Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome[1–3]

Lisa J Moran, Manny Noakes, Peter M Clifton, Gary A Wittert, Gemma Williams, and Robert J Norman

ABSTRACT

Background: Polycystic ovary syndrome (PCOS), a common condition in women, improves with weight loss. Meal replacements in short-term weight loss and strategies for weight maintenance have not been investigated in PCOS.

Objective: We compared in overweight women with PCOS the effects of meal replacements in short-term weight-loss and longer-term carbohydrate- or fat-restriction strategies on weight maintenance and improvements in reproductive and metabolic variables.

Design: Overweight women with PCOS ($n = 43$; $\bar{x} \pm$ SD age: 32.1 ± 5.2 y; weight: 96.1 ± 18.4 kg) followed an 8-wk weight-loss regimen (2 meal replacements/d, 4904.4 ± 127 kJ; phase 1) and then a 6-mo weight-maintenance carbohydrate- (<120 g/d) or fat- (<50 g/d) restriction regimen (phase 2).

Results: Thirty-four women completed phase 1, and 23 women completed phase 2; the proportion of dropouts was similar in the 2 groups. During phase 1, significant ($P < 0.05$) reductions in weight (5.6 ± 2.4 kg), waist circumference (6.1 ± 2.5 cm), body fat (4.1 ± 2.2 kg), insulin (2.8 ± 1.1 mU/L), total testosterone (0.3 ± 0.7 nmol/L), and free androgen index (3.1 ± 4.6) occurred; these changes were sustained during phase 2. No significant differences between diet groups were seen for any variables. At 6 mo, both approaches resulted in a net weight loss of 4.7 ± 4.6 kg. Improvements in menstrual cyclicity occurred for 16 (57.1%) of 28 subjects.

Conclusions: Meal replacements are an effective strategy for the short-term management of PCOS. Advice on moderate fat or carbohydrate restriction was equally effective in maintaining weight reduction and improving reproductive and metabolic variables. *Am J Clin Nutr* 2006;84:77–87.

KEY WORDS Polycystic ovary syndrome, weight loss, weight maintenance, glycemic index, meal replacement

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disorder in women of reproductive age; the estimated prevalence is 4%–8% (1). It is associated with menstrual dysfunction, hyperandrogenism, an increased risk of impaired glucose tolerance (IGT) or type 2 diabetes mellitus, and an adverse cardiovascular disease (CVD) risk profile, including hyperlipidemia, hypertension, inflammation, and endothelial dysfunction (2, 3). Insulin resistance (IR) is implicated in the etiology of PCOS through insulin's stimulation of ovarian androgen production (4) and reduction of hepatic synthesis of sex hormone–binding globulin (SHBG; 5). Obesity, particularly central and visceral obesity, is present in 10%–65% of Western women with PCOS (6), and it worsens the associated IR and metabolic and endocrine features. For women with PCOS who are overweight and have IR, weight loss is thus the preferred initial treatment strategy; it reduces abdominal fat, IR, and hyperlipidemia and restores normal menstrual function (7, 8). Long-term lifestyle interventions also improve fertility and reproductive outcomes of assisted reproductive technology in patients with PCOS (9) and reduce the risk of progression from IGT to diabetes (10) in the general population.

In general, ≤15% of subjects undergoing weight-loss interventions maintain their reduced weight when followed for up to 14 y (11). Because of potential abnormalities in energy expenditure (12) and appetite regulation and hormone homeostasis (13, 14), weight loss and weight-loss maintenance may be even more difficult to achieve for women with PCOS. Effective dietary approaches to achieving and maintaining weight loss and metabolic and reproductive benefits in women with PCOS in a free-living environment have been poorly studied. A simple strategy for reducing energy intake is to focus on the restriction of one macronutrient; severe carbohydrate restriction (20-30 g/d) has resulted in greater weight loss than has a 6-mo structured reduction in fat intake (moderate calorie restriction and 25%–30% of energy from fat) in the general population (15–18). Long-term weight-maintenance studies in persons with PCOS tend to be in a highly structured environment and to involve a variety of health-care professionals (9, 19), and the efficacy of a simple dietary strategy has not been assessed in this population. The concept of reducing dietary glycemic index (GI) or glycemic load (GL) in the treatment of PCOS has also received considerable interest. In the general population, this approach can optimally improve the metabolic profile (20). However, data are conflicting on the effect of modulation of GI or GL on insulin sensitivity (21, 22), acute satiety (23, 24) and long-term weight loss and

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[2] Supported by a National Health and Medical Research Council Program grant (to RJN), The University of Adelaide Faculty of Health Sciences Small Research Grants Scheme, and Colin Matthews Research Grants for Clinically Based Research. Unilever contributed study supplies.

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Received December 22, 2005.

