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Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: randomized controlled trial

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Abstract

Recent studies suggest that obese individuals lose weight more rapidly and lose more total weight with soy protein than with animal protein as a major diet component. The purpose of the present study was to evaluate the weight-loss efficacy and changes in body composition, waist circumference, blood pressure, and levels of plasma glucose, insulin, serum lipids, C-reactive protein, and homocysteine from consumption of either 3 soy shakes or 3 casein shakes daily as part of a 16-week, energy-restricted diet for obese women. Forty-three women with body mass index values of 30 to 40 kg/m^2 were randomized to intensive dietary interventions using either casein (n = 21) or soy (n = 22) shakes. Subjects were instructed to consume 3 shakes, 1 prepackaged entrée, and 5 servings of fruits or vegetables daily to achieve an energy intake of 4.2 to 5.0 MJ/d. Subjects attended classes weekly or biweekly. Weight, body fat, lipid, and glucose measurements were obtained at baseline and at 8 and 16 weeks. For both groups combined, subjects lost 8.1% of initial body weight (7.7 kg) at 8 weeks and 13.4% (12.7 kg) at 16 weeks. Weight loss from baseline did not differ significantly by group and, for completing subjects, was 14.0% ± 1.2% (mean ± SE) for casein and 12.8% ± 1.4% for soy. With the intention-to-treat analysis, weight losses at 16 weeks were 12.5% ± 1.4% for casein and 11.3% ± 1.2% for soy. Body fat losses were 23.7% ± 2.0% for casein and 21.8% ± 2.4% for soy and did not differ significantly. Both study groups lost significant amounts of weight with a highly structured behavioral program incorporating 4 meal replacements and vegetables and fruits. Differences in weight loss and body composition changes between casein and soy treatments were not significant.

1. Introduction

Obesity is a major health problem in the United States [1] and is increasing at epidemic proportions worldwide [2,3]. Approximately two thirds of adults in the United States are overweight or obese [1], and the prevalence of overweight adolescents has increased 3-fold in the last 2 decades [4]. Obesity is accompanied by significantly higher risks of developing diabetes, hypertension, and coronary heart disease [5]. Popular diets and weight-loss regimens do not enable most obese individuals to lose significant amounts of weight or maintain reduced body weight long term [6-9]. Current pharmacotherapeutic approaches have limited effectiveness. [10] Clearly, we need more effective therapeutic approaches for the overweight individual.

Meal replacements in the form of shakes, bars, and prepackaged meals are emerging as very effective tools for weight management [7,11,12]. Long-term weight maintenance is better when individuals lose a substantial percentage of their excess weight [8] and when they continue to use meal replacements daily [13].

Soy protein appears to be one of the best choices for inclusion in a weight-loss regimen. Epidemiologic observations indicate that persons with higher soy food consumption have lower body weights than those with lower soy intakes [14,15]. Although some recent studies suggest that obese individuals lose weight more rapidly and lose more total weight with soy protein than with animal protein as a major diet component [7,16,17], another report did not confirm these observations [18]. Studies in vitro and with experimental animals suggest that soy protein and its components (peptides and isoflavones) act in a large variety of ways to promote weight loss and weight maintenance [19-24].

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The purpose of the present study was to evaluate the weight-loss efficacy, body composition changes, and other effects of either 3 soy shakes or 3 casein shakes daily as part of a 16-week, energy-restricted diet for obese women by using a randomized, controlled, blinded design. The primary study end points included mean change from baseline in body weight, body fat composition, and visceral adipose tissue (VAT). This intensive intervention included 13 classes and weekly midweek phone calls over 16 weeks and use of 3 shakes, 1 entrée, and at least 5 servings of vegetables or fruits daily.

2. Materials and methods

2.1. Subjects

This study was conducted by the Metabolic Research Group at the University of Kentucky. A subject was eligible for inclusion in this study only if all of the following criteria were met: female; aged 20 to 65 years; with body mass index (BMI) of 30 to 40 kg/m^2; motivated to lose weight; otherwise healthy as determined by the principal investigator; could read, comprehend, and write English at a sufficient level to complete study-related materials; could provide a signed and dated written informed consent before study participation; was available for participation in the study for up to 21 weeks; and was either of nonchildbearing potential or agreed to follow an acceptable birth control method. A woman was not eligible for inclusion in this study if any of the following criteria apply: history of bulimia or anorexia nervosa; cardiovascular disease; uncontrolled hypertension; type 1 or type 2 diabetes mellitus or fasting blood glucose level of 126 mg/dL or higher; waist circumference greater than 48 in. (required for midsagittal computed tomography [CT] scan to be done); untreated hypothyroidism; significant variation in weight ($\geq$4 kg) in the past 3 months; use of other medications or herbal remedies for weight loss in the past 3 months; had surgical intervention for the treatment of obesity; history of severe renal, hepatic, neurologic, chronic pulmonary disease, or any other unstable medical disorder; had gallbladder disease; depression, panic disorder, psychosis, or bipolar disorder; history of alcohol or substance abuse and dependence within the past year; breast-feeding; or subject's reservations about class attendance and use of shakes for 16 weeks.

Each subject signed and dated an informed consent form that was witnessed before undertaking any screening procedures. This protocol was approved by the University of Kentucky Institutional Review Board.

