REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Metabolic effects of soy supplementation in postmenopausal Caucasian and African American women: a randomized, placebo-controlled trial

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OBJECTIVE: We sought to determine the effect of daily soy supplementation on abdominal fat, glucose metabolism, and circulating inflammatory markers and adipokines in obese, postmenopausal Caucasian and African American women.

STUDY DESIGN: In a double-blinded controlled trial, 39 postmenopausal women were randomized to soy supplementation or to a casein placebo without isoflavones. In all, 33 completed the study and were analyzed. At baseline and at 3 months, glucose disposal and insulin secretion were measured using hyperglycemic clamps, body composition and body fat distribution were measured by computed tomographic scan and dual energy x-ray absorptiometry, and serum levels of C-reactive protein, interleukin-6, tumor necrosis factor-α, leptin, and adiponectin were measured by immunoassay.

RESULTS: Soy supplementation reduced total and subcutaneous abdominal fat and interleukin-6. No difference between groups was noted for glucose metabolism, C-reactive protein, tumor necrosis factor-α, leptin, or adiponectin.

CONCLUSION: Soy supplementation reduced abdominal fat in obese postmenopausal women. Caucasians primarily lost subcutaneous and total abdominal fat, and African Americans primarily lost total body fat.

Key words: body composition, body fat distribution, glucose metabolism, insulin secretion, isoflavones, menopause, obesity, race, soy

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Cardiovascular disease increases with advancing age and with the menopause transition in women.[1-4] Specifically, menopause is associated with changes in several metabolic cardiovascular risk factors, including increased abdominal fat,[5] decreased insulin sensitivity, decreased adiponectin,[6] and increased circulating inflammatory markers such as tumor necrosis factor (TNF)-α.[7] Traditionally, these risk factors, along with a worsening lipid profile, can be modified by weight loss and exercise to reduce cardiovascular disease risk.

Information is limited regarding the effect of alternative therapies such as soy supplementation, on the modification of metabolic cardiovascular risk factors. Animal studies suggest a beneficial effect, with soy supplementation decreasing visceral fat and increasing insulin sensitivity in male rats,[8] and decreasing weight, visceral fat, and plasma leptin in female rats.[9] In male monkeys, soy protein alone reduced body weight, and soy protein with isoflavones increased insulin secretion.[10] Beneficial effects of soy supplementation might be due to the isoflavone binding to estrogen receptors in fat depots, or to increases in peroxisome proliferator-activator receptors in muscle with soy protein that are important for insulin action.[10]

In human beings, our group previously reported a beneficial effect of a daily supplement of soy supplementation, with a reduced gain in total abdominal and subcutaneous abdominal fat compared with a daily casein placebo in Caucasian menopausal women.[11] Information is mixed with regard to the effect of soy isoflavones on glucose and insulin metabolism in menopausal women, with our group previously reporting no change in insulin secretion with the soy isoflavone supplement, and others reporting that genistein without soy protein reduced fasting glucose and insulin in menopausal women.[12]

Little information is available with regard to the effect of soy supplementation on circulating inflammatory markers and adipokines in menopausal women,[13,14] and we are not aware of any studies that consider the effect of soy supplementation on body composition in populations of African Americans. In this study, we hypothesized that a daily soy supplement would reduce abdominal fat and improve measures of glucose and insulin metabolism compared to a casein placebo in a population of obese, nondiabetic Caucasian and African

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American menopausal women. Furthermore, we sought to determine if changes in fat or glucose metabolism were related to changes in cytokines or adipokines with soy isoflavone supplementation in this population.

MATERIALS AND METHODS

Subjects

In all, 39 postmenopausal women from the Birmingham, AL, region were recruited through study advertisements, enrolled, and randomly assigned by the hospital research pharmacy, using a block design of 6, to consume a daily shake supplement containing either soy protein plus isoflavones or an isocaloric casein placebo containing no isoflavones (supplements and placebo donated by Revival Soy, Kernersville, NC). Inclusion for our study mandated that female subjects must be between the ages of 45-60 years, be amenorrheic for at least 12 months, have a documented follicle-stimulating hormone >30 mIU/mL, and have a body mass index between 30-40 kg/m^2.

