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The Effect of Reduced Dietary Fat and Soy Supplementation on Circulating Adipocytokines in Postmenopausal Women: A Randomized Controlled 2-Month Trial

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Abstract

The reduced risk of breast cancer observed in Asia has been linked with diets rich in soy foods, and observational studies suggest that regular soy food intake is related to lower circulating levels of some inflammatory markers which have been implicated in breast cancer risk. However, short-term intervention studies with soy-based diets in small numbers of women have shown few significant changes in adipocytokine levels. This 8-wk dietary intervention study in 57 healthy postmenopausal women investigated whether soy food supplementation (50 mg isoflavones or 15 g soy protein in the form of tofu) or a very low-fat diet (11.3% of total energy), similar to the traditional Asian diet, is associated with beneficial effects on serum levels of the following adipocytokines: TNF-α, IL-6, adiponectin, and resistin. We found no statistically significant changes in the levels of these adipocytokines in association with the very low-fat diet or soy supplementation. Only the change in TNF-α levels between the very low-fat and control diet groups had borderline statistical significance. We conclude that ingestion of a very low-fat diet or a soy food supplemented diet for 8 wk does not significantly alter important circulating adipocytokines.

Introduction

The role of soy foods in relation to risk of coronary heart disease and breast cancer and other cancers has been studied extensively over the past 25 yr (1). Meta-analyses of case-control and prospective cohort studies have consistently found a reduced risk of breast cancer in relation to regular soy food intake (2,3), although the mechanisms of action remain elusive. Short-term intervention studies have not found consistent effects of soy on circulating estrogen levels (4) and mammographic density (5). Despite promising initial findings of a cholesterol-lowering effect of soy, more recent studies concluded that the lipid benefits conferred by soy may be quite small (6). Soy intake was unrelated to risk of cardiovascular

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mortality among men in cohort studies conducted in Singapore and Shanghai (7,8), but it appears to have some beneficial effects on risk of cardiovascular disease in women (8,9). In a cross-sectional study of 1,005 middle-aged women in Shanghai, soy food intake was inversely associated with circulating levels of interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) (10).

Obesity is a known breast cancer risk factor in postmenopausal women (11). Because of the connection between obesity, a chronic inflammatory state, and insulin resistance, the adipocytokines adiponectin and leptin have emerged as potential independent biomarkers for the relationship between obesity and breast cancer risk (12,13). Adipose tissue is not only a passive reservoir for energy storage, but also the largest endocrine organ in the human body, secreting adipocytokines that have multiple metabolic and immunological functions controlling energy intake and expenditure, insulin sensitivity, and inflammation. Increased adiposity with its elevated secretion of adipocytokines leads to a chronic inflammatory state and contributes to the pathogenesis of insulin resistance and diabetes (14). Adiponectin plays a role in improving insulin sensitivity, but in obesity adiponectin levels are reduced; although leptin levels increase, multiple factors contribute to an inhibition of leptin signaling resulting in a state known as leptin resistance (15).

In a dietary intervention study we conducted in healthy postmenopausal women (16), we found that a 2-month consumption of a very low-fat diet either with or without soy supplementation significantly reduced serum leptin compared to baseline (−39.5%, $P =$ 0.001). The soy group also showed a significant reduction in insulin levels (−32.7%, $P =$ 0.002). However, the reductions in leptin and insulin were not significantly different to those seen in a control diet group. Using this completed intervention study, we further investigated if soy food supplementation (50 mg isoflavones or 15 g soy protein in the form of tofu) and a low-fat diet (11.3% of total energy), similar to the traditional Asian diet, may be associated with beneficial effects on adipocytokines that have been implicated in breast cancer risk in some studies (26). Specifically, in this analysis, we measured levels of TNF-α, IL-6, adiponectin, and resistin.

