.

Isoflavone Content

FINDING: *Isoflavone content should be expressed as the aglycone weight.*

Isoflavones naturally occur in the soybean in the form of glycosides – a glucose attached to the isoflavone molecule. The weight of the sugar is approximately 40 percent of the total weight of the isoflavone glycoside. Of course, the sugar is biologically irrelevant.

The situation with isoflavones is analogous to calcium salts such as calcium carbonate. A 500 mg tablet of calcium

carbonate provides only 200 mg of elemental calcium. A 100 mg isoflavone tablet containing isoflavones in the glycoside form provides only 60 mg of biologically active isoflavones. Unfortunately, information about the isoflavone content of products usually does not indicate whether the isoflavone amount refers to the aglycone weight or glycoside weight. To avoid confusion, the recommendation is for all isoflavone amounts to refer to the aglycone weight.

Weight Loss

FINDING: *Data suggesting soy protein specifically aids in weight loss is very limited but the health advantages of soy protein make it a good choice for high protein diets.*

Since soy protein modestly lowers serum cholesterol and perhaps blood pressure, and favorably affects renal function compared to animal proteins, soyfoods are good options for increasing protein intake.

Soy Protein and Renal Function

FINDING: *In comparison to casein, soy protein improved the nutritional status of chronic renal dialysis patients.*

The principal investigator of this three-week study suggested that the improvement was due to soy protein having an anti-inflammatory effect. These results are generally consistent with previously published research showing that soy protein favorably affects renal function in both healthy adults and diabetic patients, including a new seven-week study that compared the effects of consuming a low protein diet with or without soy protein on renal function in

diabetic subjects with normal renal function.⁷

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product that served as a positive control. After 24 weeks, spinal BMD significantly decreased in the placebo group, whereas in the isoflavone groups and the positive control, there were modest increases at all bone sites, although when compared to baseline values these increases were not statistically significant. Also, a marker (urinary deoxypyridinoline) of bone resorption in the isoflavone groups and the estrogen group significantly declined, indicating reduced bone breakdown; the absolute change and level of these groups were significantly lower than for the placebo group.

Finally, the BMD of the spine and hip of 202 older Dutch women was measured before and at one year after receiving on a daily basis either 36 g isolated soy protein containing 99 mg isoflavones or the same amount of casein. Women in this study were 60-75 years of age. In contrast to the two studies discussed above there was no difference in the BMD between the two groups.

Cognitive Function

After the publication of an epidemiologic study in 2000, some concerns arose about the possible adverse effects of soy consumption on cognitive function.¹⁷ In this study, Japanese men who consumed tofu approximately 2-4 times per week were about twice as likely to develop cognitive impairment as were men who consumed tofu infrequently. Of course, as has already been noted, epidemiologic studies can't demonstrate causal relationships. And this study did have some methodological limitations. Investigators recorded the impact of 26 foods – today, it would be common to have data on 100 or more foods. Also, the way in which the investigators asked about tofu intake changed over the course of the study. Furthermore, the primary endpoint of the

study was actually coronary heart disease, not cognition. Still, the results should not be dismissed. Certainly, they were unexpected because of suggestive data indicating that estrogen favorably affects cognition.

Fortunately, three clinical trials have now examined the effects of soy or isoflavones on cognitive function. One study, which lasted for 10 weeks, involved young men and women who consumed either their usual diet or a high soy diet.¹⁸ The other two trials involved postmenopausal women who were given isoflavone supplements for 12 weeks in one study,¹⁹ and 24 in the other.²⁰ Importantly, all three trials reported the intervention led to significant increases in one or more aspects of cognitive function. Of course, these trials were conducted for a relatively short duration. This is why a study presented by Kreijkamp-Kaspers et al from the University Medical Center Utrecht in the Netherlands is noteworthy.

In this study, the cognitive function of 202 older Dutch women was measured before and one year after receiving on a daily basis either 36 g casein or a similar amount of isolated soy protein containing 99 mg isoflavones. Women in this study were 60-75 years of age. In contrast to the three published trials this study found no effects of isoflavones on cognitive function. Because the study was conducted for much longer than the three trials that showed benefits, at first glance these results seriously weaken the notion that soy exerts cognitive benefits.

However, there is an important element to this study by Kreijkamp-Kaspers et al that must be considered. Women in this study were at least 60 years of age. In the other two studies involving postmenopausal women, the age range was 55-74 years, and 50-65 years. There is evidence that to reap the cognitive benefits of estrogen, and by

inference possibly isoflavones, women need to begin estrogen administration soon after menopause. For example, in ovariectomized rats, a recently published study found that estrogen administration beginning 12 days after surgery did not increase synaptic density in the hippocampal whereas when begun 4 days after ovariectomy, significant increases in density were noted.²¹ It may be that this Dutch study shows is that isoflavones are not beneficial but that timing of exposure very much influences efficacy. At the very least, this study showed that isoflavones were not harmful, which means it can be added to the other three clinical trials as evidence that contrasts with the Hawaiian epidemiologic study noted at the onset.

ABOUT THE AUTHOR

Mark Messina, Ph.D., is the co-owner of Nutrition Matters, Inc., a nutrition consulting company, and is an adjunct associate professor at Loma Linda University. From 1987 to 1992, Messina was a program director in the Diet and Cancer Branch, National Cancer Institute, National Institutes of Health. His primary responsibility was to identify research needs in diet and cancer prevention and to make recommendations for government funding of research projects.

Since leaving the National Cancer Institute, Messina has devoted his time primarily to the study of health benefits of soyfoods. He writes extensively on this subject, and has given more than 325 presentations to both consumer and professional groups throughout the U.S. and in more than 29 countries. He organized and chaired all five international symposia on the role of soy in preventing and treating chronic disease.

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Symposium Findings and Perspectives (Continued from Page 5)

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