Serum Concentrations of Estradiol and Dehydroepiandrosterone Sulfate and Soy Product Intake in Relation to Psychologic Well-Being in Peri- and Postmenopausal Japanese Women

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The effect of steroid hormones, such as estrogen and dehydroepiandrosterone (DHEA) on psychologic well-being of women has been suggested. Dietary estrogen may also affect psychologic status. We examined the cross-sectional relationships of serum concentrations of estradiol (E2) and DHEA sulfate (DHEAS) and dietary intake of soy products to psychologic status measured using the Center for Epidemiologic Studies Depression Scale (CES-D) and General Health Questionnaire (GHQ)-12 scales in 86 peri- and postmenopausal Japanese women. Intake of soy products and other dietary components was estimated from a validated semiquantitative food frequency questionnaire. A fasting blood sample was obtained from each woman to measure serum concentrations of E2 and DHEAS. Serum DHEAS was significantly inversely correlated with CES-D scale ($r = -.22$, $P = .04$) and GHQ-12 scale ($r = -.27$, $P = .01$). Soy product intake was significantly inversely correlated with CES-D scale ($r = -.22$, $P = .04$). Neither serum E2 concentration nor the ratio of serum E2 to sex hormone-binding globulin (SHBG) was associated with any of the psychologic measurements. These data suggest a possibility that endogenous DHEA sulfate and dietary soy may modulate psychologic well-being of peri- and postmenopausal women.

THERE HAS BEEN an increasing interest in the role of steroid hormones in psychologic well-being.[1] The hypothesis that estrogens effect emotional and mental health has been supported by laboratory data. For example, estrogen was reported to affect neuroreceptor activity and density, neurotransmitter activity and metabolism, and neuron excitability in the central nervous system.[2-4] Some, but not all, clinical studies of hormone replacement therapy have found improvement of depression and sense of well-being in postmenopausal women.[5-8] Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are known as ''neurosteroids'' and have been shown to be allosteric activators of the γ-aminobutyric acid ($GABA_A$) receptor-channel.[9,10] The important role of GABA in the modulation of behaviors and emotions has been recently recognized.[11] However, there are limited epidemiologic and clinical data currently available on associations of psychologic well-being with serum estrogen and DHEA or DHEAS.

Soy beans contain large quantities of isoflavones, which are structurally similar to estrogens, and possess some estrogenic activity.[12] Therefore, there is a possibility that dietary soy may also modulate psychologic well-being. There have been no studies in humans or animals on dietary soy and psychologic parameters such as fear, anxiety, and depression.

We, therefore, evaluated the relationships of serum concentrations of estradiol (E2) and DHEAS and soy product intake to psychological well-being in peri- and postmenopausal Japanese women.

SUBJECTS AND METHODS

Subjects were participants in the health check-up program provided by a general hospital in Gifu, Japan between September 1996 and August 1997. We previously studied these women regarding the relationships between hot flushes and other menopausal symptoms and soy product intake.[13] The present study included peri- and postmenopausal women (defined as cessation of menses for 12 or more months). A total of 103 peri- and postmenopausal women completed a self-administered questionnaire including demographic information, smoking and drinking habits, diet, exercise, and menstrual and reproductive histories (the response rate was 96.4%). Those who returned questionnaire with incomplete information were interviewed by a nurse epidemiologist to obtain complete data. Informed consent was obtained from each subject. The procedures of the present study received approval with the institutional review board.

Depression was measured using the Center for Epidemiologic Studies Depression (CES-D) Scale.[14] This is a 20-item self-report scale, which measures current or immediate previous status of depression. Twelve items of General Health Questionnaire (GHQ)[15] were also included to measure psychiatric impairment. A high score on the CES-D or GHQ means that women have more psychologic symptomatology. Menopausal symptoms were assessed using the Kupperman Scale,[16] which includes 17 signs related to 11 symptoms: vasomotor complaints, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness or fatigue, arthralgia and myalgia, headache, palpitation, and formication. This scoring device allocates numbers in relation to the severity of symptoms and gives added weight to symptoms particularly associated with the menopause. Severity of each symptom was scored as follows: 0 = no complaints, 1 = mildly unpleasant, but not limiting activity, 2 = moderate, limiting social or other activities, but able to work, 3 = severe, incapacitating, causing inability to work or mix socially.

Diet was assessed by a semiquantitative food frequency questionnaire. The women were asked to indicate the average frequency of 169 food items during the year before the study and the usual serving size of each food item. We included 9 food items for soy products (miso soup, tofu, deep-fried tofu, fried bean curd, dried bean curd, fermented soy beans, houba-miso, soymilk, and boiled soy beans). The total intake of soy products was calculated as the sum of these 9 food items. Isoflavone intake from soy products was estimated using isoflavone concentration data summarized by Wakai et al.[17] Individual nutrient intake was estimated from frequency of intake and portion size using the Standard Tables of Food Composition in Japan, 4th ed, published by the Science and Technology Agency of Japan. Detailed information on the questionnaire including results from validity tests have been described else-

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where.[18,19] In brief, the Spearman correlation coefficient comparing intake of soy products from the questionnaire and 12 daily diet records over 1 year was 0.71. The correlation coefficients for nutrient intakes such as fat, carbohydrate, cholesterol, fiber, salt, calcium, carotene, retinol, and vitamins varied from 0.45 for vitamin C to 0.76 for calcium, with a median of 0.57.