2.2. Protocol

This was a 21-week, randomized, single-blind, controlled, parallel-group study. Subjects volunteered for the study after seeing newspaper advertisements, hearing about the study, or being contacted because of a prior interest in this type of research. After prescreening by telephone, subjects who met initial inclusion and exclusion criteria participated in a 2-week assessment period. During the first screening visit, the informed consent was reviewed and signed, a detailed history and medication review was performed, and blood and urine specimens were obtained for screening. Additional medical history information was obtained and a psychological assessment and a detailed physical examination were performed by an experienced physician at the second visit. Subjects that met all inclusion/exclusion criteria at the end of the 2-week assessment period were randomized to a 16-week single-blind treatment period. Subjects were randomized to use either 3 soy-based or 3 casein-based meal replacement shakes daily.

Subjects were advised to maintain their usual diet and exercise routines until they received formal diet instruction at the randomization visit (the baseline visit or week 0). During the run-in period at visit 2 (1 week before baseline), subjects were given both flavors of the soy- and casein-based shakes and instructed to try all 4 types of shakes for tolerability and to use 2 shakes daily. They were also given a pedometer and a lifestyle diary where they recorded information about daily steps, physical activity, and meal replacement use. At the randomization visit, subjects were instructed in a low-energy diet providing 4.5 to 5.0 MJ/d. Their prescription included consumption of 3 packets of product and 1 entrée daily during the 16-week weight-loss

Table 1
Nutrient and energy content of the casein and soy shakes and estimated total energy and nutrient intake from shakes, entrees, fruits, and vegetables

Component	Casein		Soy		Minimum daily intake
	Vanilla	Chocolate	Vanilla	Chocolate	
Mjoules	0.54	0.59	0.51	0.56	4.40
Total fat (g)	0.6	1.3	0.7	1.2	9.0
Total carbohydrate (g)	8.5	10.1	8.1	10.4	151.0
Protein (g)	22.4	22.6	20.7	20.5	91
Calcium (mg)	190	166	792	770	1580
Sodium (mg)	297	298	290	327	1640
Potassium (mg)	164	354	354	574	3300
Isoflavones (aglycones) (mg)	4	3	51	47	10 (150)[a]
Dietary fiber (g)[b]	0	2	0	2	19.0

Values were analyzed by the Nestle Purina Analytical Laboratories.

[a] Casein (soy).

[b] From product information.

period. Shakes (21 per week) and entrees (7 per week) were provided. The prepackaged entrées (purchased from Health Management Resources [HMR]) provided about 0.84 MJ and 15 g of protein daily. Subjects were encouraged to eat at least 5 servings of vegetables and fresh fruit and no other food. They were instructed to keep daily records of food intake, meal replacement use, and physical activity in the lifestyle diary during the 16-week study period. Subjects were given detailed instructions by a registered dietitian about the low-energy diet and about the incorporation of the 3 shakes and the entrée into their daily diet. They were given specific instructions for preparation of shakes and recipes for "smoothies." The nutrient and energy composition of the shakes are presented in Table 1. Nutrient values are similar for both types of shakes with the exception of calcium and isoflavone content. Casein and soy shakes were prepared and packaged specifically for this study by Revival Soy, Physicians Pharmaceuticals (Kernersville, NC).

Shakes were provided in identical packages and the boxes were labeled A or B. Subjects did not know their assignment. Shakes were sweetened with Splenda; both vanilla shakes were formulated similar to Vanilla Pleasure Splenda and the chocolate shakes were similar to Chocolate Daydream Splenda (Physicians Pharmaceuticals). The 4 types of shakes were analyzed by the Nestle Purina Analytical Laboratories (St Louis, MO) per arrangement of Glenna Hughes (Solae, St Louis, MO). Analytical values are very similar to values on the label for the branded products. Dietary fiber was not analyzed and the values stated on the label are presented in the table.

All subjects attended a group orientation (baseline, week 0) where the study procedures were outlined in detail. Subjects were scheduled to attend 9 weekly classes (baseline, weeks 1-8) and 4 biweekly classes (weeks 10-16) during the program. They were expected to attend every class or make-up class with an individual appointment with the dietitian-educator. They were instructed to call the educator at midweek with a progress report. They were instructed to keep a record of all food and supplement use in their lifestyle diary. During the first 16 weeks, subjects were instructed to use a modification of the HMR Healthy Solutions Program that included 3 shakes daily, 1 prepackaged entrée daily, and 5 or more fruits or vegetables daily [25]. Subjects were encouraged to achieve physical activity levels of at least 8.4 MJ weekly [25]. Because some individuals encounter difficulty resuming their usual diet after 16 weeks of very limited food choices, we provided a "refeed" program with specific instructions about a gradual resumption of usual foods, phone availability, and one final follow-up visit. Thus, at week 16, after completing 16 weeks of the weight loss regimen, subjects were instructed in a refeed program that was followed for the last 2 weeks of the program (weeks 16-18). Two groups of subjects were recruited, with the first group orientation in June 2004 and the second group orientation in August 2004.

2.3. Assessments

Subjects made 16 clinic visits in 21 weeks (at −3,−2. 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 weeks). Screening laboratory measurements included an electrocardiogram, chemistry panel, hematology panel, thyrotropin test, urine pregnancy test, and outcome measures (serum glucose and lipids). Efficacy assessments included the following: weight (every clinic visit); waist circumference (weeks 0 and 16); BMI (weeks 0 and 16); blood pressure (weeks 0, 8, and 16); fasting serum glucose, insulin, and lipids (cholesterol, triglycerides, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol) at weeks 0, 8, and 16. Fasting serum glucose and insulin concentrations were used for calculation of the homeostasis model assessment (HOMA) indicator of insulin sensitivity as previously described [26]. Safety assessments included adverse events as self-reported and a chemistry panel at 16 weeks.