Accepted for publication March 10, 2006.

weight-loss maintenance (25, 26); no data are available that assess the effect of dietary GI or GL on weight loss and reproductive and metabolic outcomes in persons with PCOS.

The objective of this study, therefore, was to examine the effect of acute energy restriction on the reproductive and metabolic characteristics of PCOS. We also compared 2 long-term dietary strategies (moderate carbohydrate restriction with low GI or moderate fat restriction with low GI) with respect to the effect on weight loss, weight-loss maintenance, body composition, energy expenditure, and hormonal, metabolic, and reproductive characteristics in overweight women with PCOS.

SUBJECTS AND METHODS

Subjects

Overweight women (European whites) with PCOS ($n = 43$) were recruited through public advertisement. Consort criteria are documented in **Figure 1**. Inclusion criteria were a diagnosis of PCOS, according to the Rotterdam Consensus Workshop Group, by 2 of the following 3 criteria: menstrual irregularity (cycle length < 26 d or > 31 d or variation between consecutive cycles of > 3 d); clinical (hirsutism assessed by a Ferriman-Gallwey score > 8) or biochemical [free androgen index (FAI) > 5.4 or testosterone > 1.4 nmol/L] hyperandrogenism; or positive ultrasound presentation of polycystic ovaries by transvaginal scan (27). Exclusion criteria were pregnancy, breastfeeding, body mass index (BMI; in kg/m^2) < 25, type 2 diabetes mellitus, and related endocrinopathic disorders [identified by assessment of thyroid-stimulating hormone (TSH), prolactin, and 17α-hydroxyprogesterone]. The use of endocrine hormonal treatment or insulin-sensitizing agents was not permitted during either phase of the study, and the use of oral contraceptives was not permitted during phase 1 of the study. Subjects were required to cease taking oral contraceptives 4 wk and hormonal treatment or insulin-sensitizing agents 2 wk before commencement of the short-term study phase. From weeks 8–32 (phase 2), subjects were allowed to take oral contraceptives with containing <35 μg ethinyl estrogen.

All subjects gave written informed consent. The study was approved by the human ethics committees of the Commonwealth Scientific and Industrial Research Organisation Division of Health Sciences and Nutrition, The Royal Adelaide Hospital, and the Women's and Children's Hospital of South Australia.

Study design

The study was conducted on an outpatient basis over a period 32 wk and consisted of 8 wk of energy restriction during which all subjects followed the same dietary protocol (phase 1) and 24 wk of weight-loss maintenance during which subjects followed either a carbohydrate-counting (CC) or fat-counting (FC) protocol (phase 2). Subjects were stratified to ensure equal distribution for age, BMI, smoking status, and use of oral contraceptives, and then the 2 groups were randomized to the CC or FC protocol before study commencement by an independent observer using the computer program CLINSTAT (St George's Hospital Medical School, London, United Kingdom).

In phases 1 and 2, subjects attended the clinic fortnightly and monthly, respectively. At these visits, they were weighed while wearing light clothes but no shoes (Mettler scales, model AMZ14; A&D Mercury, Kinomoto, Japan), BMI was calculated, and waist circumference was measured to the nearest 0.5 cm directly on the skin with a soft tape at the level of midway between the lateral lower rib margin and the iliac crest. At weeks 0, 2, 4, 6, 8, 20, and 32, resting blood pressure was measured by automated oscillometry (845XT/XT-IEC; Dinamapt, Tampa, FL) while subjects were in a seated position, and overnight fasting venous blood samples were taken for assessment of plasma glucose, insulin, ghrelin, and serum lipid concentrations of C-reactive protein (CRP), testosterone, and SHBG.