Materials and methods

Subjects

Details of the study subjects have been reported previously (16). Briefly, this study included healthy postmenopausal women (defined as having not had a period for at least 1 yr) at least 50 yr of age and not currently receiving menopausal hormone therapy (defined as having stopped usage of hormone therapy for at least 6 months before entering the study). Subjects were excluded due to the following criteria: consumption of a “special diet” (e.g., low-fat, high-fiber, low sodium, etc.); history of cancer (other than non-melanoma skin cancers); and diagnosis of diabetes mellitus or other chronic disease(s). A total of 274 women completed an initial telephone screening; 130 were considered eligible and 70 subjects completed the baseline assessment and consented to random assignment to 1 of 3 dietary arms: a very low-fat diet (VLFD), a soy food diet (SFD), and a control diet (CD). During the first 2 wk of the study 6 women withdrew, citing difficulties in adhering to our diet protocol. An additional 7 women were excluded (1 from the CD group, 5 from the SFD group, and 1 from the VLFD

group), as their baseline circulating estrogen concentrations indicated that they were not postmenopausal. The final analysis was based on the remaining 57 women (20 from the CD group, 17 from the SFD group, and 20 from the VLFD group), who represented the racial and ethnic diversity in the study (17 Caucasians, 22 Hispanics, 11 African Americans, and 7 Asians). The study protocol was approved by the USC Institutional Review Board, and written informed consent was obtained from all study subjects.

Diets

The diets in this study were prepared in the Bionutrition Department's Research Kitchen at the General Clinical Research Center (GCRC) at the Los Angeles County (LAC) USC Medical Center. The composition of the diets was described in our previous study (16). During the 8 wk of the study, subjects received all of their meals on a weekly basis, packed and stored in insulated coolers, from the research kitchen at the GCRC. Daily menus included breakfast, lunch, and dinner meals, as well as a morning and evening snack. Written instructions regarding food safety and reheating methods were provided to all subjects, who were also given a daily journal to log all foods on the menu that they consumed by checking them on the list provided. Subjects were requested to eat only the foods we provided and to record any additional foods consumed that were not part of the study's menu, and to return any uneaten food in its original containers to the kitchen, so that this could be weighed and deducted from the subject's daily nutrient intake. The CD for this study provided 50% of energy from carbohydrates, 30% from fat, and 20% from protein, as recommended for a healthy, balanced diet by the American Dietetic Association. The VLFD provided 12% of energy from fat, 68% from carbohydrate, and 20% from protein which consisted of legumes, fish, lean chicken, and low-fat dairy products. The SFD had the same macronutrient composition as the CD but included 15 g soy protein per day providing 50 mg soy isoflavones/day, and was developed in the GCRC Research Kitchen from modified recipes provided by Mori-Nu Tofu (Morinaga Nutritional Foods, Torrance, CA).

Baseline assessment and data and sample collection

Interested subjects who met the eligibility criteria were mailed a 3-day food record, with instructions to record their usual food intake on 2 weekdays of their "typical" diet, as well as on 1 weekend day. Subjects were randomly assigned to treatment groups at the time of the pre-entry visit and were blinded to the diet to which they were randomly assigned. During the initial screening interview, we administered a baseline questionnaire to each potential subject, requesting information regarding their menstrual, reproductive, and menopausal factors. Each subject's body weight, blood pressure measurements, and blood samples were obtained at baseline, as well as at 2, 4, 6, and 8 wk intervals during the study. Fasting blood specimens were collected between 0600 and 1100, and were processed to obtain serum and plasma. On the day of the blood draw, subjects were asked to collect an overnight urine specimen into plastic bottles that contained 1 g ascorbic acid. Urine specimens were separated into 100-ml aliquots and stored at −20°C. Daily food records were used as a measure of compliance with the study. In addition, urinary isoflavone concentrations were determined at baseline, at least once during the intervention, and again at the completion of the study. Urinary isoflavone concentrations were used as a measure of compliance with the SFD. Although an objective measure of compliance for the CD or the VLFD is not available,

we used reductions in high-density lipoprotein cholesterol and increases in triacylglycerol concentrations as indicators of compliance.

Blood serum analysis

Adiponectin was measured using a radioimmunoassay kit (Millipore Linco, St. Charles, MO) with intra/inter-assay coefficients of variability (CVs) of <7% and <10%, respectively. Resistin was measured by enzyme-linked immunosorbent assay (ELISA) using a kit purchased from Millipore Inc. (Billerica, MA), where the intra/inter-assay CVs are <7%/ <7%. Lastly, TNF-α and IL-6 were both measured by ELISA purchased from R&D Systems (Minneapolis, MN). The intra/inter-assay CVs for these assays are <9% /<11% and <8%/ <10%, respectively.