Adherence was objectively assessed as follows: subjects signed an attendance sheet to verify attendance and a staff member inspected the lifestyle diary to record completion. The following information was self-reported by the subjects and recorded on a data sheet at each visit: number of shakes, entrees, and fruits plus vegetables consumed per week. Subjects also estimated their physical activity daily, recorded it in the lifestyle diary, and recorded the weekly total on the data sheet in the clinic. Energy expenditure with physical activity was estimated in kilocalories with the HMR calorie system [25,27]. All lifestyle calculations were based on active subjects and adjustments were not made for subjects after their withdrawal.

LabCorp (Louisville, KY) performed routine laboratory studies for this study. The General Clinical Research Center (GCRC) laboratory at the University of Kentucky performed serum C-reactive protein (CRP) and homocysteine measurements.

Body composition changes were assessed by these measures: air displacement plethysmography with the BOD POD at the GCRC as previously described; [28] dual-energy x-ray absorptiometry (DEXA, GE Lunar Prodigy, Madison, WI) at the GCRC; and midabdominal CT in the Department of Diagnostic Radiology, University of Kentucky, as described by Akazawa et al [29]. The single-slice axial CT at the L4-L5 level gives a very specific estimate of the area for VAT and for non-VAT in the abdomen [30].

2.4. Statistical analyses

The use of 3 meal replacements, soy shakes, or casein shakes per day was evaluated. The primary end points were the absolute and percentage changes from baseline in body weight at 16 weeks. The conservative power analysis approach leads to an unpaired *t*-test analysis. We used completer or available subject data for analysis of all variables but also used last-observation-carried-forward (intention-to-treat) analysis for weight changes.

We planned to randomize approximately 40 subjects to one of 2 treatment groups. Sample size calculations were based on data from previous clinical trials at the University of Kentucky [31,32]. We calculated the minimum sample size to detect a difference in body weight change of 4% and assumed a standard deviation of 4%. We calculated that 16 subjects would be required per treatment group to detect a 4% difference with a significance of $\alpha = .05$ and a power of 80%.

3. Results

3.1. Screened subjects

Subjects were prescreened by telephone, e-mail, or Internet database, and appropriate subjects were invited for a screening visit to the clinic. Of 57 screened subjects, 43 qualified and were randomized. The remaining 14 subjects were not randomized for these reasons: unable to commit to weekly classes or the dietary regimen (8), BMI too high (2), BMI too low (1), dyslipidemia (1), newly discovered diabetes mellitus (1), and pregnancy (1).

3.2. Randomization

Thirty-five subjects completed this study. The overall completion rate for those subjects randomized in the study was 81%. Twenty-one subjects were randomized to the casein shakes and 18 (86%) completed the study; 22 subjects were randomized to the soy shakes and 17 (77%) completed the study.

3.3. Demographic characteristics of subjects

Age and racial/ethnic group did not differ significantly between groups (Table 2). The average age was approximately 45 years. Of the completers, 30 were Caucasian, 4 were African American, and 1 was Hispanic. Per study protocol, all subjects were women in both groups. The baseline BMI values were almost identical at approximately 35 kg/m^2 for both groups (Table 2).

3.4. Early withdrawals

Early withdrawals were related to these reasons: at 4 weeks, 1 subject (soy) was not able to get to class on time; at 5 and 8 weeks, 2 subjects (1 casein and 1 soy) had job changes that conflicted with class time; and at 12 to 14 weeks, 5 subjects (2 casein, 3 soy) were unable to continue compliance with the diet. None of the subjects indicated that intolerance to the shakes were responsible for their discontinuation.

Table 2
Baseline demographics of subjects by study group

	Casein MR	Soy MR
Average age (y)	44.0 ± 12.2	46.5 ± 8.4
Race (n)		
Caucasian	17	20
African American	3	2
Hispanic	1	0
Average BMI (kg/m^2)	34.9 ± 3.2	34.6 ± 3.6

Values are means ± SD. MR indicates meal replacement.

3.5. Supplement and lifestyle diary compliance

A number of subjects initially found it difficult to use 3 shakes daily; with coaching from the dietitian and with sharing experiences with other class members, all enrolled subjects used 3 shakes daily on most days. Subjects consumed 3 shakes, either casein or soy, 1 entrée, and a minimum of 5 servings of vegetables or fruits daily. Table 1 presents an estimate of minimum daily intake calculated for 3 shakes, 1 entrée, 3 vegetables, and 2 fruits. The minimum daily intake is estimated as follows: 4.4 MJ; protein, 91 g, fat, 9 g; carbohydrate, 151 g; calcium, 670 mg (casein) and 1690 mg (soy); sodium, 1638 mg; potassium, 3206 mg; and dietary fiber, 18.9 g. Isoflavone intake, as aglycones, was approximately 10 mg/d in the casein group and approximately 150 mg/d in the soy group.