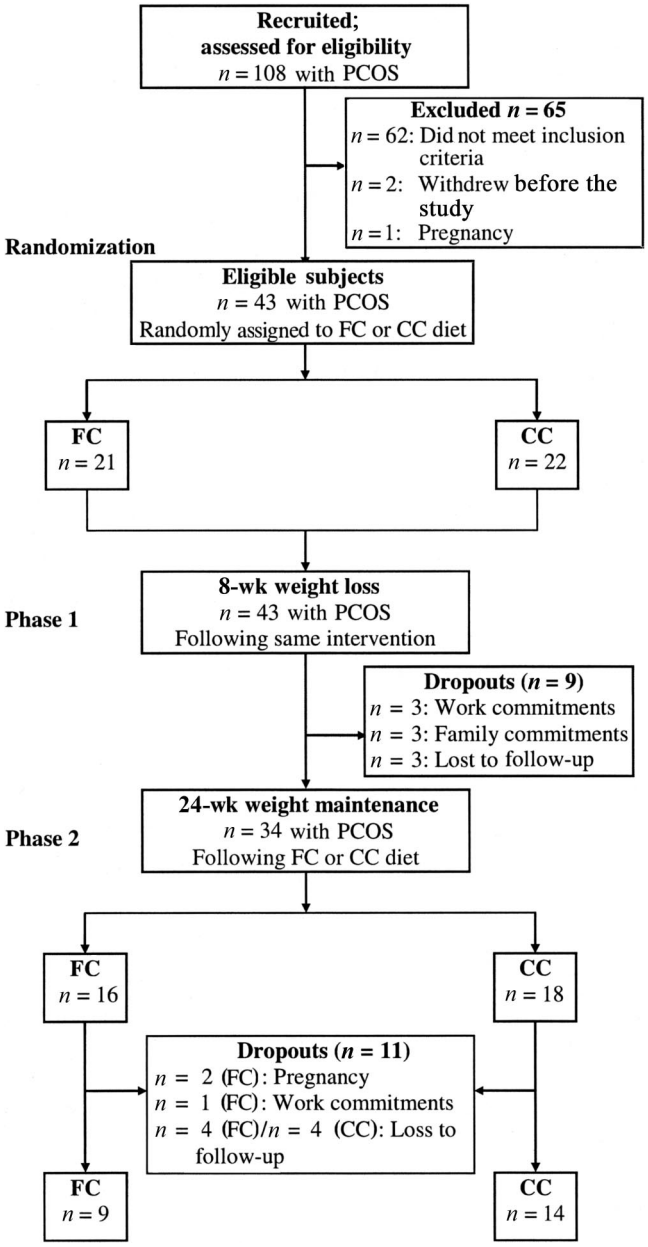

FIGURE 1. Flow diagram of subjects' enrollment, random assignment, and completion of the 32-wk protocol incorporating phase 1 (8 wk during which all subjects followed the same intervention of twice-daily meal replacements) and phase 2 [24 wk during which subjects followed either a fat-counting (FC) or carbohydrate-counting (CC) diet]. PCOS, polycystic ovary syndrome.

At weeks 0, 8, and 32, resting energy expenditure (REE) was measured in a subset of subjects ($n = 13$) as previously described (28). Total fat mass (TFM) and total fat-free mass (TFFM) were measured by using bioelectrical impedance analysis (IMP5; Impedimed Pty Ltd, Brisbane, Australia). A 2-h oral-glucose-tolerance test (OGTT; 75-g load) was conducted with assessment of venous glucose and insulin at 0 and 120 min. Exercise was assessed by using a 24-h physical activity record for all 7 d/wk in weeks 0, 8, 20, and 32 (29). During week 0, dietary restraint, disinhibition, and hunger were measured by using the Three-Factor Eating Questionnaire (30). Health-related quality of life was assessed by using the validated PCOS quality-of-life questionnaire at weeks 0, 8, and 32 (31).

Subjects began to document their menstrual cycles 6 mo before the beginning of the study and continued to do so throughout the study. During phase 1, the first morning urine samples were collected twice weekly and assessed for total urinary pregnanediol-3-glucuronide to ascertain ovulation status (7). Results were compared with the menses calendars to ascertain ovulation status. Improvements in menstrual cyclicity were defined as a change from nonovulatory to ovulatory cycles or from irregular to regular cycles or as an improvement in consecutive intercycle variation.

Dietary treatment

The aim of the overall dietary protocol was to achieve and maintain a 10% reduction in weight. Subjects were provided with a pedometer and were encouraged to take 8000 steps/d for the entire study duration. In phase 1 (weeks 0–8), subjects followed an energy-restricted diet in which 2 meals/d were replaced with commercially available meal replacements (Slimfast; Unilever Australasia, Epping, Australia) that were provided fortnightly. The dietary intervention for this term meal-replacement protocol was described in detail elsewhere (32). Alcohol consumption was not permitted. For phase 2 (weeks 9–32), subjects followed either a CC (<120 g carbohydrate/d) or an FC (<50 g fat/d) regimen. Subjects were provided with a CC or FC resource and asked to document their daily intake of carbohydrate or fat from selected foods. All subjects also received advice on reducing the GI and the saturated fat content of their diet. A semi–ad libitum approach was followed. Subjects were allowed to consume their specified fat (50 g) or carbohydrate (120 g) intake. In addition, subjects were advised to eat until full from unlimited quantities of additional foods whose fat or carbohydrate they were not required to count. Subjects were allowed to consume moderate amounts of alcohol (≤2 standard drinks/d and ≥2 alcohol-free days/wk).

Subjects initially met with a qualified dietitian for training in quantifying and recording their daily food intake and to assess and modify the dietary regimen based on compliance and weight loss. Subjects then met with the dietitian fortnightly during phase 1 and monthly during phase 2. Nutrient intakes were calculated by using DIET 1/NUTRIENT CALCULATION software (version 4.2; Xyris Software, Highgate Hill, Australia) based on data from Australian food-composition tables. The database had been extensively modified by our group to include new foods and recipes. In phase 1, nutritional intake was assessed from fortnightly 3-d consecutive dietary food records (1 weekday and 2 weekend days) and daily dietary checklists. For prestudy dietary intake and during phase 2, nutritional intake and GI and GL were assessed from 3-mo food-frequency questionnaires (Anti-Cancer Foundation, Carlton, Australia) and a monthly 24-h dietary recall. Dietary compliance was ascertained by subject adherence to the meal-replacement regimen in phase 1 and to daily fat and carbohydrate counting in phase 2.

