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ORIGINAL ARTICLE

Influences of a dietary supplement in combination with an exercise and diet regimen on adipocytokines and adiposity in women who are overweight

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Abstract The influence of a proprietary blend of modified cellulose and cetylated fatty acids on adipocytokine and regional body composition responses to a weight loss program was examined. Twenty-two women (Supplement group (S) ($n = 11$): age = 36.8 ± 7.2 years; weight = 87.1 ± 6.2 kg; % body fat = 43.4 ± 4.1; Placebo group (P) ($n = 11$): age = 38.3 ± 6.8 years; weight = 86.9 ± 4.7 kg; % body fat = 44.3 ± 2.0) completed an 8-week placebo-controlled, double-blind study consisting of a caloric restricted diet and cardiovascular exercise. Body composition and serum insulin, leptin, and adiponectin were assessed at pre-, mid-, and post-intervention. From pre- to post-intervention, significant decreases ($P < 0.05$) were observed for body weight (S: 87.1 ± 6.2–77.9 ± 5.1 kg; P: 86.9 ± 4.7–82.7 ± 3.8 kg) ($P < 0.05$ S vs. P), % body fat (S: 43.4 ± 4.1–36.1 ± 3.6; P: 44.3 ± 2.0–40.6 ± 1.2) ($P < 0.05$ S vs. P), leptin (S: 28.3 ± 3.5–16.2 ± 2.6 ng ml^{-1}; P: 29.4 ± 3.2–19.9 ± 1.1 ng ml^{-1}) ($P < 0.05$ S vs. P), and insulin (S: 7.3 ± 0.8–5.1 ± 0.2 mU l^{-1}; P: 7.7 ± 0.9–5.1 ± 0.3 mU l^{-1}). Serum adiponectin increased ($P < 0.05$) (S: 12.2 ± 2.4–26.3 ± 3.0 μg ml^{-1}: 12.6 ± 2.0–21.8 ± 3.1 μg ml^{-1}) ($P < 0.05$ for S vs. P). Supplementation with a proprietary blend of modified cellulose and cetylated fatty acids during an 8-week weight loss program exhibited favorable effects on adipocytokines and regional body composition.

Keywords Dietary supplement · Weight loss · Adipocytokines · Diet · Exercise

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Introduction

Weight loss programs combining exercise and diet strategies appear to be more effective than either of these strategies administered alone (Wadden et al. 2001). The mechanisms by which these intervention strategies modulate weight loss is believed to be regulated by the influence of circulating adipocytokines (signaling molecules secreted by adipose (Koerner et al. 2005) on the hypothalamic pathways and integration between the brain, adipose tissue and other peripheral organs involved in the weight regulatory pathway. Leptin and insulin appear to work synergistically to modulate appetite regulatory pathways in the hypothalamus (Horvath et al. 2001; Kalra and Kalra 2003), while adiponectin appears to influence insulin sensitivity (Meier and Gressner 2004). The progression of obesity and its co-morbidities may be explained by the effects of lower adiponectin expression in adipose tissue of obese individuals on hormone-sensitive lipase activity and fatty acid oxidation (Bullo et al. 2005). With weight loss, circulating adiponectin concentrations typically increase (Shapses and Riedt 2006; Wolfe et al. 2004) while insulin sensitivity improves (Wing et al. 1987; Hara et al. 2005).

Leptin regulates body fat storage through the central nervous system by modulating satiation, appetite, glycemic control, and metabolism (Bell-Anderson and Bryson 2004; Klok et al. 2007). Leptin inhibits orexigenic effects of the

hormone ghrelin, which plays a role in the regulation of feeding, by centrally countering its appetite promoting effects in the hypothalamus and peripherally by attenuating gastric ghrelin secretion (Ueno et al. 2004). Leptin is also a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss (Klok et al. 2007). Leptin is strongly correlated with obesity and weight loss (Pelleymounter et al. 1995). Diet (Wolfe et al. 2004) and combined diet and exercise strategies (Volek et al. 2002a) have been shown effective at decreasing body fat and plasma leptin concentrations. In addition, some evidence suggests that leptin may restrain adipocyte adiponectin secretion (Ueno et al. 2004). Despite, the regulatory effects of leptin on energy balance, obese individuals exhibit elevated circulating levels of leptin due likely to a resistance to leptin (Eikelis and Esler 2005; Klok et al. 2007). Leptin is strongly correlated with obesity and weight loss (Pelleymounter et al. 1995). Diet (Wolfe et al. 2004) and combined diet and exercise strategies (Volek et al. 2002a) have been shown effective at decreasing body fat and plasma leptin concentrations.

While the understanding of these pathways is progressing, efforts to develop successful pharmacological or supplemental strategies to influence these pathways has been disappointing. This study examined the effects of a dietary supplement containing a proprietary blend of modified cellulose and cetylated fatty acids on weight loss induced by diet and exercise on body composition, regional anthropometric changes, and serum insulin, leptin, and adiponectin. Since this supplement predominantly contains a non-fermentable, modified cellulose, it is believed to exhibit a similar profile to dietary fibers in slowing gastric emptying (Karhunen et al. 2008; Reimer and Russell 2008) and possibly delaying glucose absorption (Maki et al. 2008). While this supplement is marketed as a weight loss aid, no data currently exist to support this claim. To our knowledge, the present investigation is the first investigation to examine the additive role of supplementation with a proprietary blend of modified cellulose and cetylated fatty acids in a weight loss program for women.