Average class attendance, as summarized in Table 3, was excellent (≥95%) for casein (96%) and soy groups (96%). Lifestyle diary completion averages also were very good (≥90%) to excellent for both groups (96% for casein and 92% for soy). Other lifestyle variables, although self-reported, were excellent for casein and soy groups, respectively. Three shakes were prescribed for daily use (21/wk) and shake consumption averaged 20.6/wk for casein (98% of goal) and 20.4/wk for soy (97%). One entrée was provided for daily use (7/wk) and entrée consumption averaged 6.8/wk for casein (97%) and 6.9/wk for soy (99%). Subjects were instructed to consume 5 servings of fruits or vegetables daily (≥35/wk) and they reported 54.4 servings per week for casein (155% of goal) and 51.4 servings per week for soy (147% of goal). All but one subject averaged more than 35 servings per week of fruits or vegetables, with the average intake over 16 weeks ranging from 34 to 106 servings per week. Subjects were encouraged to achieve expenditure of 8.4 MJ/wk in physical activity and values averaged 10.6 ± 0.8 MJ/wk for casein (127% of goal) and 11.9 ± 0.9 MJ/wk for soy (142%). Average physical activity over the 16 weeks ranged from 5.7 to 21.5 MJ/wk, and 77% of subjects averaged more than 8.4 MJ/wk. There were no significant differences between class attendance, lifestyle diary completion, and other lifestyle behaviors (shake, entrée, and fruit/vegetable consumption, and physical activity) between casein and soy groups, and there were no observed correlations between weight loss or serum LDL-cholesterol changes and lifestyle behaviors.

3.6. Weight loss

Average weight losses were significant after 1 week in both groups and were significant ($P < .0001$) at 8 and 16 weeks in both groups (Table 4). Weight loss for available subjects was similar between the 2 groups and did not differ significantly at any time point (Fig. 1). At 8 weeks, weight loss averaged 8.3% (95% confidence interval [CI],

Table 3
Class attendance and self-reported values for food intake and physical activity

	Casein		Soy	
	Average	95% CI	Average	95% CI
No. of subjects	21		22	
Attendance (%)	96.1	92.8-99.4	96.4	94.2-98.6
Range	81.8-100		85.7-100	
Records (%)	96.4	94.0-98.8	92.2	85.7-98.7
Range	81.8-100		36.4-100	
Shake use (no./wk)	20.6	20.4-20.9	20.4	19.8-21
Range	19.6-21		14.2-21	
Entree use (no./wk)	6.8	6.1-7.0	6.9	6.8-6.9
Range	5.9-7.0		6.6-7.0	
Fruits, vegetables (no./wk)	54.4	46-63	51.1	47-55
Range	36-106		34-69	
Physical activity (MJ/wk)	10.6	9.1-12.2	11.9	10.1-13.6
Range	5.7-19.21		6.5-21.5	

Averages are provided for class attendance over 16 weeks and completed record summaries reviewed by the dietitian in the class. These self-reported values per week are presented: numbers of shakes used, entrees used, fruits and vegetables consumed, and physical activity.

6.9%-9.7%) of baseline weight for casein and 7.9% (95% CI, 6.5%-9.3%) for soy. Weight loss for completing subjects was 14.0% (95% CI, 11.6%-16.4%) for casein and 12.8% (95% CI, 10.1%-15.5%) for soy. By the intention-to-treat or last-observation-carried-forward analyses, the weight losses at 16 weeks for casein and soy, respectively, were 12.5% (95% CI, 9.8%-15.2%) and 11.3% (95% CI, 8.9%-13.7%) from baseline. None of the weight change differences between casein and soy were significantly different.

3.7. Waist circumference changes

Baseline waist measurements were similar in the 2 groups (Table 4) and decreased by 13.3% ($P = .0002$) with casein and 11.6% ($P < .0001$) with soy. Reductions in waist circumferences closely paralleled reductions in body weight.

3.8. Blood pressure changes

Significant reductions in systolic and diastolic blood pressures occurred in both groups at 8 and 16 weeks. Systolic blood pressure decreased approximately 4.1% with casein (average of 8- and 16-week values) and approximately 6.2% with soy, but the differences between the groups were not significant (Table 4). Diastolic blood pressure reductions averaged approximately 9% in both groups.

3.9. Body composition changes

BOD POD. Body composition changes for individuals as measured by BOD POD and DEXA were almost identical (Table 4). The total fat losses at 8 weeks by both measurements were proportional to the weight losses. The changes in BOD POD measurements at 16 weeks were as follows: total body fat loss, casein, 23.4% ($P < .0001$), and soy, 21.6% ($P < .0001$; casein vs soy, not significant [NS]); total body lean tissue loss, casein, 3.4%, and soy, 4.3% (both NS).

DEXA. The changes at 16 weeks were as follows: total body fat loss, casein, 23.7% ($P < .0001$), and soy, 21.8%

Table 4
Body weight, waist circumference, blood pressure, and body composition changes for available subjects