Biochemical measurements

Blood for serum was collected in tubes with no additives and allowed to clot at room temperature for 30 min. Blood for plasma was collected in tubes containing NAF/EDTA for glucose or K/EDTA and 500 KIU blood aprotinin/mL (Roche; Indianapolis, IN) for ghrelin measurement and stored on ice. Serum and plasma were isolated by centrifugation for 10 min at 3000 × *g* at 5 °C (Beckman GS-6R; Beckman, Fullerton, CA), and aliquots were stored at −80 °C. Serum SHBG, total testosterone (bound and unbound), TSH, prolactin, 17α-hydroxyprogesterone (8), LDL cholesterol, and ghrelin (13) were measured as previously described. Serum total and HDL cholesterol, triacylglycerols, and CRP and plasma glucose were measured on a Hitachi Cobas-Bio centrifugal analyzer (Roche) using standard enzymatic kits (Roche). Insulin was measured in duplicate by using a commercial enzyme immunoassay kit (Mercodia, Uppsala, Sweden). The homeostasis model assessment (HOMA) was used as a surrogate measure of insulin sensitivity and was calculated as [fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5] (33). The FAI (testosterone/SHBG × 100) and equilibrium-binding equations for measurement of free testosterone (34) were used as surrogate estimates of free testosterone. Study subjects were categorized as having diabetes if their fasting glucose was ≥ 7.0 mmol/L or if 2-h OGTT glucose was ≥ 11.0 mmol/L or both, as having impaired glucose tolerance (IGT) if the 2-h OGGT was 7.8–11.1 mmol/L, and as having impaired fasting glucose if the fasting glucose was 5.5−6.9 mmol/L (35). Study subjects were classified as having the metabolic syndrome if they had ≥3 of the following abnormalities: waist circumference > 88 cm, fasting triacylglycerols ≥ 1.7 mmol/L, fasting HDL cholesterol ≤ 1.3 mmol/L, blood pressure ≥ 130/≥85 mm Hg, and fasting glucose ≥ 6.1 mmol/L (36). Biochemical assays were performed in a single assay at the completion of the study, and all samples for individuals were analyzed in the same assay.

Statistical analysis

When data relating to the characteristics of the subjects were parametric, data were presented as means ± SEMs except where indicated. Nonparametric data (Three-Factor Eating Questionnaire and PCOS quality-of-life questionnaire) were presented as medians ± ranges. Normality was assessed by using the Kolmogorov-Smirnov test. When data were nonnormally distributed, data were log transformed for analysis. For phase 1, results are presented for 34 subjects except in the case of ovulation ($n = 33$), menses ($n = 28$), TFM and TFFM ($n = 33$), 2-h glucose ($n = 33$), REE and respiratory quotient ($n = 13$), CRP ($n = 29$), and ghrelin ($n = 26$), for which the data were incomplete. For phase 2, results are presented for 23 subjects except in in the case of REE and respiratory quotient ($n = 11$), CRP ($n = 18$), and ghrelin ($n = 19$). Five subjects renewed oral contraceptive or hormone treatment in phase 2, and their data were excluded from reproductive hormone analysis. Chi-square tests were used to assess changes in proportions between diet groups. Two-tailed statistical analysis was performed by using SPSS for

WINDOWS software (version 10.0; SPSS Inc, Chicago, IL) with statistical significance set at an α level of $P < 0.05$. Baseline data were assessed by using a one-factor analysis of variance for parametric data and a Kruskal-Wallis test for nonparametric data. Comparisons between time points were assessed by using a 2-factor analysis of variance with time as the within-subject factor and diet as the between-subject factor. In specific analyses, baseline percentage total fat, percentage monounsaturated fat, and percentage carbohydrate intake were included as covariates. In the event of an interaction, post hoc pairwise comparisons (Bonferroni) were performed. Relations between variables were examined by using bivariate and partial correlations and analysis of covariance. Weight, insulin, HOMA, testosterone, and free testosterone data were assessed by using a completers analysis (including data from subjects who competed each phase) and a baseline intention-to-treat analysis (with the baseline values from the dropouts carried forward) or a carried-forward intention-to-treat analysis (with the last clinical value from dropouts carried forward). Because there was a time × insulin interaction but no time × treatment × insulin or treatment × insulin interaction, subjects with higher insulin concentrations at baseline (above the median of 10.45 mU/L) were assessed separately from those with lower fasting insulin concentrations at baseline (below the median of 10.45 mU/L), and insulin status was used as the between-subject factor. This study had 40% power to detect a difference between diet groups of 1.6 kg for net weight loss to statistical significance of $P < 0.05$. To confirm the observed differences between the diet groups of 1.6 kg net weight loss to statistical significance of $P < 0.05$ and 80% power, a total of 37 subjects in each diet group would be needed. This study was able to detect a difference of 2.6 kg between the diet groups at 80% power and statistical significance of $P < 0.05$.