Methods

Experimental approach

Women who were overweight (BMI > 25) but otherwise healthy were recruited to participate in a supplemented 8-week, double-blinded, placebo-controlled weight loss program that included dietary guidance and exercise. The intervention was designed to created a caloric deficit resulting in approximately 0.5–1 kg/week loss in body mass by the combination of diet and exercise. Participants were matched (body mass, percent fat, menstrual status, oral contraceptives (i.e., two pair), activity background, and endurance capacity) with prelimnary testing. From these matched pairs, each woman was randomly placed into either a group that consumed the proprietary blend of modified cellulose and cetylated fatty acids supplement or in a control group that consumed visually identical placebo capsules. Prior to participation, all participants were informed of the study procedures and risks and were required to complete an informed consent document approved by the Review Board for the Use of Human Subjects at the University of Connecticut. In addition, each subject was medically cleared by a physician to participate in the study.

Participants

Twenty-two healthy matched women who were overweight (Supplement group (S): ($N = 11$) Age 36.8 ± 7.2 years; Height 163.8 ± 9.1 cm; BMI 32.6 ± 2.7 kg/m^2; Placebo group (P) ($N = 11$) 38.3 ± 6.8 years; Height 162.7 ± 9.3 cm; BMI 32.8 ± 2.0 kg/m^2) participated in the study. No participants demonstrated any endocrine, metabolic, orthopedic, or other pathological disorders, except for being overweight. Participants were excluded if they were on any medications for treatment of illnesses or that would impact weight loss (e.g., antihistamines, decongestants, etc.). Participants were weight-stable (within 5 pounds) for at least 3 months before enrollment, were not pregnant or trying to become pregnant, did not use tobacco products, nor consume more than two alcoholic beverages per day.

Supplement

Participants consumed either three supplement (S) or placebo capsules at the two largest meals each day (six capsules total per day), per the manufacturer's recommendation. Each supplement capsule contained 400 mg of (a proprietary blend of modified cellulose and cetylated fatty acids). The modified cellulose is a food grade ingredient that has generally recognized as safe (GRAS) status. Cetylated fatty acids have no known side effects or adverse reactions. The placebo contained 400 mg of magnesium stearate per capsule. Participants logged their supplement consumption each day and returned the bottles when emptied and after the study. Additionally, participants were required to complete daily symptoms and side effect questionnaires, which asked participants to cite any symptoms they experienced each day during the duration of the study (whether or not they believed they were or were not associated with supplement use).

Weight-loss program dietetic counseling

Using the methods described by Volek et al. (2002a) all participants consumed a moderately caloric restricted diet of self-selected commercially available foods in a free-living environment to allow dietary modifications that could be continued with ease by participants after the duration of the study. Caloric needs were calculated for each participant by estimating their needs during moderate physical activity and then creating a 500 kcal deficit to initiate weight loss (30–500 kcal/kg). They were also instructed to restrict dietary fat (<30% total, <10% saturated, <300 mg dietary cholesterol) based on recommendations by the American Heart Association. All participants were required to attend mandatory weekly nutritional counseling meetings led by a registered dietitian. Nutritional counseling meetings focused on techniques for behavior modification and implementation of a healthy, well-balanced restricted diet, using concepts of variety, balance and modification. Topics included measuring portion sizes, choices to make when eating out, strategies for food shopping, modifications and substitutions of recipes, self monitoring, and recent scientific research.

Diet logs

Participants met with a registered dietitian to learn how to effectively complete a weighed dietary food record. Participants recorded their food and beverage intake for 7 days for the week prior to the weight loss intervention (baseline), and during mid-intervention. Three representative days (two weekdays, and one weekend day) were analyzed. Three days of dietary food recording has been shown to be a reliable assessment method for classifying macronutrient intake (Marr and Heady 1986). The subjects confirmed that these were "representative" days of their usual intake, rather than a day when they may have been ill or traveling for example. A Registered Dietician reviewed logs with participants to qualify completeness. Total food energy and nutrient content was analyzed with Nutritionist Pro Software (version 2.5.1). Participants also kept 7-day food analog scales during the same time points as the dietary logs week prior to the intervention and the first, fourth, and seventh weeks of the intervention. Three representative days were selected by the same registered dietitian and analyzed for total food energy and nutrient content (Nutritionist V, Version 2.1, N-Squared Computing, First Databank Division, The Hearst Corporation, San Bruno, CA, USA).

Exercise training

All participants underwent an 8-week supervised exercise program consisting of cardiovascular exercise (including walking, jogging, cycling, high-lo aerobics, kick-boxing and cycling), four to five times per week in our exercise facilities. Trainers recorded the mode of exercise, duration and heart rates for all exercise sessions. Exercise duration ranged from 30–60 min at an intensity of 60–90% of age-predicted maximal heart rate according to procedures recommended by the American College of Sports Medicine. Each session was supervised by an exercise specialist to maintain the quality of the workout and optimize the exercise prescription. Both the duration and the intensity progressed throughout the 8 weeks in accordance with the American College of Sports Medicine (2006) guidelines for exercise prescription.