Statistical analysis

We used analysis of variance to compare the 4 adipocytokines (adiponectin, resistin, IL-6, and TNF-α) between the three groups. We also used Student's *t*-test to compare each of the biomarkers at baseline between the SFD and CD groups and between the VLFD and CD groups. The main outcome of interest in this analysis was the relation between diet intervention and the individual differences (i.e., Week 8 compared with baseline) in the biomarkers of interest. We also tested whether the individual differences varied by diet by examining paired differences in biomarkers of interest at baseline compared with Week 8 (paired *t*-test).

Results

Women in the three diets did not differ in age (mean age was 60.2 ± 7.2 for CD, 56.9 ± 6.1 for SFD, and 59.7 ± 7.2 for VLFD, $P = 0.32$) or weight (mean weight (kg) was 72.2 ± 8.4 for CD, 72.2 ± 11.5 for SFD, and 75.9 ± 11.9 for VLFD, $P = 0.47$) at baseline. A reduction in weight was observed in all three dietary groups during the 8 wk of intervention but their weight at Week 8 did not differ significantly (mean weight (kg) was 70.9 ± 8.8 for CD, 70.2 ± 11.1 for SFD, and 73.8 ± 11.6 for VLFD, $P = 0.53$). There were no statistically significant differences between the three groups with respect to baseline serum levels of the four adipocytokines (adiponectin, resistin, IL-6, and TNF-α) (Table 1). Small statistically nonsignificant reductions (1–7%) in adiponectin were found in all three groups. Resistin levels increased in the SFD group ($P = 0.49$) but decreased in the VLFD ($P = 0.29$) and the CD ($P = 0.67$) groups; these changes in the SFD and VLFD groups did not differ from the changes in the CD group. IL-6 levels increased 4–14% in the three groups but none of these increases were statistically significant. TNF-α levels increased in the CD and SFD groups (2–10%), but decreased (21%) in the VLFD ($P = 0.17$) after 8 wk of intervention. This difference in change in TNF-α levels between the VLFD and CD groups was borderline statistically significant ($P = 0.07$) (Table 1).

Discussion

In this well-controlled randomized 8-wk intervention study in which all the meals for the three dietary arms were prepared by the metabolic kitchen of the LAC-USC Medical Center

GCRC, we found no statistically significant changes in serum adipocytokine levels (adiponectin, resistin, IL-6, and TNF-α) in association with VLFD (11.3% of total energy) or soy supplementation (50 mg isoflavones or 15 g soy protein in the form of tofu) in healthy postmenopausal women. The only change that was borderline statistically significant was the change in TNF-α levels between the VLFD and CD groups.

The strongest evidence that regular soy food intake is related to lower circulating levels of inflammatory markers is from a cross-sectional analysis of 1,005 middle-aged Chinese women in Shanghai. Mean IL-6 levels were highest (4.35 pg/ml) among those in the lowest quintile of soy intake (9.9 mg isoflavones) and lowest (3.29 pg/ml) among women consuming the highest quintile (59.7 mg isoflavones) of soy (P trend = 0.006). TNF-α levels also decreased with increasing soy intake (6.26 pg/ml in quintile 1 vs. 5.60 pg/ml in quintile 5; P trend = 0.04) (10). In contrast to the above findings on usual soy intake and inflammatory markers, short-term intervention studies on the effects of soy on various inflammatory markers have shown few significant or consistent changes in women (17–25, summarized in Table 2). The duration of soy intervention in these studies ranged from 2 wk to 24 months and most of the studies had fewer than 30 women in each intervention group.

Four of the nine short-term soy intervention studies measured IL-6 levels. One study found a reduction in IL-6 levels in the soy group and an increase in the placebo group; these changes differed significantly between the two groups (17). However, no significant changes in IL-6 levels were found in the other three studies (18–20). TNF-α levels did not change significantly in four interventions (17–19,21), but decreased significantly in two studies (22,23). In a 24-month intervention study, the changes in TNF-α differed significantly between the soy and placebo groups (23).

