The Potential of Soybean Phytoestrogens for Postmenopausal Hormone Replacement Therapy (44246)

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Abstract. **Hormone replacement therapy for postmenopausal women greatly reduces their risk of coronary heart disease. However, current pharmaceutical regimens have a low acceptance rate among postmenopausal women. We have sought to identify an alternative treatment that would retain the beneficial health effects of current standard therapy without its negative aspects. We have concentrated our research on naturally occurring estrogens (called phytoestrogens) found in soybeans, in the belief that delivery of phytoestrogens *via* the diet would be more acceptable than pharmaceutical regimens. Using a well-established nonhuman primate model of postmenopausal women, we have investigated the effects of soy phytoestrogens on cardiovascular risk factors and the reproductive system. In this review, we summarize the results of our ongoing research.** [P.S.E.B.M. 1998, Vol 217]

Among the clinical consequences of postmenopausal estrogen deficiency, deaths associated with coronary heart disease represent the largest public health concern. Coronary heart disease is the leading cause of death among women, accounting for 36% of all deaths (1), about three times more deaths than from breast and lung cancers combined. Over the past 50 years, a mixture of estrogens from pregnant mares' urine (conjugated equine estrogens [CEE], or Premarin) has been used widely to replace the lack of endogenously produced estrogen among postmenopausal subjects. The favorable impact of postmenopausal estrogen replacement therapy (ERT) on coronary heart disease morbidity and mortality among postmenopausal women is large (2–7). A meta-analysis of these various studies has indicated that coronary heart disease risk is nearly 50% lower in women who take postmenopausal estrogen compared to those who do not (8).

The potential public health impact on morbidity and mortality from coronary heart disease by postmenopausal estrogen therapy has been minimized, however, because the majority of women find the treatment unacceptable. Compliance with postmenopausal ERT has been studied by a number of investigators (9–14), and if one averages their estimates of compliance, only about 8% of women who are naturally menopausal use ERT.

Ravnikar has studied reasons for lack of compliance with ERT among postmenopausal women (15, 16). Lack of compliance stems primarily from fear of breast cancer and complications related to the necessity of accompanying progestin therapy (i.e., continuing menstrual periods).

In order to find a regimen of postmenopausal ERT that would be more acceptable to postmenopausal women, we have sought to identify an alternative that would protect against breast cancer, obviate the need for a progestin, and still provide protection against CHD.

Rationale for Soybean Estrogens

For more than 50 years, soy protein has been recognized to have beneficial effects in retarding the progression of atherosclerosis (17). However, the components of the soy responsible for this effect were not understood clearly (18–24). Recently, we provided evidence that the phytoestrogens in soy induce striking improvements in the plasma lipids and lipoproteins of macaques (24). In those studies, we fed a moderately atherogenic diet, with the source of dietary protein either containing only traces of phytoestrogens, 0.17 mg phytoestrogens/g of isolate (Soy(–)), or containing 1.7

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Table I. Effects of Soy Protein Diets with (Soy(+)) or Without (Soy(−)) Isoflavones on Lipids and Lipoproteins in Female Rhesus Macaques[a]

Parameters	Soy(+)	Soy(−)	*P* value[b]
Total plasma cholesterol	246 ± 16	338 ± 28	0.009
LDL + VLDLC	161 ± 14	264 ± 31	0.003
HDLC	85 ± 5	74 ± 7	0.05
Total:HDLC ratio	3.01 ± 0.21	5.87 ± 1.01	0.005
Apolipoprotein A-I	297 ± 17.6	219 ± 17.6	0.004
Apolipoprotein A-2	18.6 ± 1.17	16.0 ± 0.88	0.03

Note. HDLC = high density lipoprotein cholesterol; LDLC = low density lipoprotein cholesterol; TPC = total plasma cholesterol; VLDLC = very low density lipoprotein cholesterol.
[a] Values are mean ± SEM. All values in mg/dl unless otherwise noted. Details of diet compositions given in text.
[b] Analysis by paired *t*-test.
Adapted from Ref. 24.

mg phytoestrogens/g of protein (Soy(+)). The differences that we observed in the plasma lipid and lipoprotein concentrations in the two groups among the female animals are summarized in Table I.