Experimental variables

Prior to the intervention, during each week, and at the completion of the intervention, body mass was measured to the nearest 0.1 kg using a calibrated clinical scale. Circumference measurements using of the abdomen, hips, and thighs on the right side of the body were also measured prior to the intervention, mid-intervention, and at the completion of the 8-week intervention using a standard spring-loaded measuring tape. Body composition was obtained using dual-energy X-ray absorptiometry (DEXA) using a total body scanner (Prodigy™, Lunar Corporation, Madison, WI, USA) [as previously described by Volek et al. (2002b)] prior to the intervention, mid-intervention, and at the completion of the 8-week intervention. Percentage body fat was calculated as fat tissue mass divided by the total soft tissue mass plus the estimated bone mineral content. Fat-free mass was calculated as lean soft tissue plus bone mineral content. Regional body composition of the trunk, arm, and leg regions was calculated by the computer program using anatomical landmarks as boundaries. Aerobic fitness gains were validated using a "Yo-Yo Endurance Test" based on 20-m running intervals at progressively increasing speeds. This test has shown to be both valid to evaluate aerobic endurance and sensitive to detect changes in fitness (Krustrup et al. 2003; Leger and Lambert 1982).

Blood collection and biochemical analyses

Blood samples were obtained from a forearm vein after a 12-h overnight fast and a 24-h abstinence from alcohol and strenuous activity prior to the intervention, mid-intervention, and at the completion of the 8-week intervention. Blood was collected into a 10-ml vacutainer tube. Whole blood was centrifuged at 1,000×*g* for 20 min at 10°C and the resultant serum was divided into aliquots and immediately stored frozen at −80°C. Insulin was determined in duplicate using an enzyme immunoassay (ALPCO Diagnostics, Salem, NH, USA). Serum leptin was determined in

duplicate using an enzyme-linked immunosorbent assay (ELISA) (Diagnostic Systems Laboratory, Webster, TX, USA). All samples were run in the same assay with an intra-assay variance of 3.2%. Serum adiponectin was determined in duplicate using an enzyme immunoassay (ALPCO Diagnostics, Salem, NH, USA). All samples for each hormone were determined in the same assay to avoid inter-assay variance and were thawed only once for each assay procedure. Assay intra-assay variance was ≤5%.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Statistical analyses

Dependent variables were analyzed using a two-way analysis of variance or co-variance when appropriate with repeated measures with group (S vs. P) and time (0, 4, 8 weeks) as main effects. All data sets were analyzed for statistical assumptions for linear statistics and if not met were appropriately transformed and reanalyzed again prior to statistical treatment. All data sets satisfied statistical requirements for the linear approaches used. When a significant *F*-value was achieved, a Fisher's LSD test or *t* test, depending upon the variance, were used to locate the pairwise differences between means. Pearson correlation coefficients were used to determine associations of leptin, using the nQuery Advisor® software (Statistical Solutions, Saugus, MA, USA). Statistical power was determined apriori based on probability equations by Cohen (1988). The statistical power for the *n* size estimation represents the needed number of subjects to defend the 0.05 level of significance fourfold and allow detection of a 5–10% treatment effect. The statistical power for the calculated *n* size ranged from 0.80 to 0.87. This estimated n size is consistant with similar previous study designs (Kraemer et al. 2007; Volek et al. 2002a, b). The test-retest reliability of the tests used in our laboratory showed intra-class Rs ≥ 0.95. All data are presented as means and standard deviations. The level of significance was set at $P \leq 0.05$.

Results

The weight loss regimen was effective at inducing anthropometric and body composition changes in these women. Mean ± SD values for anthropometric and body composition data variables measured at baseline (week 0), midway (week 4), and after the intervention (week 8) for both the S and P are shown in Table 1. Both a main effect for time and an interaction effect were observed for body weight. Body weight significantly decreased ($P < 0.05$) for both the S and the P over the 8 weeks. The S lost significantly more weight as compared to the P ($P < 0.05$ between groups) over the 8 weeks (Table 1). Again, a main effect for time and an interaction effect was observed for percent body fat. Percent body fat significantly ($P < 0.05$) decreased for both the S and the P over the 8 weeks. The S lost significantly more body fat as compared to the P over the 8 weeks ($P < 0.05$ between groups) (Table 1). There was a main effect for time but no interaction effects for BMI which significantly decreased ($P < 0.05$) for both the S and the P over the 8 weeks. However, no significant differences in BMI changes were observed between the S and the P.