Although adiponectin levels increased significantly (19,22) while leptin levels decreased significantly (22,24) in association with soy intervention in some studies, these changes did not differ significantly between the soy and the placebo groups. No increase in adiponectin was seen with soy supplementation in two studies (17,20) despite reductions in abdominal fat (17), and in fact a decrease in adiponectin with soy was observed in one study, particularly among nonobese women (25).

Several strengths and limitations of this study should be mentioned. This was one of the few intervention studies in which all the meals were prepared uniformly in the GCRC and the diets of study subjects were tightly controlled for 8 wk. Subjects were blinded to the diet regimen to which they were randomly assigned. However, there were also several study limitations which included the modest sample size, the short-term nature of the intervention, and that we only had single measurements of the biomarkers of interest at each time point (baseline, end of intervention). In addition, it is possible that the study subjects had relatively low levels of chronic inflammation, and thus a dietary intervention would not be able to modify the biomarkers of interest in any substantial way. Finally, the inflammatory markers may change rapidly over time, and thus obtaining multiple measurements during the intervention would have been preferable.

In conclusion, the present study adds to the body of evidence that short-term ingestion of a VLFD or a soy food supplemented diet, resembling the traditional Asian diet, does not significantly alter important circulating adipocytokines.

Acknowledgments

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Table 1.

Mean adipocytokine levels in control, very low fat, and soy food groups during the 2-month intervention.

	Control (CD) (n = 20)		Very low fat (VLFD) (n = 20)		Soy food (SFD) (n = 17)		Between-group comparisons		
Adipocytokine	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**P^1 (3 diets)**	**P^2 (CD vs. VLFD)**	**P^3 (CD vs. SFD)**
Adiponectin (μg/ml)									
Baseline	6.38	5.40, 7.54	6.52	5.52, 7.71	5.74	4.79, 6.88	0.57	1.00	0.26
Week 8	6.34	5.50, 7.30	6.06	5.26, 6.97	5.49	4.71, 6.40			
Change	0.99	0.90, 1.09	0.93	0.84, 1.02	0.96	0.86, 1.06	0.61	0.40	0.47
P^4 value	0.97		0.18		0.28				
Resistin (ng/ml)									
Baseline	11.25	9.66, 13.09	10.36	8.91, 12.06	10.89	9.24, 12.84	0.75	0.44	0.63
Week 8	10.71	8.94, 12.83	9.71	8.11, 11.64	11.58	9.51, 14.09			
Change	0.95	0.82, 1.10	0.94	0.81, 1.09	1.06	0.91, 1.25	0.48	0.72	0.26
P^4 value	0.67		0.29		0.49				
IL-6 (pg/ml)									
Baseline	2.05	1.55, 2.72	2.58	1.94, 3.42	2.78	2.05, 3.78	0.33	0.24	0.13
Week 8	2.29	1.72, 3.05	2.69	2.02, 3.57	3.17	2.32, 4.32			
Change	1.11	0.88, 1.41	1.04	0.83, 1.31	1.14	0.88, 1.46	0.87	0.67	0.80
P^4 value	0.21		0.88		0.20				
TNF-α (pg/ml)									
Baseline	1.19	0.92, 1.56	1.07	0.82, 1.40	1.11	0.84, 1.49	0.86	0.55	0.74
Week 8	1.32	0.97, 1.79	0.85	0.62, 1.15	1.14	0.82, 1.59			
Change	1.10	0.86, 1.42	0.79	0.61, 1.01	1.02	0.78, 1.33	0.16	0.07	0.59
P^4 value	0.57		0.17		0.71				

P^1 For difference between the three diet groups at baseline (ANOVA for continuous variables)

P^2 For difference between control (CD) versus very low-fat (VLFD) group

P^3 For difference between control (CD) versus soy food (SFD) group

P^4 For paired difference in biomarkers of interest at baseline compared with Week 8 (paired t-test).

Table 2.

Short-term soy intervention studies and inflammatory markers including adiponectin, leptin, IL-6, TNF-α, and resistin.