Measurement	Casein MR			Soy MR		
	Baseline	8 wk (% change)	16 wk (% change)	Baseline	8 wk (% change)	16 wk (% change)
Weight (kg)*	96.4 (2.3)	−8.3 (0.7)*	−14.0 (1.2)*	93.6 (2.5)	−7.9 (0.7)*	−12.8 (1.4)*
Waist circumference (in.)	41.7 (0.9)		−13.3 (2.4)*	40.6 (0.7)		−11.6 (1.4)*
Systolic blood pressure (mm Hg)	119.8 (2.5)	−4.3 (1.5)*	−3.9 (2.0)*	128.2 (4.0)	−6.1 (1.9)*	−6.3 (3.2)*
Diastolic blood pressure (mm Hg)	78.5 (2.1)	−6.9 (2.7)*	−11.6 (1.9)*	83.4 (2.1)	−10.4 (2.2)*	−8.5 (2.5)*
BOD POD						
Fat weight (kg)	44.2 (1.7)	−16.4 (1.5)*	−23.4 (2.7)*	44.6 (1.9)	−13.9 (1.3)*	−21.6 (2.9)*
Lean weight (kg)	49.2 (1.0)	0.7 (1.0)	−3.4 (1.3)	47.9 (1.3)	−1.3 (0.9)	−4.3 (1.4)
DEXA						
Total fat (kg)	44.4 (1.4)	−13.0 (1.0)*	−23.7 (2.0)*	43.5 (1.6)	−12.5 (1.0)*	−21.8 (2.4)*
Truncal fat (kg)	22.5 (0.9)	−13.7 (2.6)*	−26.1 (2.1)*	21.8 (0.8)	−13.5 (1.3)*	−22.5 (3.0)*
Total lean tissue (kg)	45.4 (1.3)	−2.8 (0.9)*	−3.6 (1.3)*	46.3 (1.1)	−2.1 (0.7)*	−3.1 (1.0)*
CT						
Non-VAT fat area (cm^2)	523 (14.5)		−25.3 (3.0)*	521 (22.2)		−25.0 (2.8)*
VAT fat area (cm^2)	103 (11)		−27.2 (3.7)*	101 (7.4)		−30.3 (4.2)*

Baseline values are given in units and changes are expressed as percentages. Values in parentheses are SEs.

* $P < .05$ compared with baseline value.

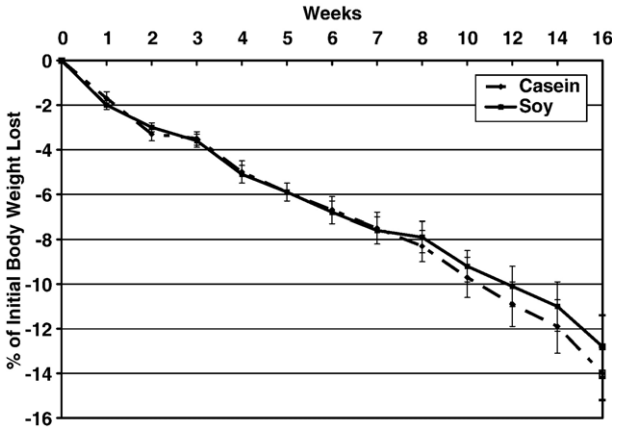

Fig. 1. Weight loss over time as percentage of baseline weight.

($P < .0001$, casein vs soy, NS); total body lean tissue loss, casein, 3.6%, and soy, 3.1% (both significant, $P = .01$). Losses in truncal fat paralleled losses in total body fat and did not differ significantly between casein and soy.

CT. Reductions in non-VAT area were similar for casein (25.3%) and soy (25.0%; $P < .0001$ for both). Significant reductions in VAT were seen for casein (28.3%, $P < .0001$) and soy (30.3%, $P < .0001$), but differences between the 2 groups were not statistically significant.

3.10. Plasma glucose, insulin, and HOMA changes

Fasting plasma glucose values decreased in both groups by approximately 4.3%, with this reduction being statistically significant at 16 weeks with soy ($P = .018$, Table 5). Plasma insulin values decreased in both groups with reductions at 16 weeks of 19.9% ($P = .0219$) for casein and 15.4% ($P = .0518$) for soy.

The HOMA, an estimation of insulin sensitivity, was calculated by using the fasting plasma glucose and insulin values, with lower values indicating better sensitivity to insulin. The HOMA values decreased significantly, with absolute values of 3.1 ($P = .036$) for casein and 2.3 ($P = .038$) for soy. These changes and differences did not differ significantly between casein and soy.

3.11. Serum lipid changes

Weight loss was associated with significant reductions in serum total cholesterol and LDL-cholesterol. The largest reductions in total cholesterol values were seen at 8 weeks with values for casein of −12.0% ($P = .0024$) and for soy of −13.7% ($P < .0001$, Table 5). Reductions in total cholesterol at 16 weeks were −7.6% ($P = .0141$) for casein and −11.0% ($P = .004$) for soy. Serum LDL-cholesterol changes followed the same pattern. For casein and soy, respectively, reductions at 8 weeks were 13.3% ($P = .0028$) and 16.4% ($P < .0001$), and at 16 weeks were 7.7% ($P = .0245$) and 12.5% ($P = .0071$). Differences between soy and casein were not statistically significant. With weight loss in women, reductions in HDL-cholesterol values usually occur over the short term [33]. Accordingly, in this study, values decreased significantly in casein and soy by 10% to 11% at 8 weeks but returned to values not significantly below baseline at 16 weeks. The nutrition content of the shakes and the increased intake of fruits without counterbalancing grain fiber probably contributed to the small increase in fasting serum triglycerides at 8 weeks. By 16 weeks, changes in serum triglycerides were not significant (−6.7% with casein and −12.5% with soy), and no significant differences were seen between groups.

3.12. Serum CRP and homocysteine changes

Serum CRP values were insignificantly decreased at 16 weeks with casein (7.6%) and soy (15.4%), but these differences between treatments were not significant. Serum homocysteine values increased in both groups and were significantly increased at 8 weeks with soy, but there were no significant differences between treatments (Table 5).