Table 1 Anthropometric responses to the weight loss intervention

	Week 0	Week 4	Week 8
Body mass (kg)			
Supplement	87.1 ± 6.2	84.3 ± 6.2[a]	77.9 ± 5.1[a,b,c]
Placebo	86.9 ± 4.7	85.1 ± 4.1[a]	82.7 ± 3.8[a,b]
Body fat (%)			
Supplement	43.4 ± 4.1	39.9 ± 3.3[a]	36.1 ± 3.6[a,b,c]
Placebo	44.3 ± 2.0	41.9 ± 1.7[a]	40.6 ± 1.2[a,b]
BMI			
Supplement	32.6 ± 2.7	31.4 ± 2.4[a]	29.0 ± 2.2[a,b]
Placebo	32.8 ± 2.0	32.0 ± 1.9[a]	31.1 ± 1.6[a,b]
Circumference			
Waist			
Supplement	101.9 ± 4.4	96.5 ± 3.7[a]	92.1 ± 3.9[a,c]
Placebo	102.5 ± 3.6	99.2 ± 4.0[a]	97.4 ± 4.0[a]
Hip			
Supplement	117.3 ± 5.4	112.3 ± 3.5[a]	109.9 ± 3.8[a]
Placebo	118.2 ± 2.6	113.3 ± 2.5[a]	110.8 ± 2.9[a]
Thigh			
Supplement	71.2 ± 7.1	70.2 ± 7.1[a]	68.1 ± 6.7[a]
Placebo	72.3 ± 3.0	71.1 ± 2.9[a]	69.1 ± 2.1[a]

Values are mean ± SD

[a] $P < 0.05$ from corresponding week 0 value

[b] $P < 0.05$ from corresponding week 4 value

[c] $P < 0.05$ from corresponding Placebo group value

Again, there was a main effect for time and an interaction effect observed for waist circumference. Waist circumference significantly decreased ($P < 0.05$) for both the S and the P at 4 weeks and over the 8 weeks (Table 1). Although reductions in waist circumference from baseline were observed in both groups, at week 8 the S showed a significantly ($P < 0.05$) greater reduction in waist circumference than the P. With a main effect for time, both the hip and thigh circumferences significantly decreased ($P < 0.05$) for the S and the P over the eight weeks. No significant differences were observed between groups.

Mean ± SD values for serum adiponectin, insulin, and leptin are shown in Table 2. A main effect for time and

Table 2 Responses of serum adipocytokines to the 8-week weight loss intervention

	Week 0	Week 4	Week 8
Adiponectin (μg/ml)			
Supplement	12.2 ± 2.4	18.2 ± 2.6[a]	26.3 ± 3.0[a,b,c]
Placebo	12.6 ± 2.0	19.3 ± 3.3[a]	21.8 ± 3.1[a,b]
Leptin (ng/ml)			
Supplement	28.3 ± 3.5	22.4 ± 2.4[a]	16.2 ± 2.6[a,b,c]
Placebo	29.4 ± 3.2	23.4 ± 2.1[a]	19.9 ± 1.1[a,b]
Insulin (mU/l)			
Supplement	7.3 ± 0.8	4.7 ± 0.1[a]	5.1 ± 0.2[a]
Placebo	7.7 ± 0.9	4.8 ± 0.4[a]	5.1 ± 0.3[a]

Values are mean ± SD

[a] $P < 0.05$ from corresponding week 0 value

[b] $P < 0.05$ from corresponding week 4 value

[c] $P < 0.05$ from corresponding Placebo group value

interaction effects were observed for both the adiponectin and the leptin concentrations. Fasting serum adiponectin (μg/ml) significantly increased ($P < 0.05$) for both the S and the P over the 8 weeks. At week 8, a significant difference ($P < 0.05$) in serum adiponectin was apparent between groups, with significantly higher concentrations measured in the S. Fasting serum insulin (mU/l) significantly decreased ($P < 0.05$) for both the S and the P over the 8 weeks. There were no differences between groups at any time point. Fasting serum leptin (ng/ml) significantly decreased ($P < 0.05$) for the S and the P over the 8 weeks. At week 8, a significant difference ($P < 0.05$) in serum leptin was apparent between groups, with significantly lower concentrations measured in the S.

Dietary analyses indicated that both groups significantly ($P < 0.05$) decreased intake of total food energy during the intervention. No differences in reported total food energy were observed between the groups. Total caloric intake for the S was 1,989 ± 545 kcal (baseline) to: 1,475 ± 385 kcal (week 4) to: 1,409 ± 388 (week 8) and for the P was 1,862 ± 485 kcal (baseline) to: 1,483 ± 472 kcal (week 4) to: 1,402 ± 399 kcal (week 8). Additionally, the exercise training resulted in a significant increase in the number of stages performed in the Yo-Yo Test over the 8 weeks of training in both groups (S: 2.8 ± 1.0–3.5 ± 1.6; P: 2.9 ± 1.1–3.4 ± 1.4 stages) demonstrating an increase in endurance fitness.

Symptom side effects questionnaires showed very limited side effects for both the P and S. No differences between frequency and type of side effects were observed between the P and S. There were occasional reports of symptoms such as nausea, abdominal pain, headache, ringing in ears and bloating, which may or may not be associated with supplement use. Furthermore, reported side effects were only reported on isolated days and not throughout the duration of the 8 weeks.