We have focused on the phytoestrogens of soybeans (SBE) as a potential nutritional alternative based upon the putative protective effect of these compounds against the development of breast cancer (25–30), the likely lack of a harmful effect on the uterus (31–37), and an experimental basis for assuming probable favorable effects on coronary artery atherosclerosis, including antioxidant properties (38) and inhibition of smooth muscle cell proliferation (39). Additionally, a nutritional supplement derived from a natural product may be more acceptable than a pharmacologic therapy and thus improve compliance.

Effects of CEE and SBE on Plasma Lipids and Lipoproteins

We have compared the effects of CEE and SBE on the plasma lipids and lipoproteins of surgically postmenopausal cynomolgus monkeys. In that study, 189 surgically postmenopausal monkeys were randomized into three groups (all fed a moderately atherogenic diet): one group fed a soy isolate with only trace amounts of genistein and daidzein as the source of dietary protein (Soy(−)); one fed a soy isolate with the naturally occurring amounts of genistein and daidzein (1.7 mg/g) (Soy(+)); and one fed the Soy(−) diet with CEE added at a dose equivalent for a woman of 0.625 mg/day (Soy(−) + CEE). Our preliminary observations are summarized in Table II. Generally, SBE (Soy(+)) has the same beneficial effects as CEE on the plasma lipids and lipoproteins of postmenopausal monkeys. There are at least two ways in which SBE appears to be superior to CEE. First, SBE does not result in hypertriglyceridemia, which is consistent with the effect of all mammalian estrogens. Second, SBE results in strikingly beneficial increases in concentrations of apo A-I.

Effects of SBE on Hormone Concentrations and Reproductive System Organ Weights

As we have indicated, it is important to explore if and to what extent SBE affects adversely various hormone concentrations and the reproductive system. Particularly important is whether SBE changes plasma estradiol concentrations or is uterotrophic. We have reported a study in which we compared peripubertal female rhesus monkeys fed diets containing either Soy(−) or Soy(+) isolates. The lack of effect of SBE on hormone concentrations and uterine weight is summarized in Table III.

Further evidence for a lack of SBE effect on the female reproductive system has been reported by our group previously (40). In that study, the maturation index of exfoliated vaginal cells of monkeys treated either with CEE or SBE was compared. CEE resulted in the expected increase in maturation index, whereas no effect of SBE was found (Fig. 1). CEE had its expected effect on the keratinization of exfoliated vaginal cells, whereas no effect of SBE was seen.

Evidence of Arterial Estrogen Agonist Effects

Both mammalian and synthetic estrogens have been shown to have beneficial effects on coronary artery endothelium-derived relaxation (41, 42). In those experiments, atherosclerotic cynomolgus macaque females were shown

Table II. Effects of Conjugated Equine Estrogens (CEE) Versus Soy Protein Diets With (Soy(+)) or Without (Soy(−)) Isoflavones on Lipids and Lipoproteins in Surgically Postmenopausal Cynomolgus Macaques[a]

Parameters	Soy(−) (*n* = 41)	Soy(+) (*n* = 56)	CEE (*n* = 41)	*P* values[b]		
				Soy(−) vs Soy(+)	Soy(−) vs CEE	Soy(+) vs CEE
TPC	391	340	334	0.01	0.008	NS
Triglycerides	30	33	49	NS	0.0001	0.0001
HDLC	66	70	54	NS	0.002	0.0001
LDLC + VLDLC	325	272	278	0.02	0.05	NS
TPC/HDLC ratio	8.02	6.25	9.04	NS	NS	NS
Apolipoprotein A-I	211	265	220	0.0003	NS	0.002

Note. HDLC = high density lipoprotein cholesterol; LDLC = low density lipoprotein cholesterol; NS = not significant; TPC = total plasma cholesterol; VLDLC = very low density lipoprotein cholesterol.
[a] All values in mg/dl. Details of diet compositions given in text.
[b] Analysis by ANCOVA, baseline variable and premenopausal treatment group used as covariates.