3.13. Side effects

Gastrointestinal side effects were reported initially, but both soy and casein shakes were well tolerated. No moderate or severe side effects or serious adverse events were reported. None of the "early" withdrawals appear related to the type of protein shake being used. Subjects were blinded to their assignment, and most did not know

Table 5
Plasma and serum measurement changes

Measurement	Casein			Soy		
	Baseline	8 wk (% change)	16 wk (% change)	Baseline	8 wk (% change)	16 wk (% change)
Plasma glucose (mmol/L)	5.3 (0.12)	−3.2 (2.3)	−4.4 (2.9)	5.4 (0.12)	−1.4 (1.7)	−4.2 (1.6)*
Plasma insulin (μU/mL)	19.1 (3.0)	−25.1 (7.4)*	−19.9 (8.7)*	15.3 (1.5)	−13.9 (7.9)*	−15.4 (8.7)
HOMA (units)	4.7 (0.9)	2.7 (0.3)	3.1 (0.6)*	3.8 (0.4)	3.1 (0.4)	2.3 (0.2)*
Serum cholesterol (mmol/L)	4.5 (0.21)	−12.0 (4.6)*	−7.6 (3.4)*	4.9 (0.19)	−13.7 (2.5)*	−11.0 (3.3)*
Serum LDL-cholesterol (mmol/L)	2.8 (0.16)	−13.3 (6.0)*	−7.7 (4.4)*	3.2 (0.14)	−16.4 (3.1)*	−12.5 (4.2)*
Serum HDL-cholesterol (mmol/L)	1.18 (0.05)	−10.0 (3.5)*	−3.0 (3.5)	1.14 (0.04)	−11.0 (3.5)*	−3.5 (3.3)
Serum triglycerides (mmol/L)	1.17 (0.15)	7.6 (8.6)	−6.7 (7.7)	1.23 (0.14)	5.6 (9.6)	−12.5 (8.1)
Serum CRP (ng/mL)	0.8 (0.1)	3.5 (10.8)	−7.6 (6.6)	0.8 (0.2)	−2.1 (9.3)	−15.4 (6.1)
Serum homocysteine (μmol/L)	8.8 (0.4)	12.9 (6.4)	9.9 (6.4)	8.6 (0.5)	28.4 (9.3)*	18.8 (12.1)

Values are for available subjects. Baseline values are given in units and follow-up values are given as percentage change from baseline except for HOMA values, which are given in units. Values in parentheses are SEs.

* $P < .05$ compared with baseline value.

which protein shake they were receiving. Subjects were queried at each visit about shake acceptability by the dietitian (J.F.) and nutrition graduate student (K.P.). Overall, both vanilla and chocolate casein shakes were reported to be well tolerated and the vanilla soy shake was well tolerated. The chocolate soy shake was the least favorite shake.

4. Discussion

Meal replacement (shakes and entrees) use coupled with fruit and vegetable consumption are excellent strategies for weight loss and weight maintenance [7,11,34]. In the current study, subjects who completed 16 weeks of treatment lost an average of 13.4% of initial body weight (12.7 kg). These weight losses are very similar to those for patients treated in the HMR Program with the Healthy Solution option, where weight loss over 20 weeks averaged 15.4% for patients who completed the 12-week core classes [34]. To account for individuals who enter treatment but do not complete the 12 or 16 weeks of core classes, weight loss for subjects in this research study was 11.9% of initial body weight, whereas weight loss for patients in the HMR Program was 11.2% (unpublished observations). These weight losses of 11% to 15% of initial body weight are substantially higher than reported for meal replacement use alone [7,11] or energy-restricted diets [7] and are equivalent to average weight losses over 24 weeks for intensive behavioral programs using low-energy diets [7,35,36]. Only use of very low energy or low-energy diets using meal replacements (shakes and entrees) without other foods (such as fruits and vegetables) appears to be a more effective dietary intervention for obese individuals [7,8].

Based on preliminary studies in humans [7,12,16,17,37] and on animal studies [19-24], we hypothesized that a soy-based meal replacement intervention would have greater weight-loss efficacy than use of a casein-based meal replacement. Although lifestyle behaviors and meal replacement use did not differ between the casein and soy groups, we saw no significant differences in weight loss. The casein group had slightly more weight loss and greater total fat loss, whereas the soy group had slightly greater reductions in systolic blood pressure, visceral fat, and serum total and LDL-cholesterol values. It is possible that the intensity of intervention—considerably higher than in our previous study [12]—may have minimized differences between soy and casein effects. Previous controlled studies in humans [18,38], including our own [12], have also failed to document significantly greater effects of soy protein on body weight loss, indicating that more research is required to support the hypothesis that soy protein fosters weight loss more effectively than milk protein.

Isolated soy protein, as used in this study, provides soy protein, soy peptides, and isoflavones. Evidence is emerging, especially in experimental animals and in vitro studies, that all 3 of these components have important physiologic and biochemical effects. Soy peptides, for example, have greater hypocholesterolemic effects in humans than intact soy protein [39,40]. In rodents, feeding soy peptides has a slightly greater effect in slowing fat accumulation and decreasing visceral fat accumulation than does intact soy protein [19,41]. In rodents, soy peptides also increase postprandial energy expenditure [20], decrease food intake [22,42], and have appetite-suppressant effects [21]. Isoflavones, both in vitro and in vivo, have distinct effects on fat accumulation and metabolism. In rodents, isoflavone administration decreases fat accumulation [23,43-45]. When isoflavones are incubated with isolated adipocytes, significant changes in lipid metabolisms occur [46,47]. In aggregate, the animal and in vitro studies using soy protein, soy peptides, and isoflavones suggest that these soy components may significantly affect weight regulation in humans.