Discussion

To our knowledge, the present investigation is the first investigation to examine the additive role of supplementation with a proprietary blend of modified cellulose and cetylated fatty acids in a weight loss program for women. This matched, double-blind, placebo-controlled study demonstrated that supplementation combined with endurance exercise and a reduced-calorie diet produced significantly greater weight loss and fat loss than the diet and exercise intervention alone. A weight loss of 9.2 and 4.2 kg for the S and P, respectively, may be regarded a clinically significant weight loss in 8 weeks.

A previous study (Volek et al. 2002a) utilizing a similar 8-week diet and exercise program in women found similar weight loss to our P of 4.3 kg over 8-weeks. The weight loss observed from both the S and P in the current study can be explained by the aggressive dietary and exercise interventions. Previous combined dietary and exercise weight loss intervenitions have observed mean weight losses of 6.8 kg over 12 weeks in women following a less intensive exercise program of only 3 days per week at 30–50 min per session (Kraemer et al. 1997). In the present study, participants in both groups exercised 4–5 days per week for 30–60 min per session at an intensity of 60–90% of age-predicted maximal heart rate according to procedures recommended by the American College of Sports Medicine. In addition to this rigorous exercise program, participants in both groups were adhering to a hypocaloric diet. The combined exercise and diet regimen followed by these women may be considered more rigorous than other weight loss interventions, thus explaining the large observed weight loss.

Both groups lost weight over the 8 weeks, with significantly more weight being lost in the group receiving the compared to the placebo after 8 weeks. The observed differences in weight loss could be explained by either increased energy expenditure or decreased energy intake in the S. However, both groups followed both identical exercise programs and nutritional interventions. Both groups followed identical nutritional counseling and the reported dietary intakes did not differ between groups. Thus the supplement unlikely provided any appetite suppressing effects leading to a lower energy intake in the group receiving the supplement. Thus, the differences are likely attributed to other influences of the supplement. The differences in observed weight loss may be explained by several other factors; (1) differences in total daily energy expenditure, which was not directly measured by this study; (2)

differences in dietary intake over the 8 weeks, which were not detected by the dietary log sampling; or by (3) the components of the supplement decreasing the energy efficiency of the diet.

Since this supplement predominantly contains a non-fermentable, modified cellulose, it is believed to exhibit a similar profile to dietary fibers in slowing gastric emptying (Karhunen et al. 2008; Reimer and Russell 2008) and possibly delaying glucose absorption (Maki et al. 2008). Consumption of the supplement with meals may have decreased the caloric availability of the food, causing a greater imbalance in the energy balance equation in individuals consuming the supplement. How the supplement affects peptide release within the stomach, pancreas, and lower intestine remains to be answered.

Not only did the S experience greater weight loss, body fat loss was also significantly greater as well. Significant improvements in body composition were observed for both groups over the 8 weeks. Since both groups followed an identical exercise program, the supplement may have influenced energy substrate utilization during rest and/or exercise. BMI also significantly decreased over the 8-week program for both groups, although significant group differences were not observed. Since BMI measures do not incorporate body composition, the null finding of between group differences in BMI can likely be explained by different changes in lean and fat mass between the groups.

It is also possible that the cetylated fatty acids of the supplement can explain the greater observed fat loss in the individuals taking the supplement. The cetylated fatty acid component of the supplement may have had a greater effect on lipolysis at the adipocyte level. Previous data have demonstrated that dietary fatty acids can influence overall lipid metabolism through the plasma lipid profile and body fat deposition (Garaulet et al. 2006). In the present study, it is possible that the cetylated fatty acids played a role in signaling adipocyte responses since there is evidence that fatty acids and their derivatives can function in cell signaling by acting like hormones (Farnier et al. 2003). Specifically, they can regulate gene expression in preadipocytes to affect adipocyte proliferation and differentiation (Duplus et al. 2000). As previous research has demonstrated a relationship between fat cell size and number and fatty acid composition in adipose in overweight/obese humans, the fatty acids in the supplement may play a role in the adipocyte lipolysis (Garaulet et al. 2006).

In addition to weight loss and fat loss, experimental results indicated that leptin and insulin levels were significantly reduced, and serum adiponectin levels were significantly increased after the weight loss regimen. Furthermore, significant group differences were observed between the S and P for leptin and adiponectin at 8 weeks. Baseline concentrations of leptin of these women who were overweight were consistent with other investigations as women generally have higher leptin concentrations than men (Lonnqvist et al. 1997; Shih et al. 2006). The decreased circulating leptin concentrations during the weight loss protocol is a finding in agreement with several other investigations (Giannopoulou et al. 2005; Lazzer et al. 2005; Lofgren et al. 2005; Reinehr et al. 2005; Shih et al. 2006; Thompson et al. 2005; Thong et al. 2000). Since leptin is a regulator of body fat storage and mediator long-term regulation of energy of the body, the decreased concentrations associated with weight loss were expected. Morevover, since leptin is produced and secreted from the adipose cells, the greater reductions in leptin concentrations in the S is likely a result of the greater amounts of fat loss. Additionally, the decreased circulating insulin concentrations during the weight loss protocol is a finding in agreement with previous research (Lofgren et al. 2005). It is likely indicative of improved insulin sensitivity as previous research has shown both an elimination in the prevalence of insulin resistance and the metabolic syndrome in women undergoing a similar weight loss program (Lofgren et al. 2005).

