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Hormonal Response to Diets High in Soy or Animal Protein Without and With Isoflavones in Moderately Hypercholesterolemic Subjects

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Abstract: *Consumption of soy protein has been associated with altered risk of developing endocrine-regulated cancers. This study was designed to assess the independent effect of soy relative to animal protein and soy-derived isoflavones on circulating estrogen and androgen concentrations in postmenopausal women and older men. Forty-two subjects (> 50 yr) with low-density lipoprotein cholesterol levels of ≥3.36 mmol/l were fed each of 4 diets in randomized order for 6 wk/phase. All food and drink were provided. Diets contained 25 g soy or common sources of animal protein/4.2 MJ containing trace or 50 mg isoflavones/4.2 MJ. At the end of each diet phase, concentrations of estrone sulfate, estrone, estradiol, testosterone, androstendione, dihydrotestosterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate were measured. In postmenopausal women, concentrations of estrone were higher and its precursor, dehydroepiandrosterone, lower after consuming the soy compared with animal protein diets (*P *= 0.0396 and 0.0374, respectively). There was no significant effect of isoflavones on any of the hormones measured. In older men, dehydroepiandrosterone sulfate concentrations were lower after consuming the isoflavone (*P *= 0.0106) and higher after soy, compared with the animal protein diets (*P *= 0.0118). These data suggest that relatively large amounts of soy protein or soy-derived isoflavones had modest and limited sex-specific effects on circulating hormone levels.*

Introduction

Women in Asian populations consuming high amounts of soy products have been reported to be at lower risk for developing breast cancer than Western women (1–3). A number of studies have reported an inverse relationship between soy intake and circulating levels and urinary excretion of estrogen in both Asian and non-Asian women and men (4–11). Pooled analysis of prospective studies of postmenopausal women have indicated that serum estradiol levels were approximately 15% higher in women who had breast cancer compared with women who did not develop the disease (12). Other studies, which focused on determining the association between soy food consumption and sex hormone levels, have been less consistent (13–19). Menstrual status, the type of soy product, and whether the measurements were based on urinary or serum estrogens can all be factors contributing to these inconsistencies.

The role of estrogens and androgens in prostate cancer is controversial. Estrogen treatment slows the growth of prostatic cancer (1). Plasma estradiol levels are lower in men with prostate cancer compared with patients with benign prostatic hyperplasia (20).

This article describes a study involving four diets fed in a randomized order to postmenopausal women and older men. The study was designed to determine whether soy protein or soy-derived isoflavone alter serum sex hormone levels. This is the first controlled diet intervention that investigates separately the association between soy protein and isoflavones on the concentration of serum hormones.

Methods

A description of the study design, subjects, and diets has appeared in a prior publication that focused on the effect of soy protein and isoflavones on plasma lipids and lipoprotein concentrations (21). This report addresses a different experimental question. An abbreviated description of the experimental design, subjects, and diets follows. This study protocol was approved by the Human Investigation Review Committee of New England Medical Center and Tufts University.

Subjects

Forty-two subjects over the age of 50 yr with low-density lipoprotein cholesterol levels greater than 3.36 mmol/l were recruited from the greater Boston area. Subjects were not taking

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medications known to affect blood lipid levels, and all women were postmenopausal. The mean age of the women ($n = 24$) was 64 years, and mean body mass index was 27 kg/m^2. The mean age of the men ($n = 18$) was 61 years, and mean body mass index was 26 kg/m^2. Due to limitations in the amount of plasma available for these analyses, hormonal determinations were performed on plasma samples from a subset of the original study cohort. Data for the maximal number of subjects were obtained for each measure, dependent on the availability of plasma from each of the four diet phases.

Experimental Design

Study subjects were provided with each of four experimental diets—soy protein depleted of isoflavones (soy/-), soy protein enriched in isoflavones (soy/+), animal protein with no added isoflavones (animal/-), and animal protein with added isoflavones (animal/+)—for periods of 42 days according to a double-blind randomized crossover design. All food and drink were provided to the subjects. Body weight was maintained throughout the study period. Fasting blood samples were obtained at the end of each diet phase.