RESULTS

Subjects

Thirty-four subjects completed phase 1, and 23 subjects completed phase 2. Study dropouts are documented in Figure 1. There were no differences in the characteristics between subjects who completed either phase 1 (**Table 1**) or phase 2 in each of the dietary groups at baseline. Activity levels were comparable between diet groups at week 0 and did not change throughout the study. There were no differences between the diet groups in baseline dietary restraint (11.5 ± 16), disinhibition (11 ± 13), and hunger (6 ± 12) scores. The dropouts did not differ significantly between the CC and FC groups. In phase 1, a 20.9% dropout rate was documented. Two subjects (both in the FC group) conceived during phase 2 and discontinued the intervention. In phase 2, a 27% dropout rate was documented (excluding the subjects who conceived).

In phase 1, significant differences in total fat intake (40.0 ± 1.7% and 35.6 ± 0.9%; $P = 0.02$), saturated fat intake (17.7 ± 1.1 and 13.4 ± 0.5%; $P < 0.001$), and weight loss at week 2 (1.5 ± 0.4 and 2.4 ± 0.2 kg; $P = 0.042$) existed between subjects who dropped out and those who completed the study, respectively. In phase 2, significant differences in fasting insulin and HOMA at the beginning of phase 2 (13.8 ± 2.0 and 8.7 ± 0.3 mU/L and 3.2 ± 0.5 and 2.0 ± 0.2 units, respectively; $P = 0.008$) existed between subjects who dropped out and those who completed the study, respectively. Subjects who dropped out of all phases of the study tended to have baseline hunger scores higher than those of subjects who completed the study (7.4 ± 0.7 and 5.7 ± 0.6, respectively; $P = 0.077$).

TABLE 1
Baseline subject characteristics[1]

	Phase 1 completer (weeks 0 to 8)	
	FC ($n = 16$)	CC ($n = 18$)
Age (y)	33.2 ± 4.8	32.1 ± 5.5
Weight (kg)	95.8 ± 21.9	96.1 ± 17.7
BMI (kg/m^2)	34.9 ± 7.0	34.9 ± 6.6
Glucose (mmol/L)	5.2 ± 0.4	5.2 ± 0.4
Insulin (mU/L)	10.8 ± 5.2	14.7 ± 8.5
HOMA	2.5 ± 1.3	3.5 ± 2.2
Testosterone (nmol/L)	2.9 ± 1.2	2.5 ± 0.7
Free testosterone (pmol/L)	66.3 ± 39.3	54.8 ± 24.0
SHBG (nmol/L)	28.1 ± 18.5	28.1 ± 13.6
Free androgen index	14.6 ± 12.2	11.6 ± 7.1

[1] All values are $\bar{x}$ ± SD. FC, fat counting; CC, carbohydrate counting; HOMA: homeostasis model assessment; SHBG: sex hormone–binding globulin. Measurements were made at the week 0 visit and were assessed by using one-way ANOVA with diet as the fixed factor. There were no baseline differences between the subjects in the 2 groups.

Physical activity, dietary intake, and compliance

All diets in phase 1 and phase 2 were well tolerated, and no adverse events occurred. The energy, macronutrient content, and micronutrient content of the diet in phase 1 are shown in **Table 2**, and the diet achieved the recommended micronutrient dietary allowance (37).

The energy and macronutrient contents of diets before study commencement and for phase 2 are shown in **Table 3**. From baseline to week 20 and from baseline to week 32, total energy, carbohydrate, protein, fat, GI, and GL decreased similarly for the FC and CC groups. There were no differences in energy intake, GI, or GL between the FC and CC groups at week 20 or 32, and energy intake remained constant from weeks 20–32. From baseline to week 20, the percentage of polyunsaturated fatty acid and cholesterol decreased similarly for the FC and CC groups.

TABLE 2
Reported macronutrient and micronutrient intakes during 8 wk of energy restriction with one dietary pattern (meal replacements)

Phase 1: week 0–8	Dietary intake	Recommended dietary allowance for women aged 19–54 y
Energy (kJ)	4904.4 ± 127.8[1]	—
Fat (% of energy)	21.0 ± 0.8	—
Carbohydrate (% of energy)	52.9 ± 1.0	—
Protein (% of energy)	24.2 ± 0.4	—
Vitamin C (mg)	83.3 ± 4.2	30
Thiamine (mg)	1.36 ± 0.04	0.8
Riboflavin (mg)	2.05 ± 0.07	1.2
Niacin (mg)	18.8 ± 0.57	13
Calcium (mg)	996.1 ± 29.1	800
Iron (mg)	14.0 ± 0.3	12–16
Zinc (mg)	13.9 ± 0.3	12

[1] $\bar{x}$ ± SEM (all such values).