The significant increase in circulating adiponectin is a finding in agreement with Polak et al. (2007) who found significant increases in high, medium, and low-molecular weight quantities of adiponectin by 5.5, 8.5 and 18.1%, respectively ($P < 0.05$ for all the forms) with weight loss in women. Weight loss was associated with increased total plasma adiponectin by 36% (Polak et al. 2007). Since adiponectin is involved in the regulation of glucose and fatty acid metabolism, this increase likely influences whole body insulin sensitivity. The mechanisms by which adiponectin enhances insulin sensitivity remain unclear. However, recent advances in adiponectin biochemistry have revealed that not only does physical training change the adiponectin isoform distribution (O'Leary et al. 2007), adiponectin receptor expression also increases (Bluher et al. 2006). Thus, these advances may help to explain the increased in circulating adiponectin observed from the weight loss and exercise regimen seen in this investigation. Moreover, the increased adiponectin as a result of the weight loss regimen may facilitate skeletal muscle fat oxidation (Civitarese et al. 2006). The significantly higher adiponectin concentrations observed in the S may explain the greater weight and fat loss in this group through increases in mitochondrial mass with associated increases in the fat oxidation enzymes (Civitarese et al. 2006) (although not measured in this investigation).

The significant reduction in circumference measurements elicited in the current study is consistent with other weight loss studies in women (Lofgren et al. 2005; Shih et al. 2006) and may be associated with improved overall health. The accumulation of fat in the intra-abdominal

region is associated with a cluster of metabolic disorders including hyperinsulinemia, insulin resistance, hyperglycemia, and dyslipidemia (Bjorntorp 1991). In fact, abdominal obesity may be a better predictor for disease risks and all-cause mortality than BMI (Bigaard et al. 2005; Pouliot et al. 1994). Epidemiological data indicate that women with larger waist circumferences have significantly higher chances of having metabolic abnormalities (hypertension, diabetes, dyslipidemia, and the metabolic syndrome) compared with women with smaller waist circumferences (Hadaegh et al. 2007; Janssen et al. 2004). Additionally, since waist girth decreases were significantly greater for the S in the present investigation, it is possible that these changes may correspond to health improvements related to central adiposity, although health outcomes were not examined in this investigation.

The pharmacological mechanisms underlying the metabolic effects of the proprietary blend of modified cellulose and cetylated fatty acids have not been explained. It can be hypothesized that the current mixture elicits an effect not only on gastric emptying, but also through a nutrient or substrate signal. These pathways induce a sensory and chemical sequence that must be interpreted within the effector organs (e.g. liver, brain and skeletal muscle) to initiate a re-balancing of energy stores. Peptides, such as leptin, insulin, and adiponectin, which act on the brain and the periphery to control appetite and feeding signals, are speculated to play a role. In the current study, those individuals consuming the proprietary mixture exhibited lower body fat stores and an associated reduction in serum leptin. In addition, these individuals had a reduced body waist circumference in accordance with the action of an altered energy state. This energy state may be reflected by the increased serum adiponectin which is known to regulate numerous pathways associated with glucose homeostasis, cellular metabolism and fatty acid oxidation (Civitarese et al. 2006; Okamoto et al. 2008). The cetylated fatty acids and modified cellulose ingredients in the supplement may influence the neural feedback loop of energy regulation and fatty acid metabolism involving these peptides; however, the precise mechanisms are currently unknown.

In summary, this study showed greater weight loss and fat loss in women receiving the supplement during an 8-week weight loss program accompanied by greater effects on circulating adipocytokine concentrations. This investigation demonstrates the additive role of supplementation with a proprietary blend of modified cellulose and cetylated fatty acids in a weight loss program including diet and exercise for women. Thus, over and above diet and exercise, supplementation with may facilitate the effectiveness of a weight loss program for overweight women by mechanisms that remain unclear.

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References

American College of Sports Medicine (2006) ACSM's guidelines for exercise testing and prescription, 7th edn. Lippincott Williams & Wilkins, Philadelphia

Bell-Anderson KS, Bryson JM (2004) Leptin as a potential treatment for obesity: progress to date. Treat Endocrinol 3(1):11–18. doi:10.2165/00024677-200403010-00002

Bigaard J, Frederiksen K, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI (2005) Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women. Int J Obes Lond 29(7):778–784. doi:10.1038/sj.ijo.0802976

Bjorntorp P (1991) Metabolic implications of body fat distribution. Diabetes Care 14(12):1132–1143. doi:10.2337/diacare.14.12.1132

Bluher M, Bullen JW Jr, Lee JH, Kralisch S, Fasshauer M, Kloting N, Niebauer J, Schon MR, Williams CJ, Mantzoros CS (2006) Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: associations with metabolic parameters and insulin resistance and regulation by physical training. J Clin Endocrinol Metab 91(6):2310–2316. doi:10.1210/jc.2005-2556