Diets

For animal/- and animal/+ diets, the variable protein component was contributed by dairy and meat. Isoflavones, in the form of a powdered concentrate (Archer Daniels Midland Company, Decatur, IL), were mixed into different food items of the animal/+ diet. For the soy/- and soy/+ diets, the variable protein component was contributed by specially prepared batches of isolated soy protein, one depleted (0.12 mg aglycone/g protein) and one enriched (1.96 mg aglycone/g protein) in isoflavones (Protein Technologies, St Louis, MO). Mean soy protein intake of the female subjects was 55 ± 6 g/day and male subjects was 71 ± 18 g/day. The mean isoflavone intake of the female subjects was 108 ± 12 mg/day and male subjects was 139 ± 35 mg/day. Chemical analysis of food homogenates was carried out by Covance Laboratories Inc. (Madison, WI); dietary isoflavones analysis was carried out in the laboratory of Dr. Patricia A. Murphy (Iowa State University, Ames IA). The diet composition is expressed as percent of energy for the macronutrients and per 4.2 MJ for the fiber, cholesterol, and isoflavones (Table 1).

Hormone Analysis

The plasma concentrations of estrone, estrone sulfate, estradiol, testosterone, dehydroepiandrosterone, dihydrotestosterone (DHT), and dehydroepiandrosteone sulfate (DHEAS) were measured using radioimmunoassays (ICN, Costa Mesa, CA). Celite column chromatography was used for sample separation prior to the analysis of estrone,

Table 1. Nutrient Composition of Each of the Experimental Diets as Determined by Chemical Analysis of Food[a]

Constituent	Soy/-	Soy/+	Animal/-	Animal/+
		(percent of energy)[b]		
Carbohydrate	45	46	47	48
Protein	17	16	17	15
Fat	38	37	36	36
Saturated fatty acids	12.7	11.3	12.0	11.8
16:0	5.7	5.1	5.9	5.7
18:0	2.4	2.2	2.4	2.4
Monounsaturated fatty acids	14.7	14.4	14.2	14.3
18:1	14.0	13.8	13.5	13.6
Polyunsaturated fatty acids	6.1	6.1	5.6	5.7
18:2	5.1	5.1	4.7	4.8
18:3	0.7	0.7	0.6	0.6
		(per 4.2 MJ)		
Fiber	1.0	1.1	1.2	1.1
Cholesterol	151	150	154	168
Total isoflavones	1.25	46.21	N.D.	51.71
Genistein	0.37	27.17	N.D.	26.80
Daidzein	0.84	13.89	N.D.	20.68
Glycitein	ND[c]	5.16	N.D.	4.23

a: Soy/- denotes soy protein depleted of isoflavones, soy/+ denotes soy protein enriched in isoflavones, animal/- denotes animal protein without isoflavones, and animal/+ denotes animal protein with isoflavones.
b: Because of rounding, percentages may not total 100.
c: ND denotes not detectable.

estradiol, and testosterone. The estrone standard curve was used for the quantification of estrone sulfate. Hormone measurements were batched for each subject so that samples for all four diet cycles were measured in the same assay.

Isoflavone Analysis

Plasma genistein and daidzein in fasting plasma samples were measured by time-resolved fluoroimmunoassay using a validated method (22).

Statistical Analysis

Prior to the analysis, descriptive statistics and graphs (PROC UNIVARIATE and PROC MEANS; SAS, Cary, NC) were used to summarize the overall effects of diets. All hormone variables were log transformed before analysis. A two-way analysis of variance (PROC GLM; SAS) with main effects of dietary protein type and isoflavone content (trace or supplemented) with subject as a repeated measure was carried out for each outcome measure.

Results

Effect of Dietary Isoflavones on Plasma Isoflavone Levels

Fasting plasma genistein levels were 50 ± 37, 617 ± 498, 7 ± 12, and 695 ± 443 nmol/l, for subjects fed the soy/-, soy/+, animal/-, and animal/+ diets, respectively. Fasting plasma diadzein levels were 15 ± 9, 139 ± 91, 3 ± 5, and 275 ± 211 nmol/l for the same groups. In all cases, the diets high in isoflavones resulted in at least a nine-fold increase in circulating levels relative to the diets low in isoflavones.

Effect of Protein Source and/or Isoflavones on Plasma Hormone Concentrations for Postmenopausal Women

The nature of dietary protein, but not presence of isoflavones, had a significant effect on the concentration of circulating estrone levels in the female subjects (Table 2). Levels were 13% lower after the women ate the animal/- compared with soy/- diets and 25% higher after women ate the animal/+ compared with the soy/+ diets. In contrast, the animal protein diets resulted in higher plasma concentrations of the androgen dehydroepiandrosterone relative to the soy protein diet, independent of isoflavone content. Levels were 8% higher after the women ate the animal/- compared with soy/- diets and 17% higher after women ate the animal/+ compared with the soy/+ diets.