Table III. Effects of Soy Protein Diets With (Soy(+)) or Without (Soy(−)) Isoflavones on Hormone Concentrations and Uterine Weights in Female Cynomolgus Macaques[a]

Parameters	Soy(+)	Soy(−)	*P* value
Free thyroxine (ng/dl)[b]	0.58 ± 0.067	0.51 ± 0.064	0.29
Sex hormone-binding globulin (μg/dl)[c]	2.21 ± 0.115	2.31 ± 0.115	0.33
Dehydroepiandrosterone sulfate (μg/dl)[b]	47.2 ± 6.68	48.6 ± 6.91	0.87
Estradiol (pg/ml)[b]	9.9 ± 1.87	12.5 ± 2.52	0.42
Uterine weight (g)[c]	1.12 ± 0.087	1.07 ± 0.087	0.72

Note. Adapted from Ref. 24.
[a] Values are mean ± SEM. Details of diet compositions given in text.
[b] Analysis by paired *t*-test.
[c] Analysis by ANCOVA, age and body weight used as covariates.

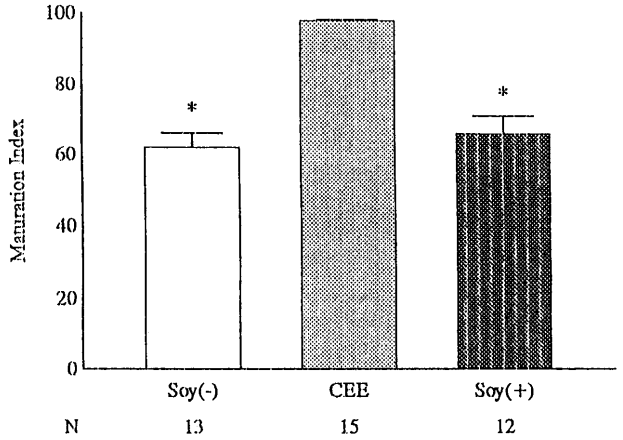

Figure 1. Maturation index, a descriptor of vaginal cytologic characteristics, in surgically postmenopausal cynomolgus monkeys given conjugated equine estrogens (CEE) versus soy protein diets with (Soy(+)) or without (Soy(−)) isoflavones. Numbers below bars indicate numbers of animals per group. Adapted from Ref. 40.

to undergo constriction of coronary arteries following acetylcholine infusion. Pretreatment of the animals with estrogen restores their normal endothelial-derived vasomotion, and atherosclerotic female monkeys with pretreatment constriction had normal vasodilation restored. Estrogen is normally combined with a progestin, most commonly medroxyprogesterone acetate (MPA) in the United States, in postmenopausal hormone replacement. We found that the combined hormone therapy was not as beneficial as estrogen-only therapy on vasodilation of atherosclerotic coronary arteries (43). Thus, the progestin in usual hormone replacement antagonized the benefits of estrogen. We have viewed the therapeutic effect of estrogen as an indicator of estrogen agonist effects on the coronary arteries, and thus have sought to determine how SBE compared with estrogen-only and combined hormone replacement on coronary artery vasomotion.

In Figure 2 we summarize the results of two experiments in which atherosclerotic female monkeys were treated with CEE (estrogen-only), CEE + MPA (combined hormone replacement), or SBE (Soy(+)) (44). These data suggest to us an estrogen agonist effect of SBE on coronary arteries that is comparable to that of CEE and that both these treatments are superior to the usual combined hormone replacement regimen of CEE + MPA.

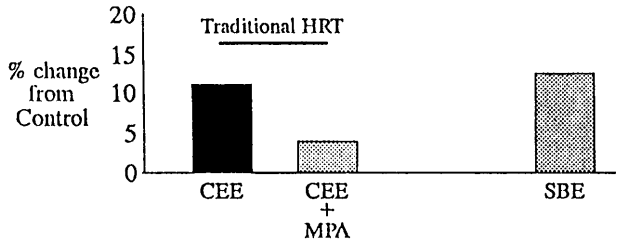

Figure 2. Effects of conjugated equine estrogens (CEE), combined hormone replacement therapy (HRT) given as CEE plus medroxyprogesterone acetate (CEE + MPA), and dietary soybean estrogens (SBE) on coronary artery reactivity, expressed as percentage change in dilation from control, in atherosclerotic female monkeys. Adapted from Ref. 43 and Ref. 44.

Summary

In the early stages of our investigation, it appears that SBE has some effects that may warrant its consideration as a postmenopausal estrogen replacement moiety. A favorable effect on postmenopausal lipoprotein and lipid concentrations along with a lack of effect on the female reproductive system, are considered favorable findings relative to its potential usefulness. Remaining to be assessed, however, are the effects (if any) of SBE on postmenopausal bone loss and if and to what extent SBE has estrogen agonist effects on the brain.

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