Bullo M, Salas-Salvado J, Garcia-Lorda P (2005) Adiponectin expression and adipose tissue lipolytic activity in lean and obese women. Obes Surg 15(3):382–386. doi:10.1381/0960892053576776

Civitarese AE, Ukropcova B, Carling S, Hulver M, DeFronzo RA, Mandarino L, Ravussin E, Smith SR (2006) Role of adiponectin in human skeletal muscle bioenergetics. Cell Metab 4(1):75–87. doi:10.1016/j.cmet.2006.05.002

Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Lawrence Erlbaum, Hillsdale

Duplus E, Glorian M, Forest C (2000) Fatty acid regulation of gene transcription. J Biol Chem 275(40):30749–30752. doi:10.1074/jbc.R000015200

Eikelis N, Esler M (2005) The neurobiology of human obesity. Exp Physiol 90(5):673–682. doi:10.1113/expphysiol.2005.031385

Farnier C, Krief S, Blache M, Diot-Dupuy F, Mory G, Ferre P, Bazin R (2003) Adipocyte functions are modulated by cell size change: potential involvement of an integrin/ERK signalling pathway. Int J Obes Relat Metab Disord 27(10):1178–1186. doi:10.1038/sj.ijo.0802399

Garaulet M, Hernandez-Morante JJ, Lujan J, Tebar FJ, Zamora S (2006) Relationship between fat cell size and number and fatty acid composition in adipose tissue from different fat depots in overweight/obese humans. Int J Obes Lond 30(6):899–905. doi:10.1038/sj.ijo.0803219

Giannopoulou I, Fernhall B, Carhart R, Weinstock RS, Baynard T, Figueroa A, Kanaley JA (2005) Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. Metabolism 54(7):866–875. doi:10.1016/j.metabol.2005.01.033

Hadaegh F, Esmaillzadeh A, Azizi F (2007) Metabolic risks in individuals with normal body mass index and normal waist circumference. Eur J Cardiovasc Prev Rehabil 14(2):200–207. doi:10.1097/01.hjr.0000230096.73579.64

Hara T, Fujiwara H, Nakao H, Mimura T, Yoshikawa T, Fujimoto S (2005) Body composition is related to increase in plasma adiponectin levels rather than training in young obese men. Eur J Appl Physiol 94(5–6):520–526

Horvath TL, Diano S, Sotonyi P, Heiman M, Tschop M (2001) Minireview: ghrelin and the regulation of energy balance—a hypothalamic perspective. Endocrinology 142(10):4163–4169. doi:10.1210/en.142.10.4163

Janssen I, Katzmarzyk PT, Ross R (2004) Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 79(3):379–384

Kalra SP, Kalra PS (2003) Neuropeptide Y: a physiological orexigen modulated by the feedback action of ghrelin and leptin. Endocrine 22(1):49–56. doi:10.1385/ENDO:22:1:49

Karhunen LJ, Juvonen KR, Huotari A, Purhonen AK, Herzig KH (2008) Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans. Regul Pept 149(1–3):70–78

Klok MD, Jakobsdottir S, Drent ML (2007) The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 8(1):21–34. doi:10.1111/j.1467-789X.2006.00270.x

Koerner A, Kratzsch J, Kiess W (2005) Adipocytokines: leptin—the classical, resistin—the controversical, adiponectin—the promising, and more to come. Best Pract Res Clin Endocrinol Metab 19(4):525–546. doi:10.1016/j.beem.2005.07.008

Kraemer WJ, Volek JS, Clark KL, Gordon SE, Incledon T, Puhl SM, Triplett-McBride NT, McBride JM, Putukian M, Sebastianelli WJ (1997) Physiological adaptations to a weight-loss dietary regimen and exercise programs in women. J Appl Physiol 83(1):270–279

Kraemer WJ, Vingren JL, Silvestre R, Spiering BA, Hatfield DL, Ho JY, Fragala MS, Maresh CM, Volek JS (2007) Effect of adding exercise to a diet containing glucomannan. Metabolism 56(8):1149–1158. doi:10.1016/j.metabol.2007.04.010

Krustrup P, Mohr M, Amstrup T, Rysgaard T, Johansen J, Steensberg A, Pedersen PK, Bangsbo J (2003) The yo-yo intermittent recovery test: physiological response, reliability, and validity. Med Sci Sports Exerc 35(4):697–705. doi:10.1249/01.MSS.0000058441.94520.32

Lazzer S, Vermorel M, Montaurier C, Meyer M, Boirie Y (2005) Changes in adipocyte hormones and lipid oxidation associated with weight loss and regain in severely obese adolescents. Int J Obes Lond 29(10):1184–1191. doi:10.1038/sj.ijo.0802977

Leger LA, Lambert J (1982) A maximal multistage 20-m shuttle run test to predict VO_2 max. Eur J Appl Physiol Occup Physiol 49(1):1–12. doi:10.1007/BF00428958

Lofgren IE, Herron KL, West KL, Zern TL, Brownbill RA, Ilich JZ, Koo SI, Fernandez ML (2005) Weight loss favorably modifies anthropometrics and reverses the metabolic syndrome in premenopausal women. J Am Coll Nutr 24(6):486–493