The relatively high intakes of soy protein did not significantly alter levels of the other steroid hormones monitored. In addition, there were no significant effects of isoflavones, per se, on the outcome measures.

Effect of Protein Source and/or Isoflavones on Plasma Hormone Concentrations for Middle-Aged and Older Male Subjects

In middle-aged and older male subjects, consumption of soy relative to animal protein resulted in a higher circulating concentration of the androgen DHEAS (8%; Table 3). In contrast, the presence of isoflavones resulted in lower plasma levels of DHEAS (14%). There were no other significant ef-

Table 2. Postmenopausal Female Fasting Plasma Hormone Concentration at the End of Each Diet Phase[a]

Variable	Soy/-	Soy/+	Animal/-	Animal/+	*P* Values[b]	
					Protein	Isoflavones
Estrone Sulfate [11]	388 (326 ± 461)	347 (290 ± 415)	375 (316 ± 446)	330 (275 ± 396)	0.0683	0.2826
Estradiol 17-β [10]	54.3 (44.4 ± 66.5)	56.1 (52.9 ± 59.5)	56.3 (52.5 ± 60.2)	55.9 (52.4 ± 59.6)	0.6715	0.6140
Estrone [10]	92.5 (60.6 ± 141.1)	96.0 (79.0 ± 116.6)	80.3 (67.9 ± 95.1)	71.7 (60.7 ± 84.6)	0.0396	0.6956
Testosterone [5]	197 (168 ± 230)	193 (174 ± 213)	185 (163 ± 210)	198 (169 ± 231)	0.6556	0.5937
Androstendione [20]	1,435 (1,280 ± 1,610)	1,237 (1,101 ± 1,390)	1,215 (1,105 ± 1,336)	1,542 (1,394 ± 1,711)	0.7927	0.5471
Dihydrotestosterone [23]	98.5 (87.8 ± 110.6)	90.8 (81.7 ± 100.8)	96.4 (86.1 ± 107.9)	92.1 (81.8 ± 103.7)	0.9471	0.1468
Dehydroepiandrosterone [22]	2,296 (1,966 ± 2,683)	2,324 (2,014 ± 2,682)	2,479 (2,158 ± 2,848)	2,718 (2,392 ± 3,088)	0.0374	0.5414
Dehydroepiandrosterone Sulfate [21]	394 (330 ± 468)	415 (355 ± 485)	435 (369 ± 513)	410 (347 ± 484)	0.6254	0.9473

a: Soy/- denotes soy protein depleted of isoflavones, soy/+ denotes soy protein enriched in isoflavones, animal/- denotes animal protein without isoflavones, and animal/+ denotes animal protein with isoflavones. Number in brackets is number of subjects studied. Values are geometric means in pg/ml. Values in parentheses are mean ± standard error of the mean.
b: The *P* values for the two-way analysis of variance (on log 10 transformed values) are given.

Table 3. Older Male Fasting Plasma Hormone Concentrations at the End of Each Diet Phase[a]

					P Values[b]	
Variable	Soy/-	Soy/+	Animal/-	Animal/+	Protein	Isoflavones
Estrone Sulfate [11]	351.3 (311 ± 397)	346.5 (296 ± 406)	380.0 (338 ± 426)	349.2 (309 ± 394)	0.6357	0.2656
Estradiol 17-β [10]	41.6 (37.9 ± 45.6)	37.8 (36.0 ± 39.8)	39.3 (36.3 ± 42.6)	35.6 (28.1 ± 45.0)	0.8803	0.2487
Estrone [9]	90.2 (69.5 ± 117.0)	87.9 (46.0 ± 167.7)	82.0 (39.7 ± 169.1)	95.6 (39.4 ± 232.0)	0.9079	0.4477
Testosterone [15]	4,099 (3,653 ± 4,600)	4,187 (3,747 ± 4,678)	3,800 (3,293 ± 4,384)	4,281 (3,845 ± 4,768)	0.5635	0.1223
Androstendione [18]	2,044 (1,837 ± 2,276)	2,090 (1,837 ± 2,276)	1,840 (1,659 ± 2,042)	2,082 (1,871 ± 2,318)	0.5182	0.5152
Dihydrotestosterone [15]	470 (423 ± 525)	506 (454 ± 564)	497 (441 ± 560)	545 (493 ± 603)	0.3198	0.3815
Dehydroepiandrosterone [15]	2,963 (2,546 ± 3,448)	3,087 (2,687 ± 3,549)	3,128 (2,746 ± 3,564)	2,905 (2,478 ± 3,405)	0.9379	0.8303
Dehydroepiandrosterone sulfate [14]	1,156 (1,013 ± 1,318)	1,112 (1,004 ± 1,233)	1,065 (964 ± 1,177)	956 (842 ± 1,086)	0.0118	0.0106