A fasting blood sample was collected from each subject in the morning. The blood were centrifuged, and the serum was separated. The samples were stored at −80°C until assayed. The assays were performed by the same person and in 1 batch. Serum E2, sex hormone-binding globulin (SHBG), and DHEAS were measured by radioimmunoassay. Serum E2 was determined after extraction using a kit purchased from Diagnostic Products, Chiba, Japan. SHBG was determined using a kit purchased from Pharmacia & Upjohn, Tokyo, Japan. Serum DHEAS was determined using a kit purchased from Diagnostic Products. The intraassay coefficients of variations (CVs) were 10.9% for E2, 7.8% for SHBG, and 4.4% for DHEAS.

For statistical analysis, we excluded women taking hormone replacement therapy or other hormones (n = 2), who were clinically diagnosed to have depression (n = 1) or autonomic imbalance (n = 1), who had a history of breast cancer (n = 3), ovarian cancer (n = 1), and endocrine diseases, such as diabetes mellitus (n = 3) and thyroid disease (n = 3). We further excluded 3 women because of insufficient sera available for hormone assays. Consequently, we studied 86 peri- and postmenopausal women.

We used Spearman correlation coefficients to assess the associations of soy product intake and serum hormone concentrations with parameters for psychologic well-being. Intake of soy product and the individual nutrients were log-transformed and adjusted for total energy using the method proposed by Willett.[20] We examined potential confounding effects of age, marital status, years of education, occupation, body size, smoking status, number of children, years since menopause, hysterectomy, exercise, age at menarche, age at first and last birth, number of births, use of analgesics and other medications, intake of alcohol, and macro- and micronutrients. Among them, the variables that were significantly related to both soy product intake and at least 1 of the psychologic indices were included in the models as covariates for the association between soy product intake and psychologic indices. Covariates for the associations between each of the serum hormone concentrations and psychologic and menopausal indices were similarly determined. All of the statistical analyses were performed using SAS programs (SAS/STAT version 6.12; SAS Institute, Cary, NC).

RESULTS

Table 1 shows characteristics of the 86 peri- and postmenopausal women. Neither serum E2 nor ratio of E2 to SHBG was significantly correlated with psychologic indices after controlling for age, smoking status, body mass index, and cause of menopause (natural or surgical) (Table 2). Serum DHEAS was significantly inversely correlated with CES-D scale ($r = -.22$, $P = .04$) and GHQ-12 scale ($r = -.27$, $P = .01$) after controlling for age. Soy product intake was significantly inversely correlated with CES-D Scale ($r = -.22$, $P = .04$), but not with GHQ-12 scale after controlling for age, energy, and cholesterol intake. The correlations of DHEAS with CES-D scale were not changed after additional adjustment for soy intake product ($r = -.22$, $P = .04$). The correlation between soy product intake and CES-D scale was also not altered after additional adjustment for DHEAS ($r = -.22$, $P = .047$).

The inverse correlation between soy product intake and Kupperman scale was not statistically significant. Kupperman scale includes 8 items related to physical symptoms. Additional adjustment for the total score for these items did not alter substantially the correlations of DHEAS with the CES-D scale ($r = -.22$, $P = .04$) and with the GHQ-12 scale ($r = -.27$,

Table 1. Selected Characteristics of 86 Peri- and Postmenopausal Japanese Women

Variables	
Age (yr)	54.3 ± 6.4
Years since menopause (yr)	6.7 ± 5.3
	[5.0; 1-23]
Body mass index (kg/m^2)	23.0 ± 2.7
No. of births	2.1 ± 0.8
	[2; 0-5]
Exercise (METs · h/wk)	2.2 ± 2.7
	[1.1; 0-12.7]
Alcohol intake (mL/d)	7.4 ± 13.6
	[1.2; 0-74.1]
Marital status, no. (%)	
Married	74 (86.4)
Separated/divorced	3 (3.4)
Widowed	8 (9.3)
Never married	1 (1.2)
Smoking status, no. (%)	
Current	8 (9.3)
Past	5 (5.8)
Nutrient and food intake per day	
Soy products (g)	62.5 ± 41.2
	[53.5; 4.9-221.6]
Isoflavone from soy products (mg)	28.5 ± 18.5
	[25.1; 1.9-103]
Energy (kcal)	2,189 ± 742
	[2,074; 903-4,205]
Protein (g)	92.5 ± 35.2
	[86.7; 35.3-178]
Fat (g)	62.2 ± 25.6
	[56.8; 21.8-130.8]
Carbohydrate (g)	299 ± 103
	[278; 136-603]
Cholesterol (mg)	334 ± 163
	[286; 90-692]
Psychologic measurements	
CES-D	12.3 ± 6.9
	[12; 0-42]
GHQ-12	1.7 ± 2.1
	[1; 0-9]
Kupperman index	16.3 ± 10.2
	[14; 0-49]
Serum hormone concentrations	
E2 (pg/mL)	20.8 ± 35.0
	[11.9; 5.3-198]
SHBG (nmol/L)	78.2 ± 32.6
	[73; 28-180]
DHEAS (ng/mL)	887 ± 491
	[792.5; 159-2,740]

NOTE. Data are presented as mean ± SD; for parameters in which the data are not normally distributed, the median and range are also given on a subsequent line in brackets.