Lonnqvist F, Nordfors L, Jansson M, Thorne A, Schalling M, Arner P (1997) Leptin secretion from adipose tissue in women relationship to plasma levels and gene expression. J Clin Invest 99(10):2398–2404. doi:10.1172/JCI119422

Maki KC, Carson ML, Miller MP, Turowski M, Bell M, Wilder DM, Rains TM, Reeves MS (2008) Hydroxypropylmethylcellulose and methylcellulose consumption reduce postprandial insulinemia in overweight and obese men and women. J Nutr 138(2):292–296

Marr JW, Heady JA (1986) Within- and between-person variation in dietary surveys: number of days needed to classify individuals. Hum Nutr Appl Nutr 40(5):347–364

Meier U, Gressner AM (2004) Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clin Chem 50(9):1511–1525. doi:10.1373/clinchem.2004.032482

O'Leary VB, Jorett AE, Marchetti CM, Gonzalez F, Phillips SA, Ciaraldi TP, Kirwan JP (2007) Enhanced adiponectin multimer ratio and skeletal muscle adiponectin receptor expression following exercise training and diet in older insulin-resistant adults. Am J Physiol Endocrinol Metab 293(1):E421–E427. doi:10.1152/ajpendo.00123.2007

Okamoto M, Ohara-Imaizumi M, Kubota N, Hashimoto S, Eto K, Kanno T, Kubota T, Wakui M, Nagai R, Noda M, Nagamatsu S, Kadowaki T (2008) Adiponectin induces insulin secretion in vitro and in vivo at a low glucose concentration. Diabetologia 51(5):827–835. doi:10.1007/s00125-008-0944-9

Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F (1995) Effects of the obese gene product on body weight regulation in ob/ob mice. Science 269(5223):540–543. doi:10.1126/science.7624776

Polak J, Kovacova Z, Jacek M, Klimcakova E, Kovacikova M, Vitkova M, Kuda O, Sebela M, Samcova E, Stich V (2007) An increase in plasma adiponectin multimeric complexes follows hypocaloric diet-induced weight loss in obese and overweight pre-menopausal women. Clin Sci (Lond) 112(11):557–565. doi:10.1042/CS20060296

Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ (1994) Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 73(7):460–468. doi:10.1016/0002-9149(94)90676-9

Reimer RA, Russell JC (2008) Glucose tolerance, lipids, and GLP-1 secretion in JCR:LA-cp rats fed a high protein fiber diet. Obesity (Silver Spring) 16(1):40–46. doi:10.1038/oby.2007.16

Reinehr T, Kratzsch J, Kiess W, Andler W (2005) Circulating soluble leptin receptor, leptin, and insulin resistance before and after weight loss in obese children. Int J Obes Lond 29(10):1230–1235. doi:10.1038/sj.ijo.0803027

Shapses SA, Riedt CS (2006) Bone, body weight, and weight reduction: what are the concerns? J Nutr 136(6):1453–1456

Shih LY, Liou TH, Chao JC, Kau HN, Wu YJ, Shieh MJ, Yeh CY, Han BC (2006) Leptin, superoxide dismutase, and weight loss: initial leptin predicts weight loss. Obesity (Silver Spring) 14(12):2184–2192. doi:10.1038/oby.2006.256

Thompson WG, Rostad Holdman N, Janzow DJ, Slezak JM, Morris KL, Zemel MB (2005) Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. Obes Res 13(8):1344–1353. doi:10.1038/oby.2005.163

Thong FS, Hudson R, Ross R, Janssen I, Graham TE (2000) Plasma leptin in moderately obese men: independent effects of weight loss and aerobic exercise. Am J Physiol Endocrinol Metab 279(2):E307–E313

Ueno N, Dube MG, Inui A, Kalra PS, Kalra SP (2004) Leptin modulates orexigenic effects of ghrelin and attenuates adiponectin and insulin levels and selectively the dark-phase feeding as revealed by central leptin gene therapy. Endocrinology 145(9):4176–4184. doi:10.1210/en.2004-0262

Volek JS, Gomez AL, Love DM, Weyers AM, Hesslink R Jr, Wise JA, Kraemer WJ (2002a) Effects of an 8-week weight-loss program on cardiovascular disease risk factors and regional body composition. Eur J Clin Nutr 56(7):585–592. doi:10.1038/sj.ejcn.1601362

Volek JS, Sharman MJ, Love DM, Avery NG, Gomez AL, Scheett TP, Kraemer WJ (2002b) Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism 51(7):864–870. doi:10.1053/meta.2002.32037

Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C (2001) Benefits of lifestyle modification in the pharmacologic treatment of obesity: a randomized trial. Arch Intern Med 161(2):218–227. doi:10.1001/archinte.161.2.218

Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D (1987) Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med 147(10):1749–1753

Wolfe BE, Jimerson DC, Orlova C, Mantzoros CS (2004) Effect of dieting on plasma leptin, soluble leptin receptor, adiponectin and resistin levels in healthy volunteers. Clin Endocrinol (Oxf) 61(3):332–338. doi:10.1111/j.1365-2265.2004.02101.x