Phytoestrogens for a Healthier Menopause

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A woman seeking relief from menopausal.svmptoms is common in Westesn society. Many women, however, suffer in silence or take the plunge towards synthetic hormone replacement therapy (HRT). Whilst the untoward symptoms of the female climacteric (change of life) are troublesome, the postmenopausal onslaught of degenerative diseases is the real health problem that faces the mature female. New information has surfaced about the dangers of conventional HRT provided in a synthetic format or in preparations derived from mare's urine. The Committee on Safetv of Medicines in the United Kin-dom has issued recently (in September of 1996) a warning of a threefold risk of thrombotic episodes in women treated with conventional HRT.

Some Simple Facts

There are more than 40 million menopausal or postmenopausal women in the United States, and at least 25 million more will become menopausal within the next ten years. Change of life is not a disease, but it can be a very distressing interval in a woman's life. On the one hand, conservative opinion advises against any interference with the course of nature during the climacteric. On the other hand, those females who suffer its consequences may see good reason to control the hot flashes, osteoporosis, irritability, lack of psvchologic well-being, fatigue, urinary tract infections, vaginal dryness, atrophy of female organs, and coronary artery disease. While these menopausal problems are not universal among females, they are very common.

HRT-A Critical Decision

Lack of estrogen and associated hormone imbalance are responsible for many of the adverse effects of the female climacteric. Menopause poses the difficult decision for women concerning the adoption of HRT with potent, synthetic estrogens. Thus, noncompliance due to second guessing about the safety of this intervention is very common.

Estrogen may be, on occasion, a woman's best friend, but its fluctuation throughout life causes a host of problems for some women. It has been documented that in the preceding calendar year in the United States, synthetic estrogen supplements (or animal estrogens) were the most commonly prescribed and dispensed drugs in community practice. Proponents of synthetic (or horseurine-derived) hormone replacement therapy espouse the advantages of the control of unpleasant symptoms of menopause (hot flashes, profuse sweating, etc.) at the expense of considering the possible long-term side effects of these potent estrogens that are used as replacement therapy. Increasing concern is being expressed about the dangers of conventional HRT.

Estrogenic hormone replacement therapy may assist in the reduction of the risk of osteoporosis and coronary artery disease, but it carries an uncertain risk of breast cancer, endometrial cancer, endometriosis, and a wide range of frequent adverse effects, such as abdominal bloating, migraine or other kinds of headache, weight gain, anxiety or depression, and breast tenderness.[1] Conventional hormone replacement is contraindicated in many common circumstances, such as suspected genital or breast cancer, vaginal bleeding of unknown cause, significant liver disease, or a history of thrombosis or embolism. A female may start to consider the option of hormone replacement over a period of up to ten years prior to the menopause, particularly when menstruation becomes irregular prior to its cessation. [1]

Some Simple Observations

Many Asian and Oriental females do not seem to be as bothered by the menopause as are females in Western society. [2] Why? The answer seems to rest in their diet. Soy-based diets contain isoflavones which are natural "weak" estrogens of plant (phyto) origin. Considerable evidence appears to be accumulating that soy isoflavones in the diet exert “weak" estrogenic effects that may confer anti-aging benefits, help to prevent bone and joint disease and cancer, promote cardiovascular wellness, and maintain a healthy urinary tract, especially if soy protein is simulianeously incorporated in the diet. [2]

Plant estrogens are "weak" estrogens that can modulate the more powerful effects of endocenous estrogen. This receptor interaction explains, in part, why phytoestrogens may be a better option than potent synthetic or animal-derived estrogens that are used in conventional HRT. [3] Soy isoflavones have very versatile health giving benefits. [3] The principal soy isoflavones include genistein, daidzein, and glycitein. These isoflavones have become available in predictable amounts in certain dietary supplements. Much research has occurred with these isoflavones to characterize their biopharmaceutical effects. The benefit of phytoestrogens may relate both to their much weaker effects than human, animal, or synthetic estrogens and to their different target organs of action in the human body. [2,3]

Soy isoflavones are active in inhibit in the growth of many different types of cancer (breast, prostate, and colon), and they have complex metabolic effects including a role in lowering blood cholesterol. [2] It has been clearly documented by many leading world experts that soy isoflavones are hormonal in action, and this action accounts for their ability to have a beneficial effect in breast cancer prevention, and perhaps treatment. [2,4,5]

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"Hot flushes or flashes" are much less prevalent in Japanese than in Western women.