TABLE 3
Dietary intake at baseline and during 24 wk of a fat-counting (FC) or carbohydrate-counting (CC) dietary protocol (weeks 8–32)[1]

	Week 0	Week 20	Week 32	Time effect[2]	Time-by-diet interaction[2]
Energy (kJ/d)					
FC	8143 ± 868[3]	5035 ± 412[4]	6191 ± 636[4]	<0.001	0.764
CC	8082 ± 414	5287 ± 637[4]	5865 ± 511[4]		
Carbohydrate (g/d)					
FC	188 ± 22.2	135 ± 13.4[4]	156 ± 15.7[4]	<0.001	0.093
CC	209 ± 10.6	123 ± 13.6[4]	135 ± 10.7[4]		
Carbohydrate (% of energy)					
FC	39 ± 1.3[5]	46 ± 2.5[4–6]	43 ± 2.4[4,6]	0.927	<0.001
CC	44 ± 1.6	40 ± 1.4	40 ± 1.4		
Protein (g/d)					
FC	100 ± 10.8	68 ± 5.5[4]	81 ± 6.9[4]	0.003	0.803
CC	94 ± 7.2	78 ± 12.0[4]	79 ± 8.4[4]		
Protein (% of energy)					
FC	20 ± 1.0	22 ± 0.9	21 ± 0.7	<0.001	0.056
CC	19 ± 0.9	23 ± 1.1[4,6]	21 ± 1.0		
Fat (g/d)					
FC	84 ± 10.4	37 ± 3.6[4]	54 ± 8.9[4]	<0.001	0.340
CC	75 ± 5.8	48 ± 6.8[4]	56 ± 6.4[4]		
Fat (% of energy)					
FC	38 ± 1.0[5]	27 ± 2.1[4–6]	31 ± 2.2[4,6]	0.001	0.002
CC	34 ± 1.2	33 ± 1.0	35 ± 1.2		
SFA (% of energy)					
FC	14.2 ± 0.9	9.5 ± 0.6[4–6]	11.6 ± 0.9[6]	0.008	0.002
CC	12.9 ± 0.5	12.7 ± 0.5	13.6 ± 0.5		
MUFA (% of energy)					
FC	13.6 ± 0.4[5]	9.5 ± 0.7[4–6]	11.2 ± 1.0[6]	0.002	0.001
CC	12.1 ± 0.4	12.1 ± 0.3	12.5 ± 0.5		
PUFA (% of energy)					
FC	6.8 ± 0.4	5.3 ± 1.0[4]	5.3 ± 0.7	0.014	0.234
CC	5.9 ± 0.6	4.8 ± 0.3[4]	5.2 ± 0.5		
Cholesterol (mg/d)					
FC	273.7 ± 31.6	157.2 ± 12.7[4]	202.9 ± 24.6	0.001	0.117
CC	249.0 ± 28.6	213.6 ± 37.2[4]	231.6 ± 20.9		
Fiber (g/d)					
FC	20.9 ± 2.4	16.9 ± 2.1	19.1 ± 2.5	<0.001	0.022
CC	23.2 ± 1.5	14.0 ± 1.4[4,6]	16.2 ± 1.2[4,6]		
GI					
FC	53.3 ± 1.3	49.5 ± 0.9[4]	49.6 ± 1.1[4]	<0.001	0.215
CC	52.4 ± 0.8	46.5 ± 1.1[4]	49.2 ± 1.0[4]		
GL					
FC	100.7 ± 13.6	66.6 ± 6.7[4]	77.5 ± 8.9[4]	<0.001	0.180
CC	109.5 ± 6.5	57.7 ± 7.1[4]	66.4 ± 6.4[4]		

[1] SFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; GI, glycemic index; GL, glycemic load. Data were assessed by using one-factor ANOVA with diet as the fixed factor and repeated-measures ANOVA with time as the within-subject factor and diet as the between-subject factor. For all data, $n = 9$ and 14 except for week 20, when $n = 8$ and 13 for FC and CC, respectively.

[2] Weeks 0–20 and weeks 0–32.

[3] $\bar{x} \pm$ SEM (all such values).

[4] Effect of time relative to week 0 (weeks 0–20 or weeks 0–32), $P < 0.05$.

[5] Significant difference between FC and CC groups, $P < 0.05$.

[6] Effect of time-by-diet interaction for weeks 0–20 or weeks 0–32, $P < 0.05$.