a: Soy/- denotes soy protein depleted of isoflavones, soy/+ denotes soy protein enriched in isoflavones, animal/- denotes animal protein without isoflavones, and animal/+ denotes animal protein with isoflavones. Number in brackets is number of subjects studied. Values are geometric means in pg/ml. Values in parentheses are mean ± standard error of the mean Abbreivation is as follows: ANOVA, analysis of variance.
b: The *P* values for the two-way ANOVA (on log 10 transformed values) are given.

fects of type of protein or isoflavones on the steroid hormones monitored.

Discussion

The relevance of the current study is directly related to the dietary and supplement usages of soy protein and soy-derived isoflavones in the United States. The majority of Americans eat diets relatively high in animal protein with few or no soy products, which corresponds to an animal/- diet. There are an increasing number of Americans who are taking isoflavone supplements while adhering to this traditional "Western diet." These individuals would correspond to the animal/+ diet. The supplements are generally in the form of tablets containing between 45 and 55 mg of isoflavones, with a dose recommended at one to two tablets per day. There is a segment of the American population that uses soy products, such as soy milk, tofu, miso, and tempeh, as a regular component of their diets, while consuming small amounts of meat products. Tofu and the other products listed earlier are rich in soy protein and isoflavones (1). This group of people would correspond to the soy/+ diet. Finally, there are an increasing number of consumers who are attempting to lower the animal fat content of their diets. These individuals are consuming soybean isolate-containing foods, such as soy hamburgers, soy burgers, soy hot dogs, and soy bacon bits. These bulk soy ingredients are derived from dehulled, organic solvent extracted soybeans, which in the processing lose most or all of the isoflavone content of the soybean (23). Therefore, an increasing percentage of people eating non-animal derived "imitation" meats are consuming a soy protein-rich and isoflavone-low diet that corresponds to the soy/- diet.

In an attempt to elucidate a mechanism by which soy-containing foods may protect against breast cancer, the effect of soy protein and/or soy-derived isoflavones on circulating and urinary estrogen levels has been monitored in a limited number of studies (4,6–8,24–26). In a study of healthy postmenopausal Chinese women residing in Singapore, women in the highest quartile of soy intake had a significantly lower concentration of serum estrone than the lowest quartile (8). Women at the highest quartile of total isoflavone intake had significantly lower levels of estrone. There was no effect of soy or isoflavones on circulating estradiol concentration. In a breast cancer case-control study of pairs of postmenopausal Chinese women living in Shanghai, the urinary excretion of total isoflavones was lower in the women with cancer than in the control women (25). The risk of breast cancer was significantly lower with increasing urinary excretion of isoflavones.

In premenopausal women, the data have been conflicting for the effects of soy intake on sex hormones. Martini et al. (15) studied premenopausal women, about half of whom were taking oral contraceptives. Soy feeding had no effect on serum estrone, estradiol, sex hormone binding globulin (SHBG), DHEAS, prolactin, or progesterone concentrations, regardless of oral contraceptive use. Verkasalo et al. (4) reported that, in a cross-sectional study of pre- and postmenopausal British women, soy milk intake had no significant effect on plasma concentrations of estradiol, SHBG, follicle-stimulating hormone, leutinizing hormone (LH), progesterone, or menstrual cycle length. Xu et al. (26) reported that premenopausal women fed increasing amounts of soy had significantly lower urinary excretion of estradiol, estrone, and estradiol. Brown et al. (18) found no changes in serum estrogen or androgen concentrations in the luteal or follicular phase of the menstrual cycle in premenopausal women fed soy protein containing 40 mg of isoflavones for two menstrual cycles. In a rare study focusing on men, Allen et al. (19) reported that there was no significant difference among those who consumed no soy milk (< 0.25 pints/day), moderate amounts of soy milk (0.25–0.50 pints/day), or high amounts of soy milk (> 0.50 pint/day) in serum concentrations of testosterone, LH, free testosterone, androstenediol-glucuronide, and SHBG. None of the studies cited earlier were designed to look at the independent effect of soy protein and/or isoflavones. In addition, these studies used soy protein from different sources, and the dose of soy protein and isoflavones varied among studies.