Estrogenic Activities of Isoflavones

Soy isoflavones and their metabolites are estrogen mimics that are often freely bioavailable from soy protein diets.[2] Unfortunately, the individual activities of each isoflavone and its many intermediate metabolites remain to be defined adequately. A disproportionate amount of knowledge exists about the biologic activity of cenistein in comparison with the other isoflavones or their metabolites. This is primarily because genistein is often used in a pure format to study basic mechanisms of the actions of isoflavones in biologic systems. The complex biopharmacology of isoflavones indicates that some of the results of experiments that use pure genistein may not be applicable to an understanding of the effects of the natural inclusion of soy isoflavones in the diet.[2]
Other issues cloud an understanding of the bioactivity of isoflavones. Observations in animal experiments may be made with pharmacologic doses of isoflavones, as opposed to physiologic doses of isoflavones, and the metabolic fate of isoflavones may vary considerably by species of animal or perhaps administered dose. Parrots in New Zealand and captive cheetahs in zoos in North America may die when fed isoflavone-rich food but humans do not. Proposed mechanisms of the effect of isoflavones on estrogen receptors in humans are now complicated by the recent characterization of different forms of estrogen receptors in humans. Finally, isoflavones have clear nonlinear dose response effects in many animal models, including humans.[5] This nonlinear effect is common in biosystems that are tested with biopharmaceuticals. This situation is often the hallmark of hormonal effects.

Many studies that have been performed in several in vitro and in vivo models demonstrate that isoflavones are capable of binding to estrogen receptors and they often exhibit varying degrees of "weak" estrogenic activity.[5] In addition, some animal studies demonstrate an anti-estrogenic effect of isoflavones.[4,5] Furthermore, it is documented that isoflavones can counteract the effects of relatively high doses of synthetic estroclens by "competitive" receptor binding or other mechanisms.

Isoflavones and their metabolites show variable dissociation rates for estrogen receptor binding and this binding may often produce a series of cytosolic events that are very similar to the effects of estradiol. However, isoflavones do not show effective nuclear binding. The cell nucleus is a principal site of the estrogen receptors. It is recognized that the amino acid sequences of several receptors that bind hormonal steroids, or perhaps nonsteroidal phvtoestrogens, have homologies with the result that isoflavones mav regulate cellular activity by an interaction with homologous receptors.[5]

The affinity of estradiol receptors for phytoestrogens seems to be overall less than that of estradiol by a factor of about 100 times. For example, the relative binding affinity of estradiol receptors in the uteri of rabbits has been shown to be 175 times lower for genistein than for 17 beta-estradiol. Studies performed three decades ago showed that genistein, when given at the same time as estradiol, resulted in a variable displacement of estradiol from receptors in the uteri of mice that had undergone oophorectomy.[4]

Potential Significance of Estrogenic Effects of Soy Isoflavones

Phytoestrogens in soy have similar properties to other naturally occurr in nonsteroidal estrogens, such as coumestan, present in forages and legumes, resorcyclic acid lactones, and mycotoxins produced by the mold *Fusarium rosetim.* This mold can grow on several types of grains during storage and it often produces zearalenone, which can be metabolized to the compound zearalenol. Zearalenol has contraceptive properties and can be used to ameliorate menopausal symptoms. In common with zearalenol, soy isoflavones have been proposed as having potential use as postmenopausal hormone replacement therapy.[4]

Soy Isoflavones and Menopause

Earl Lindell, Ph.D.,[6] in his popular, consumer book titled *Earl Mindell's Soy Miracle,* points to the value of soy in suppressing menopausal symptoms. Dr. Mindell clearly reports the results of studies by Canadian researchers of Japanese women where menopausal complaints such as "hot flushes or flashes" are much less prevalent in Japanese than in Western women.[6] The use of a dietary supplement that contains enough isoflavones to achieve daily intakes of isoflavones similar to those taken by Japanese women in their diet may be beneficial in suppressing moderately severe symptoms of the menopause. Dietary supplementation with phytoestrogens may offer a possible alternative to the commencement of synthetic, or animal-derived, hormone therapy, with all its known drawbacks.

The female climacteric marks the emergence of cardiovascular disease, osteoporosis, and certain age-related cancers. Old age complements the development of these degenerative diseases and heralds the occurrence of cerebrovascular disease and diminished renal function. The prospect of using a natural means with soy isoflavone supplementation to reverse these adverse associations of the menopause is very exciting.