Limitations of this study include sample size and intensity of intervention. Although the sample size was appropriate for detecting meaningful differences in weight loss, it was not adequate for discerning significant differences in serum LDL-cholesterol changes or VAT changes for soy compared to casein. Higher intensity weight loss interventions may decrease the likelihood of detecting significant differences between experimental arms. Approximately 300 subjects in each group would be required to detect a weight loss difference of only 1.2%. The significant increase in serum homocysteine values after 8 weeks of soy consumption may be related to weight loss coupled with the specific soy shakes used; however, we cannot provide a reasonable hypothesis to explain these changes.

Overweight and obesity are associated with a dramatic increase in the risk of developing diabetes [48]. Studies in humans indicate that soy protein or isoflavones enhance insulin sensitivity and may have a role in protection from development of diabetes [49,50]. These observations are supported by animal [51,52] and in vitro studies [53,54] looking at potential mechanisms for these effects. Additional controlled trials are required to more critically examine these potential effects in humans.

In conclusion, this randomized controlled study confirmed that an intensive behavioral weight management program including 3 shakes, 1 entrée, and 5 fruits or vegetables daily was associated with a weight loss of 12.6 kg or 13.4% of initial body weight over a 16-week period. With subjects blinded to protein source, the weight loss with casein shakes and soy protein shakes were similar. Body fat losses were greater than 22%, and significant reductions in serum cholesterol and LDL-cholesterol occurred.

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References

[1] Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723-7.

[2] James PT, Leach R, Kalamara E, et al. The worldwide obesity epidemic. Obes Res 2001;9:228S-233S.

[3] Stein CJ, Colditz GA. The epidemic of obesity. J Clin Endocrinol Metab 2004;89:2522-5.

[4] Ogden CL, Flegal KM, Carroll MD, et al. Prevalence and trends in overweight among US children and adolescents, 1999-2000. JAMA 2002;288:1728-32.

[5] Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003; 289:76-9.

[6] Heshka S, Anderson JW, Atkinson RL, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. JAMA 2003;289:1799-805.

[7] Anderson JW, Luan J, Hoie LH. Structured weight-loss programs: a meta-analysis of weight loss at 24 weeks and assessment of effects of intensity of intervention. Adv Ther 2004;21:61-75.

[8] Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr 2001; 74:579-84.

[9] Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss programs in the United States. Ann Intern Med 2005;142:56-66.

[10] Li X, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med 2005;142:532-46.

[11] Heymsfield SB, van Mierlo C, van der Knaap HCM, et al. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. Int J Obes 2003;27:537-49.

[12] Anderson JW, Hoie LH. Weight loss and lipid changes with low-energy diets: comparison of milk-based versus soy-based liquid meal replacement interventions. J Am Coll Nutr 2005;24:210-6.

[13] Flechtner-Mors M, Ditschuneit HH, Johnson TD, et al. Metabolic and weight loss effects of long-term dietary intervention in obese patients: four-year results. Obes Res 2000;8:399-402.

[14] Goodman-Gruen D, Kritz-Silverstein D. Usual dietary isoflavone intake and body composition in postmenopausal women. Menopause 2003;10:427-32.

[15] Yamori Y. Worldwide epidemic of obesity: hope for Japanese diet. Clin Exp Pharmacol Physiol 2004;31:S2-S4.

[16] Allison DB, Gadbury G, Schwartz LG, et al. A novel soy-based meal replacement formula for weight loss among obese individuals: a randomized controlled clinical trial. Eur J Nutr 2003;57:514-22.

[17] Deibert P, Konig D, Schmidt-Trucksaess A, et al. Weight loss without losing muscle mass in pre-obese and obese subjects induced by high-soy diet. Int J Obes 2004;28:1349-52.

[18] Kok L, Kreijkamp-Kaspers S, Grobbee DE, et al. Soy isoflavones, body composition, and physical performance. Maturitas 2006;52: 102-10.

[19] Aoyama T, Fukui K, Takamatsu K, et al. Soy protein isolate and its hydrolysate reduce body fat of dietary obese rats and genetically obese mice (yellow KK). Nutrition 2000;16:349-54.

[20] Ishihara K, Oyaizu S, Fukuchi Y, et al. A soybean peptide isolate diet promotes postprandial carbohydrate oxidation and energy expenditure in type II diabetic mice. J Nutr 2003;133:752-7.

[21] Nishi T, Hara H, Asano K, et al. The soybean B-conglycinin B-51-63 fragment suppresses appetite by stimulating cholecystokinin release in rats. J Nutr 2003;133:2537-42.

[22] Pupovac J, Anderson GH. Dietary peptides induce satiety via cholecystokinin-A and peripheral opioid receptors in rats. J Nutr 2002;132:2775-80.

[23] Naaz A, Yellayi S, Zakroczymski MA, et al. The soy isoflavone genistein decreases adipose deposition in mice. Endocrinology 2003; 144:3315-20.

[24] Nagasawa A, Fukui K, Kojima M, et al. Divergent effects of soy protein diet on the expression of adipocytokines. Biochem Biophys Res Commun 2003;311:909-14.

[25] Health Management Resources. HMR program for weight management weight loss core curriculum. Boston (MA): Health Management Resources; 1999.

[26] Tripathy D, Carlsson M, Almgren P, et al. Insulin secretion and sensitivity in relation to glucose tolerance: lessons from the Botnia Study. Diabetes 2000;49:975-80.