The time-by-diet interactions from weeks 0–20 and from weeks 0–32 were significant for the percentages of carbohydrate ($P < 0.001$), fat ($P = 0.002$), saturated fatty acid (SFA; $P = 0.002$), and monounsaturated fatty acid ($P = 0.001$) and fiber ($P = 0.022$), the time × diet interaction for percentage protein trended toward significance ($P = 0.056$). From weeks 0–20 and from weeks 0–32, fiber ($P < 0.001$) and the percentage of carbohydrate ($P = 0.014$) decreased in the CC group but stayed the same in the FC group and the percentage of total fat ($P = 0.005$) decreased in the FC group and stayed the same in the CC group. From weeks 0–20, there was a time × diet effect such that the percentages of saturated ($P = 0.017$) and monounsaturated ($P = 0.011$) fatty acids decreased in the FC group and stayed the same in the CC group, and the percentage of protein increased in the CC group ($P < 0.001$) and stayed the same in the FC group.

TABLE 4
Weight, body composition, blood pressure, fasting resting energy expenditure (REE), respiratory quotient (RQ), lipids, glucose, ghrelin, C-reactive protein (CRP), and 2-h glucose before and after 8 wk of energy restriction with one dietary pattern (meal replacements) and 24 wk of follow-up with either a fat-counting (FC) or carbohydrate-counting (CC) dietary protocol.[1]

	Phase 1 completers[2]		Phase 2 completers[3]	
	Week 0 ($n = 34$)	Week 8 ($n = 34$)	Week 20 ($n = 23$)	Week 32 ($n = 23$)
Weight (kg)[4,5]	96.0 ± 3.3	90.3 ± 3.3	91.2 ± 4.5	92.5 ± 4.4
Waist circumference (cm)[4,5]	101.0 ± 2.2	94.9 ± 2.2	95.0 ± 2.8	95.9 ± 2.8
TFM (kg)[4,5]	34.9 ± 1.5	30.8 ± 1.6	—	32.4 ± 2.1
TFFM (kg)[4,5]	61.5 ± 2.1	59.8 ± 1.9	—	60.1 ± 2.5
SBP (mm Hg)[4,5]	120.2 ± 2.2	111.8 ± 1.9	117.3 ± 2.2	112.2 ± 2.5
DBP (mm Hg)	66.9 ± 1.7	66.9 ± 1.9	65.8 ± 2.0	67.1 ± 2.8
REE (MJ/d)[4]	7.7 ± 0.3	7.1 ± 0.3	—	7.4 ± 0.3
RQ[4]	0.84 ± 0.01	0.81 ± 0.01	—	0.85 ± 0.01
Fasting glucose (mmol/L)[4,5]	5.2 ± 0.1	5.1 ± 0.5	5.3 ± 0.1	5.0 ± 0.1
2-h glucose (mmol/L)	5.9 ± 0.4	5.6 ± 0.2	—	6.0 ± 0.3
Total cholesterol (mmol/L)[4,6–8]	4.7 ± 0.2	4.0 ± 0.1	4.6 ± 0.1	4.6 ± 0.2
LDL cholesterol (mmol/L)[4,8]	2.8 ± 0.2	2.4 ± 0.1	2.6 ± 0.1	2.7 ± 0.1
HDL cholesterol (mmol/L)[4,6–8]	1.3 ± 0.1	1.2 ± 0.04	1.3 ± 0.1	1.4 ± 0.1
Triacylglycerol (mmol/L)[4,6]	1.2 ± 0.1	1.0 ± 0.1	1.4 ± 01	1.2 ± 0.1
CRP (mg/L)[4]	3.3 ± 0.4	2.8 ± 0.3	2.9 ± 0.3	2.8 ± 0.5
Ghrelin (pg/mL)[4]	524.7 ± 43.2	553.1 ± 41.1	596.4 ± 6.2	563.5 ± 52.0

[1] All values are $\bar{x}$ ± SEM. FM, fat mass; FFM, fat-free mass; TFM, total FM; TFFM, total FFM; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data were assessed by using repeated-measures ANOVA with time as the within-subject factor and diet as the between-subject factor. There was no significant time × diet interaction for any variables.
[2] Subjects who finished phase 1 (weeks 0–8). $n = 34$ except FFM, FM, and 2-h glucose ($n = 33$); REE and RQ ($n = 13$); CRP ($n = 29$); and ghrelin ($n = 26$).
[3] Subjects who finished phase 2 (weeks 0–32). $n = 23$ except FFM and FM ($n = 23$), REE and RQ ($n = 11$), and CRP and ghrelin ($n = 19$).
[4] Significant effect of time from week 0 to week 8 for all treatments combined, $P < 0.05$.
[5] Significant effect of time from week 0 to week 32 for all treatments combined, $P < 0.05$.
[6] Significant effect of time from week 8 to week 20 for all treatments combined, $P < 0.05$.
[7] Significant effect of time from week 20 to week 32 for all treatments combined, $P < 0.05$.
[8] Significant effect of time from week 8 to week 32 for all treatments combined, $P < 0.05$.