There have been numerous reports showing that various dietary components can alter circulating estrogen and androgen concentrations in women (27–32) and a few studies in men (33–36). Among the most dramatic changes that have been noted is for serum estrone sulfate after premenopausal women were placed on low-fat, high-fiber diets for at least two menstrual cycles (30,32). In response to a change in diet from one containing 40% of calories from fat and 12 g/day of fiber to a diet of 20–25% of calories from fat and 40 g/day of fiber, there was a 30% decline in serum estrone sulfate in premenopausal Caucasian women (30) and a 16% reduction in African American women (28). In a separate investigation, pre- and postmenopausal women eating a Western-style diet, compared with a vegetarian or Asian diet, had higher serum estrone and estradiol levels, albeit more modest than that noted for estrone sulfate (37). Among predominantly Caucasian premenopausal women, a change from a high-fat, low-fiber diet to a low-fat, high-fiber diet resulted in a lowering of serum testosterone and androstenedione concentrations (30). Plasma concentrations of testosterone and androstenedione for Caucasian pre- and postmenopausal women eating a typical Western diet were higher than for Asian women consuming an Asian diet (37). In contrast, premenopausal African American women had higher circulating androstenedione concentrations when their diet was shifted from a high-fat, low-fiber to a low-fat, high-fiber diet (28).

There have been few studies on the effect of diet and sex hormones in men. A comparison of male vegetarians with nonvegetarian Seventh-Day Adventists and omnivorous non-Seventh Day Adventists showed lower plasma testosterone and estradiol levels for the vegetarians who consumed higher levels of dietary fiber (24). Men placed on a low-fat, low-cholesterol and high-carbohydrate diet for 26 days experienced a significant reduction in serum estradiol concentrations, but no significant change in testosterone levels (38). As previously cited, Allen et al. (19) found no effect resulting from varying amounts of soy milk on plasma concentrations of testosterone, free testosterone, LH, androstenediol-glucuronide, and SHBG in men. Similar to our study, Brown et al (18) compared the effect of a high-soy protein plus high-isoflavone diet with a high- and low-saturated fat diet without soy protein in postmenopausal women and reported no significant changes in serum estrogen or androgen concentrations. No attempt was made to look at the impact of isoflavones independent of soy protein on serum androgen and estrogen concentrations.

The major effect observed resulting from the experimental diets in the women participating in the current study was a decrease in DHEA concentrations when women ate the soy relative to the animal protein diets. This observation is consistent with the influence of these diets on estrone synthesis, because DHEA is a precursor of androstenedione, which is converted to estrone. An inhibition of the conversion of DHEA to androstenedione by animal protein would account for the elevation in DHEAS and the decrease in circulating estrone concentrations.

For the middle-aged and older male subjects in this study, DHEAS concentrations were higher after they ate the soy protein and lower after they ate the diets enriched in isoflavones. The implication of this change is not clear because none of the metabolites of DHEAS were altered, including DHEA and androstenedione. The latter can be converted into testosterone and subsequently reduced to DHT, a highly androgenic compound in the prostate. There has been speculation that high DHT levels are, in part, responsible for the occurrence of prostate cancer, and finasteride (an inhibitor of the conversion of testosterone to DHT) has been shown to reduce the incidence of prostate cancer (39). However, the data derived from the male subjects in this study do not indicate any clear pattern with regard to prostate cancer.

The observational and intervention studies to date on the effect of dietary soy protein and/or soy-derived isoflavones on circulating levels of androgens and estrogens in men and women are somewhat inconsistent. In the current highly controlled dietary intervention study, the effect of these dietary constituents on hormone levels was modest and limited. Nonetheless, it should be emphasized that small changes in circulating hormone levels that persist for many years may have cumulative effects that are difficult to ferret out from the other changes associated with advancing years.

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