Soy Isoflavones and Menopausal Symptoms-The Data

Convincing epidemiologic data imply that the lower incidence of menopausal symptoms in the Asian female, compared with Western women, may be related to an enhanced dietary intake of isoflavones of soy origin. This epidemiologic observation supports the potential role of soy isoflavones in controlling menopausal symptoms. Many recommendations have been made in contemporary medical literature and the lay press to incorporate soy into the diet during the female climacteric. Formerly, considerable anecdotal evidence existed that soy products, containing isoflavones, are effective in relieving menopausal symptoms. These observations have

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remained unconfirmed, until recently. New controlled clinical studies in several countries demonstrate unequivocal benefits of soy isoflavones in the variable control of menopausal symptoms and its negative consequences. [4,5]

Dr. John Eden[7] and his colleagues at the Royal Hospital for Women in New South Wales, Australia, are focusing their research on the potential hormonal effects of isoflavones in the menopausal female. In pilot studies of nine women given 160 mg of isoflavones daily for three months, a statistically significant reduction occurred in several menopausal symptoms, especially hot flashes. [7] These studies resulted in a conclusion that isoflavones appear to be useful therapy for females with mild to moderate symptoms of the female climacteric. These results have been confirmed to some degree in studies performed at Tufts Universitv School of Medicine in Boston, Massachusetts, where the use of a soy bar (containing isoflavones) resulted in a small decrease in menopausal symptoms over a 12-week period, compared with placebos it should be noted that the daily isoflavone intake in the latter study was much lower (at 40 mg per day) than that in the studies by Eden et al. (at 160 mg per dav). [7]

Studies in the United Kingdom[9] corroborate the findings of the benefit of soy isoflavones in the treatment of menopausal symptoms that have been observed in both Australia[7] and the United States. [8] The United Kingdom study was notable in that it included females with severe vasomotor symptoms and it was performed in a rigorous double-blinded, crossover format with a placebo control. Results in 20 of the 27 menopausal females in the study were reported at the Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. [5] (Sept. 15-18, 1996, Brussels, Belgium). In this carefully constructed study by Harding et al., [9] several hormonal parameters were measured as a consequence of soy supplementation (80 mg per day of total isoflavones) and compared with placebo. Interim analyses of the data showed that serum isoflavones were, as anticipated, high in the soy supplemented group and increases in growth hormone and prolactin were noted with soy supplementation but not with placebo. In contrast, levels of luteinizing hormone and blood cholesterol fell during the period of soy supplementation.

Of overriding significance in the Harding study was the clear demonstration that a statistically significant reduction in hot flashes was noted on the soy diet. It seems probable that these trends will be borne out on completion of the study and that these results justify the assertions of Harding et al. that these findings suggest that soy isoflavones have estrogenic properties in menopausal women. The data indicate that isoflavones mav act on the pituitary to increase prolactin and growth hormone levels, whilst conferring the benefit of reduced hot flashes and reductions in serum cholesterol. It should be noted that not all females can expect amelioration of menopausal symptoms with soy isoflavones; synthetic HRT is also not universally successful. The main issue is that soy isoflavones are natural and probably safe at controlled and "therapeutic" dosages, whereas estrogen supplements may not be quite as safe at therapeutic dosages.

Can Soy Isoflavones Be Used as Natural HRT?

Dr. Gregory L. Burke, [10] of Wake Forest University in Durham, North Carolina, has performed clinical research that supports a possible role of soy isoflavones as a natural, dietary alternative to HRT with synthetic, or animal-derived, estrogens. In a scientific paper presented recently at the symposium in 1996, in Brussels, Belgium, Dr. Burke drew attention to the demonstrable reduction in the risk of osteoporosis and cardiovascular disease with synthetic HRT but questioned the risk-benefit ratio of this therapy. Soy isoflavones present an appealing alternative to current HRT strategies.

The fact that 85 percent of postmenopausal females in the United States do not use HRT makes a dietary consideration for menopausal relief, such as soy, a major public health potentials.This situation, together with the knowledge that dietary intake of soy protein containing isoflavones may account for the reduced risk of several chronic diseases, dictates the need for further studies to clarify the role of phytoestrogens as a natural alternative to synthetic HRT.

Dr. Burke[10] has reported short-term studies of soy protein supplementation of the diet. In these studies, 50 perimenopausal women were enrolled in double-blinded, crossover studies over a period of six weeks and were shown to have improvements in both menopausal symptoms and health-related quality of life compared with those who received a placebo. Furthermore, the females who received soy showed improvements in both blood pressure and serum lipids, even despite their normal initial blood lipid and blood pressure status.

Words of Caution About Isoflavone Dosage

It should be noted that isoflavones in high doses have a number of putative adverse effects. This has led to a stern warning that nutriceutical products or dietary supplements containing isoflavones must be used with caution. Setchell[11] (and many others) have postured against what have been termed “nutrichemical supplements and pills" containing isoflavones because of negative effects that can be anticipated from the potent biologic activity of certain isoflavones.