Volunteers were excluded from our study if they were shown to have diabetes mellitus based on a 75-g oral glucose tolerance test, consumed a strict vegetarian or low-fat diet, consumed a diet high in fiber or soy based on a standard dietary screening questionnaire, or if there was a weight change of >10 pounds within the prior 12 months. Other exclusion criteria were the regular consumption of vitamin and mineral supplementation greater than the recommended daily allowance, regular participation in an exercise program (more than twice weekly), cigarette smoking, hormone replacement or selective estrogen receptor modulator therapy within the prior 12 months, known casein/milk allergy, moderate to excessive alcohol consumption (>2 drinks daily), or a known estrogen-dependent neoplasia.

A total of 50 volunteers were assessed for eligibility in the General Clinical Research Center (GCRC) after telephone screening, and 39 met all eligibility criteria. Those who did not meet criteria had diabetes mellitus diagnosed by the 2-hour oral glucose tolerance test (3), had a follicle-stimulating hormone level too low (4), had clotting irregularities (2), or refused to proceed with the study when presented with more complete information (2). In all, 39 women were randomized, and 33 completed the entire 3-month study and were analyzed. Of the 6 drop-outs, 3 dropped out as a result of unrelated illness, 2 dropped out because of discomfort during the initial overnight hospitalization, and 1 dropped out due to a work/school schedule conflict.

Shake supplements

The composition of the shakes was as follows: 120 calories, 2.5 g fat, 7 g carbohydrates, 600 mg calcium, 500 mg phosphorus, 320 mg sodium, 560 mg potassium, and 3 mg iron. The soy-containing shakes had 20 g soy protein plus 160 mg isoflavones (96 mg available as aglycones). The isocaloric placebo contained 20 g casein protein and no isoflavones. This supplement is well studied and has been used in other trials.[15] Volunteers mixed the powdered shakes with water in the morning and consumed half of the shake in the morning with breakfast and the other half in the evening with dinner. All were in regular contact with the GCRC dietician, both prior to enrollment in the study, and throughout the study's course. Subjects' weights were checked 2 weeks postenrollment, at 1 month, and at 2 months. If the weight differed by >2.3 kg from the original weight, the dietician was consulted to instruct the volunteer further on weight maintenance. Compliance with the supplements was established by measuring serum isoflavone levels at baseline, 4 weeks, 8 weeks, and 12 weeks. The study was approved by the institutional review board and the GCRC at the University of Alabama at Birmingham, and all subjects gave their consent to participate.

Insulin secretion and insulin-stimulated glucose disposal

Three days prior to testing, volunteers were given a standardized diet to follow in which meals contained 55% carbohydrates, 30% fat, and 15% protein. After 3 days, volunteers presented to the GCRC for an overnight admission. On the subsequent morning, following a 12-hour fast, we performed a hyperglycemic clamp as previously described by DeFronzo et al.[16] Briefly, a large-bore intravenous catheter was started in an antecubital vein to gain access for an infusion of 20% dextrose. A second intravenous catheter used for drawing arterialized blood samples was placed in the contralateral hand, and was kept in a 60°C hot box. When possible, this catheter was placed in a retrograde manner.

Beginning at 7:00 AM, a primed, constant infusion of [6,6-$^2H_2$]glucose (prime 16.5 μmol/kg, infusion 18.3 μmol/kg/h) was started (time 0 minutes). Blood was sampled at time points 90, 100, 110, and 120 minutes to measure glucose concentrations and enrichment. A priming dose of 20% dextrose was then started at time point 120 minutes (240 mg/kg; 15 minutes duration) followed by a variable rate infusion. First-phase insulin secretion was determined by drawing blood samples every 2 minutes beginning at time point 120 minutes, and continuing through 136 minutes; blood plasma levels of insulin, C-peptide, and plasma glucose were measured. Blood samples were then drawn every 5 minutes from time point 140-240 minutes and glucose levels were determined. Second-phase insulin secretion was determined through plasma levels of C-peptide and insulin levels measured at 15-minute intervals beginning at 140-240 minutes.

Tissue glucose uptake was estimated by averaging the glucose infusion rate from 210-240 minutes. Insulin sensitivity was estimated by dividing the average glucose infusion rate by the average insulin level over the same time period. The rate of appearance of glucose was calculated as described previously.[17] This is an index of endogenous glucose production. Total insulin-stimulated glucose disposal is estimated by determining the mean dextrose infusion used to maintain hyperglycemia during the last 30 minutes of the clamp, and the residual endogenous glucose production. Peripheral glucose disposal and endogenous glucose production were summed to determine total glucose disposal.

As described previously, insulin secretion rates were determined using plasma C-peptide levels with deconvolution