Abbreviations: METs, metabolic equivalents; CES-D, Center for Epidemiologic Studies Depression Scale; GHQ, General Health Questionnaire; E2, estradiol; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate.

Table 2. Spearman Correlation Coefficients Between Serum Hormone Concentrations and Soy Product Intake and Psychologic and Menopausal Measurements

	Scales		
	CES-D	GHQ-12	Kupperman
Serum hormone concentration			
E2*	−.003	.10	.01
E2/SHBG*	−.08	.05	−.05
DHEAS†	−.22§	−.27§	−.05
Soy product intake‡	−.22§	−.04	−.10

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; GHQ, General Health Questionnaire; E2, estradiol; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate.

*Adjusted for age, body mass index, smoking status, and cause of menopause (natural/surgical).

†Adjusted for age.

‡Adjusted for age, total energy, and cholesterol intake.

§$P < .05$.

$P = .01$) and of soy product intake with the CES-D Scale ($r = -.21$, $P = .06$).

Five women reported a past history of cancer or tumor; cervical cancer (n = 4) and bone tumor (n = 1). Exclusion of these women did not change the results substantially ($r = -.24$, $P = .04$ between DHEAS and CES-D, $r = -.22$, $P = .06$ between DHEAS and GHQ-12, and $r = -.25$, $P = .03$ between soy product intake and CES-D). Exclusion of those with a history of heart disease, hypertension, gastric ulcer, or colonic polyps did not alter the results substantially.

DISCUSSION

We found a significant inverse association between soy product intake and CES-D scale. Although the cross-sectional nature of this study cannot prove causality, the result would propose a possibility that dietary soy may modulate psychologic well-being of peri- and postmenopausal women. It has been suggested that a disorder of central serotonergic mechanisms may be responsible for depression.[21] Estrogen induces serotonin transporters in the regions of the rat forebrain, and this action is thought to be mediated by the estrogen receptor β.[1] Genistein, the most abundant in soy, binds with estrogen receptor β in the brain almost as well as endogenous estrogen.[22] We speculate that the mechanism through which dietary soy may be related to psychologic status could involve estrogenic actions of soy isoflavone mediated by receptor β. A modulatory effect on GABA receptors could also be implicated. Recent studies observed that genistein interacts with GABA receptors.[23,24]

We observed significant inverse associations between DHEAS and scores of CES-D and GHQ-12 scales in peri- and postmenopausal women. To our knowledge, there are 2 community-based cross-sectional studies on serum DHEAS and psychologic measurements,[25,26] both of which limited subjects to those who were over 65 years of age. In the study reported by Berr et al,[25] DHEAS levels were significantly lower in women with higher (more than 16) scores of the CES-D scale. In the study reported by Yaffe et al,[26] however, DHEAS was not associated with depression measured using the Geriatric Depression Scale-Shortened. Results from clinical studies of DHEA administration[27-29] have also been inconsistent. A beneficial effect of DHEA on sense of well-being among elderly women was reported by Morales et al.[27] DHEAS administration to psychiatric patients improved scores measuring depression.[29] However, no improvement of the CES-D scale or mood has been reported.[28]

We could not measure follicle stimulating hormone levels. Considering the relatively high mean of estradiol levels in the subjects, some of them may be perimenopausal and not postmenopausal, despite the cessation of menses by history. Inclusion of such women may have affected the results. We suspected that some of the women who reported their surgical menopause with at least 1 intact ovary were not postmenopausal and, therefore, reanalyzed data after excluding these women (n = 21). The mean standard deviation (SD) estradiol level changed to 11.9 (5.0) pg/mL. However, the findings were not essentially altered; the correlation coefficients of DHEAS with CES-D and GHQ-12 scales were −.20 ($P = .11$) and −.26 ($P = .04$), respectively. The correlation of soy product intake with CES-D was somewhat strengthened ($r = -.30$, $P = .02$).

The food frequency questionnaire, as in all methods of dietary assessment, is subject to measurement error. However, it is unlikely that women with higher CES-D scores would systematically underestimate the consumption of soy products.

Psychologic well-being should be influenced strongly by physical conditions. The study population consisted of participants in the health check-up program. They were generally in good physical health. In addition, we considered the potential confounding effects of chronic disease conditions by asking for medical histories and use of medications. We controlled for physical symptoms related to menopause, several lifestyle variables, and intake of macro- and micronutrients, but the possibility exists that confounding by other factors accounts for the findings.

Our results suggest a potential importance of dietary soy in relation to psychologic well-being in peri- and postmenopausal women. Further studies are needed to establish whether dietary soy can modify psychologic well-being in women.

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