[27] Heilbronn LK, de JL, Frisard MI, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA 2006;295:1539-48.

[28] Ginde SR, Geliebter A, Rubiano F, et al. Air displacement plethysmography: validation in overweight and obese subjects. Obes Res 2005;13:1232-7.

[29] Akazawa S, Sun F, Ito M, et al. Efficacy of troglitazone on body fat distribution in type 2 diabetes mellitus. Diabetes Care 2000;23: 1067-71.

[30] Shen W, Wang Z, Punyanita M, et al. Adipose tissue quantification by imaging methods: a proposed classification. Obes Res 2003;11:5-16.

[31] Anderson JW, Greenway FL, Fujioka K, et al. Bupropion SR significantly enhances weight loss: a 24-week double-blind, placebo-controlled trial with placebo group randomized to bupropion SR during 24-week extension. Obes Res 2002;10:633-41.

[32] Reynolds LR, Konz EC, Frederich RC, et al. Rosiglitazone amplifies the benefits of lifestyle intervention measures in long-standing type 2 diabetes mellitus. Diabetes Obes Metab 2002;4:270-5.

[33] Anderson JW, Konz EC. Obesity and disease management: effects of weight loss on co-morbid conditions. Obes Res 2001;9:326S-334S.

[34] Gotthelf L, Anderson JW, O'Brien B: Weight loss in overweight or obese individuals with different structured interventions in an intense behavioral program. Obes Res 12:A402004 (Abstract).

[35] Wadden TA, Foster GD, Letizia KA. One-year behavioral treatment of obesity: comparison of moderate and severe caloric restriction and the effects of weight maintenance therapy. J Consult Clin Psychol 1994;62:165-71.

[36] Wing RR, Jeffery RW, Burton LR, et al. Food provision vs structured meal plans in the behavioral treatment of obesity. Int J Obes 1996; 20:56-62.

[37] Fontaine KR, Yang D, Gadbury GL, et al. Results of soy-based meal replacement formula on weight, anthropometry, serum lipids & blood pressure during a 40-week clinical weight loss trial. Nutr J 2003;2:14.

[38] Moeller LE, Peterson CT, Hanson KB, et al. Isoflavone-rich soy protein prevents loss of hip lean mass but does not prevent the shift in regional fat distribution in perimenopausal women. Menopause 2003; 10:322-31.

[39] Wang M-F, Yamamoto S, Chung H-M, et al. Antihypocholesterolemic effect of undigested fraction of soybean protein in young female volunteers. J Nutr Sci Vitaminol 1995;41:187-95.

[40] Hori G, Wang M-F, Chan Y-C, et al. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. Biosci Biotechnol Biochem 2001; 65:72-8.

[41] Aoyama T, Fukui K, Nakamori T, et al. Effect of soy and milk whey protein isolates and their hydrolysates on weight reduction in genetically obese mice. Biosci Biotechnol Biochem 2000;64:2594-600.

[42] Nishi T, Hara H, Tomita F. Soybean B-conglycinin peptone suppresses food intake and gastric emptying by increasing plasma cholecystokinin levels in rats. J Nutr 2003;133:352-7.

[43] Ali AA, Velasquez MT, Hansen CT, et al. Effects of soybean isoflavones, probiotics, and their interaction on lipid metabolism and endocrine system in an animal model of obesity and diabetes. J Nutr Biochem 2004;15:583-90.

[44] Uesugi T, Toda T, Tsuji K, et al. Comparative study on reduction of bone loss and lipid metabolism abnormality in ovariectomized rats by

soy isoflavones, daidzin, genistin, and glycitin. Biol Pharm Bull 2001;24:368-72.

[45] Zhou J-R, Pan W, Takebe M, et al. Effects of isoflavone aglycone in the prevention of obesity in a diet-induced obesity mouse model. Atherosclerosis 1999;143:81-90.

[46] Szkudelska T, Nogowski L, Pruszynska-Oszmalek E, et al. Genistein restricts leptin secretion from rat adipocytes. J Steroid Biochem Mol Biol 2005;96:301-7.

[47] Hwang J-T, Park I-J, Shin J-I, et al. Genistein, EGCG, and capsaicin inhibit adipocyte differentiation process via activating AMP-activated protein kinase. Biochem Biophys Res Comm tbd:tbd, 2005.

[48] Anderson JW, Kendall CWC, Jenkins DJA. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr 2003;22:331-9.

[49] Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002;25:1709-14.

[50] Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. Am J Clin Nutr 2002;76:191-1201.

[51] Moriyama T, Kishimoto K, Nagai K, et al. Soybean β-conglycinin diet suppresses serum triglyceride levels in normal and genetically obese mice by induction of β-oxidation, downregulation of fatty acid synthase, and inhibition of triglyceride absorption. Biosci Biotechnol Biochem 2004;68:352-9.

[52] Ascencio C, Torres N, Isoard-Acosta F, et al. Soy protein affects serum insulin and hepatic SREBP-1 mRNA and reduces fatty liver in rats. J Nutr 2004;134:522-9.

[53] Iritani N, Sugimoto T, Fukuda H, et al. Dietary soybean protein increases insulin receptor gene expression in Wistar fatty rats when dietary polyunsaturated fatty acid level is low. J Nutr 1997;127:1077-83.

[54] Dang Z-C, Audinot V, Papapoulos SE, et al. Peroxisome proliferator–activated receptor γ (PPAR γ) as a molecular target for the soy phytoestrogen genistein. J Biol Chem 2003;278:962-7.