		Adiponectin (μg/ml)		Leptin (ng/ml)		IL-6 (pg/ml)		TNF-α (pg/ml)		Resistin (ng/ml)	
Reference Design (# subjects, duration, intervention)	**Time**[1]	**Placebo**	**Soy**	**Placebo**	**Soy**	**Placebo**	**Soy**	**Placebo**	**Soy**	**Placebo**	**Soy**
Christie et al. (17) 39 postmenopausal, 3 months Soy (96 mg agylcones) (n = 19) Placebo (20 g casein protein) (n = 20)	B					1.7	2.8	1.9	1.7		
	E					1.8	2.7	1.7	1.6		
	P value						<0.05[2]		NS[2]		
Charles et al. (18) 75 postmenopausal, 12 wk20 g soy protein, 160 mg isoflavones (n = 32) Placebo (n = 43)	B	19.7	18.6	25.2	25.9	1.61	2.18	0.61	1.93	4.08	3.81
	E	19.2	20.6	25.8	28.6	1.56	2.12	0.66	1.72	3.07	3.42
	P value[7]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Simao et al (19) 65 women[3], 90 days Control (usual diet) (n = 15) Soy (29 g/day soybean, kinako) (n = 15)	B	112.2	94.07			5.05	4.00	66.97	33.13		
	E	112.6	115.3			6.48	8.05	62.14	69.71		
	P value[7]	NS	<0.05			NS	<0.05	NS	NS		
Maskarinec et al. (20) 183 premenopausal, 2 yr Control (regular diet) (n = 93) Soy (2 servings/day, 50 mg isoflavones) (n = 90)	B	8.1	7.9	19.1	19.4	1.4	1.1				
	E	8.4	7.9	21.0	19.2	1.3	1.2				
	P value[7]	NS	NS	NS	NS	NS	NS				
Ryan-Borchers (21) 52 postmenopausal, 16 wk Control (cow milk) (n = 19) Soymilk (71.6 mg isoflavones) (n = 18); Soy supplement tablet (70 mg isoflavones) (n = 15)[4]	B							2.26	1.28		
	A							1.98	2.09		
	P value[7]							NS	NS		
Llaneza et al. (22) 87 healthy obese postmenopausal, 6 months Control (regular diet) (n = 44) Soy (80 mg isoflavones) (n = 43)	B	36.7	28.5	25.0	26.7			7.41	6.8		
	E	43.2	57.1	22.1	23.5			6.04	5.6		
	P value[7]	NS	<0.05	<0.05	<0.05			<0.05	<0.05		
Llaneza et al. (23) 75 postmenopausal, 24 months, with exercise Control (n = 35) Soy (200 mg glycine max 80 mg isoflavones) (n = 25)	B			25.2	21.3			8.7	7.9		
	E			21.1	25.6			5.5	4.6		
	P value[7]			NS	NS			0.05	0.05[5]		
Riesco et al. (24) 52 obese postmenopausal, 6 months Exercise + placebo capsules (n = 25) Exercise+ soy capsules (70 mg isoflavones) (n = 27)	B	21.3	20.3	39.3	41.4						
	E[6]	20.0	19.0	37.0	36.0						
	P value[7]	NS	NS	<0.05	<0.05						

Reference Design (# subjects, duration, intervention)	Time[1]	Adiponectin (μg/ml)		Leptin (ng/ml)		IL-6 (pg/ml)		TNF-α (pg/ml)		Resistin (ng/ml)	
		Placebo	Soy	Placebo	Soy	Placebo	Soy	Placebo	Soy	Placebo	Soy
Llanos et al. (25) 70 postmenopausal, 10 wk/2 wk/10 wk Soy (≥40 g soy protein) Placebo (lycopene daily)	B	13.0	14.4	26.1	25.7						
	E	14.1	13.0	23.3	23.6						
	P value[7]	<0.05	<0.05	NS	NS						

[1] Time period: B = baseline, E = end of intervention period, *P* = *P* value for changes during study period.

[2] *P* values shown were obtained by comparing changes between placebo and soy group.

[3] Two other treatment groups, 15 were on fish oil, and 15 were on fish oil + soy.

[4] Levels for soy milk group did not change significantly between baseline and 16 wk of intervention (data not shown in table).

[5] Change in levels differed between placebo and soy group ($P < 0.05$).

[6] Levels were estimated from Fig. 1 in Riesco et al. (24).

[7] *P* values shown were obtained by comparing differences in biomarkers of interest at baseline compared with end of study changes within treatment group (NS: not statistically significant, $P > 0.05$).

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