The circumstances are clouded, to some degree, by the lack of definition of the optimal dose of isoflavones that could be used in natural HRT. The most reasonable approach would be to choose a recommended level of daily isoflavone intake that does not exceed the amount of isoflavones that are consumed in existing diets that contain plentiful amounts of soy. In the author's opinion, this dose lies somewhere between 50 and 100 *mg* of isoflavones per day for the adult, and at this dose range, toxicity is unlikely. Considerable precedent exists for the safety of isoflavones from Asian diets that may contain up to 100 mg of isoflavones per day without adverse effects. A safe compromise may be not to exceed 80 mg of total isoflavone intake daily and this of intake certainly matches the level at which beneficial therapeutic effects have been noted in clinical research that has shown beneficial health effects of isoflavones in

In one study of postmenopausal women, feeding of 40 gm/day of soy protein containing 2.25 mg/gram of total isoflavones resulted in significant increases in bone mineral content and bone mineral density.

menopausal females. [8-10] (Isoflavone supplements are not recommended in childhood or during pregnancy and, in the author's opinion, should be monitored by an experienced and licensed health care provider.)

Soy Isoflavones and Osteoporosis

Several studies in animals and humans confirm that a soy protein diet containing isoflavones will prevent bone loss that is associated with ovarian hormone deficiency. Dr. Arjmandil[12] and his colleagues have drawn attention to the efficacy of ipriflavone (a synthetic isoflavone) in preventing bone loss in animal and human clinical trials. These scientists have examined an inference of the benefit of soy isoflavones on bone loss and have shown unequivocally in animals that soy isoflavones are effective in preventing bone loss over the short term. This observation leads support to the widely held belief that dietary incorporation of soy protein containing isoflavones can be effective in preventing postmenopausal bone loss.

In common with epidemiologic data that show a lack of menopausal symptoms in association with dietary intake of isoflavones, recent population studies indicate a lower prevalence of osteoporosis-related fractures in postmenopausal females in Asia compared with females in Western countries. One of the several proposed explanations for this latter epidemiologic observation is the relatively large intake of soybean products in the Asian diet. Prevalence data on osteoporosis in Western and Eastern communities are confusing but bone densitometry measurements are made in the "urban" Orient in Southeast Asia, where Western diets may now prevail.

The beneficial soy elements are believed to be the isoflavones that account for this effect. This hypothesis has been tested in controlled studies of changes in bone density in ovariectomized rats that were administered genistein by injection [13,14] in bone cell lines cultured with the addition of estradiol or genistein, [14] in isolated osteociasts treated with genistein, [15] and in postmenopausal females who received six months of dietary supplementation with soy protein containing isoflavones. [16,17] In addition, studies of the benefit in dietary supplementation with soy milk, containing extra calcium, are under wav with favorable preliminary results of bone gain in women with low bone mass. [18]

Overall, studies of the administration of soy isoflavones and/or soy protein containing isoflavones have produced encouraging results in the prevention of bone loss and perhaps the reversal of low bone density. Blair[15] has demonstrated that osteoclastic activity, causing bone resorption, is inhibited by genistein. The mechanism of the inhibition of osteoclastic bone resorption by genistein is believed to be related to its action as a tyrosine kinase inhibitor. In vitro experiments suggest that genisteiii exerts these effects without binding to bone and without inhibiting osteoclastic attachment to bone. [15] Observations of the effects of the inhibitory concentrations of genistein on protein synthesis in osteoclasts and safety studies in ovariectomized rats imply that the suppression of osteoclastic activity by genistein in vitro and in vivo has low, if any, potential for toxicity.

Studies by Fanti et al. [13] of the systemic administration of genistein to ovariectomized rats indicate that genistein partially prevents bone loss by a nonestrogenic mechanism. The short-term effects of soy isoflavones on bone composition in postmenopausal women fed a diet containing soy protein with isoflavones is quite striking. [16] In a study involving postmenopausal females over a 6-month period, the feeding of 40 gm/day of soy protein containing 2.25 mg/gram of total isoflavones resulted in significant increases in bone mineral content and bone mineral densitv in the lumbar spine, compared to a control group who received lower quantities of soy isoflavones or casein/non-fat dry milk in their diet. [16] The calcium intake in all groups was similar in these studies and these findings were interpreted as indicating a potential role for soy isoflavones in the promotion of skeletal health in the postmenopausal female. [16] The effects of estrogens in synthetic, animal-derived, or plant-derived format are most noticeable on canallous bone rather than cortical bone.

Overall, phytoestrogens, especially genistein in soy, appear to have effects on the prevention of osteoporosis similar to the effects seen with synthetic HRT, but perhaps without the Associated health risks of synthetic, or animal-derived, estrogens.

Soy and Cardiovascular Disease

The most relevant studies of soy in the promotion of cardiovascular health in the postmenopausal female are those that directly examine the effect of soy diets on plasma lipid profiles in the postmenopausal state. [19] In addition, several clinical studies demonstrate beneficial cardiovascular effects of soy protein and isoflavones that work in a manner that is independent of serum cholesterol reductions. [20-22]

Dr. Susan Potter[19] and her colleagues have performed many studies on the effects of soy protein and the mechanism of such effects in lowering blood cholesterol. In a recent study of 66 hypercholesterolemic postmenopausal females who received soy protein containing variable amounts of isoflavones, it was noted that soy protein with isoflavone exerted positive influences on blood lipids, thereby decreasing the risk of cardiovascular disease in the postmenopausal state. This conclusion is supported by the finding of several antiatherogenic factors in soybeans, 20 including antioxidant properties to protect against low density lipoprotein oxidation[21] and the inhibition of platelet aggregation with an antithrombotic effect. [22] The antithrombotic effects of isoflavones contrast with the thrombotic potential of conventional HRT.

Other Benefits of Soy in the Postmenopausal State

Soy protein containing isoflavones has chemoprotective effects against breast and colon cancer and its amino acid content promotes renal health and calcium retention. The prevention and potential treatment of prostatic cancer by soy isoflavones should catch the eye

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of those interested in the andropause of the mature male. [3] Messina has extensively reviewed the in vitro and in vivo evidence for the cancer-protective effects of soy. Much evidence seems to link this proposed cancer-protective action of soy with the isoflavone content of soybeans. [2]

A host of other studies suggest even more diverse health benefits of soy incorporation in the diet including observations that soy protein isolates are good protein sources in weight reduction diets. There are studies that indicate gallstone prevention is possible by soy intake. There are beneficial effects of soy on muscle tissue and even a possible role for daidzein in the suppression of alcohol intoxication and "appetites" for alcohol, at least in animals. [5]

Finally, genistein is antiangiogenic and it may play a role in the prevention or therapy of angiogenesis-dependent diseases such as cancer, psoriasis, arthritis, and ocular disease.

Are Phytoestrogens Safe?

The worldwide consumption of soy in healthy populations without evidence of reproductive problems provides good support for the safety of soy isoflavones. [2] There is much reassurance about the safety of the use of isoflavones in amounts similar to those that are consumed in Asian diets that are plentiful in soybean foods. Several investigations have failed to show anv significant untoward effects of commercial or natural soy-based diets on embryonic development or male gonadal function and soy diets have never been associated with a risk of carcinogenesis. Whitten et al.'s[23] studies in the rat have shown toxicity of coumesterol, which is the most potent estrocen of the isoflavonoid category. However, coumesterol is not detectable in the urine of humans receiving soy diets and it is present in only small amounts in soy in comparison with other isoflavones. The putative adverse effects of phytoestrogens that include developmental disorders and male gonadal dysfunction have not surfaced in humans. There is no evidence that these adverse effects occur in humans at doses of isoflavone intake that are encountered in even the most soy-rich diets. Arguments that soy protein is inferior to animal protein are fatuous and have reemerged as a consequence of the challenge that soy presents to the animal protein purveying, fast-food industry.

The isoflavones genistein and daidzein and their metabolites are potent and versatile in their biologic effects. Their broad actions and variability of biologic effects dictate that more work is required to define each isoflavone and its derivatives in terms of site of action, hormonal activities, and short- to long-term effects. [2]

Conclusion

There is a major potential for soy isoflavones contained within soy protein as potential alleviators of the negative consequences of "the change of life" in females. Soy diets have been used worldwide for thousands of years without major safety concerns. The incorporation of soy protein containing isoflavones at levels that do not exceed those obtained from an Asian diet seems to offer a simple, natural solution to many problems associated with the menopause. The risks of soy incorporation into the diet of a menopausal female or the use of appropriately formulated dietary supplements by the perimenopausal female may be, on balance, safer than the risk of hormone replacement therapy with potent synthetic or animal-derived estrogens. Therapeutic equivalence between soy isoflavones and HRT cannot be assured. Many women are considering soy protein containing, isoflavones as a first-line option for menopausal relief and this is being continuously reinforced by the media, with apparent good cause. □

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