At week 20, the FC group had lower percentage fat, SFA, and monounsaturated fatty acid and higher percentage carbohydrate intakes, and a trend toward a higher GI ($P = 0.082$); at week 32, the FC group trended toward a lower percentage SFA intake ($P = 0.054$). At week 20, on average, subjects complied with the prescribed dietary intervention (FC diet group: 37 ± 4 g fat/d; CC diet group: 123 ± 14 g carbohydrate/d). By week 32, subjects were not complying with the prescribed dietary intervention (FC diet group: 54 ± 9 g fat/d; CC diet group: 135 ± 11 g carbohydrate/d).

Weight loss, body composition, energy expenditure, and quality of life

No differential effects of diet composition on weight loss, body composition, or energy expenditure were observed. Weight decreased during phase 1 (5.6 ± 2.4 kg or 6.0 ± 0.4%; $P < 0.001$) and did not change further during phase 2 ($P = 0.133$), so that, at week 32, there was a net weight loss of 4.7 ± 1.0 kg (5.9 ± 2.1 kg with the FC diet, 4.4 ± 0.7 kg for the CC diet; time × diet interaction, $P = 0.659$; **Table 4**). At the end of phase 1, 74% of subjects had lost > 5% of their body weight, whereas, by week 20 of phase 2, 68% of subjects had lost > 5% of their body weight (ie, some subjects had regained the weight they lost in phase 1). At week 32, 44% of subjects had lost > 5% of their body weight. With an intention-to-treat analysis in which the last data point was used for subjects that dropped out, the weight loss was still maintained in phase 2. When the baseline data point was used for subjects who dropped out, weight loss was maintained overall in phase 2, but significant weight regain (2.5 ± 0.7 kg, $P = 0.028$) occurred from weeks 8–32, and thus the net weight loss from weeks 0–32 was 3.2 ± 0.7 kg (**Figure 2**).

During phase 1, significant ($P < 0.001$) decreases in waist circumference (6.1 ± 0.4%), TFFM (2.5 ± 0.5%) and TFM (12.3 ± 1.3%) occurred; they were maintained during phase 2 so that significant ($P \leq 0.001$) decreases in waist circumference (5.9 ± 1.1%), TFFM (2.5 ± 0.9%) and TFM (9.4 ± 2.0%) occurred over the entire study (Table 4).

During phase 1, REE (expressed as an absolute value) decreased 8.0 ± 1.9% ($P = 0.003$) and respiratory quotient decreased 3.3 ± 1.4% ($P = 0.04$). These decreases were not maintained, and there was no overall difference between week 0 and week 32 (Table 4).

The diet groups did not differ significantly in the quality-of-life domain scores emotional state (4.5 ± 4), hirsutism (3.9 ± 5.2), weight status (2.6 ± 4.4), infertility (6 ± 5.5), and menstrual irregularity (3.75 ± 4.25) at baseline or over the study duration. In phase 1, the weight status (from 2.6 ± 4.4 to 3.4 ± 5.6; $P = 0.013$) and the menstrual irregularity (from 3.75 ± 4.25 to 4.5 ± 4.0; $P = 0.039$) domains improved significantly. No changes in the quality-of-life domains were seen in phase 2, and no differences between quality-of-life measures were seen at the beginning or end of the study.

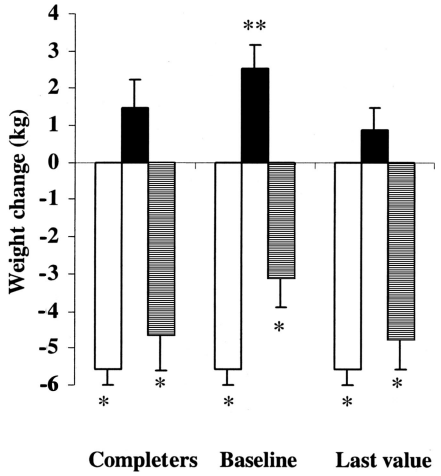

FIGURE 2. Weight change for data analyzed as completers evaluation, baseline value for study dropouts carried forward, and last clinic visit of dropouts carried forward. Phase 1, □: $n = 34$; phase 2, ■: completers, data included from subjects who competed each phase ($n = 23$); baseline, baseline values from dropouts carried forward ($n = 34$); and last value, last clinical value from dropouts carried forward ($n = 34$); total weight change, ▤. Error bars represent SEMs. *Significant effect of time relative to week 0 for all treatments combined, $P < 0.001$. **Significant effect of time from weeks 8–32 for all treatments combined, $P = 0.028$. The time × diet interaction was not significant for any variable.

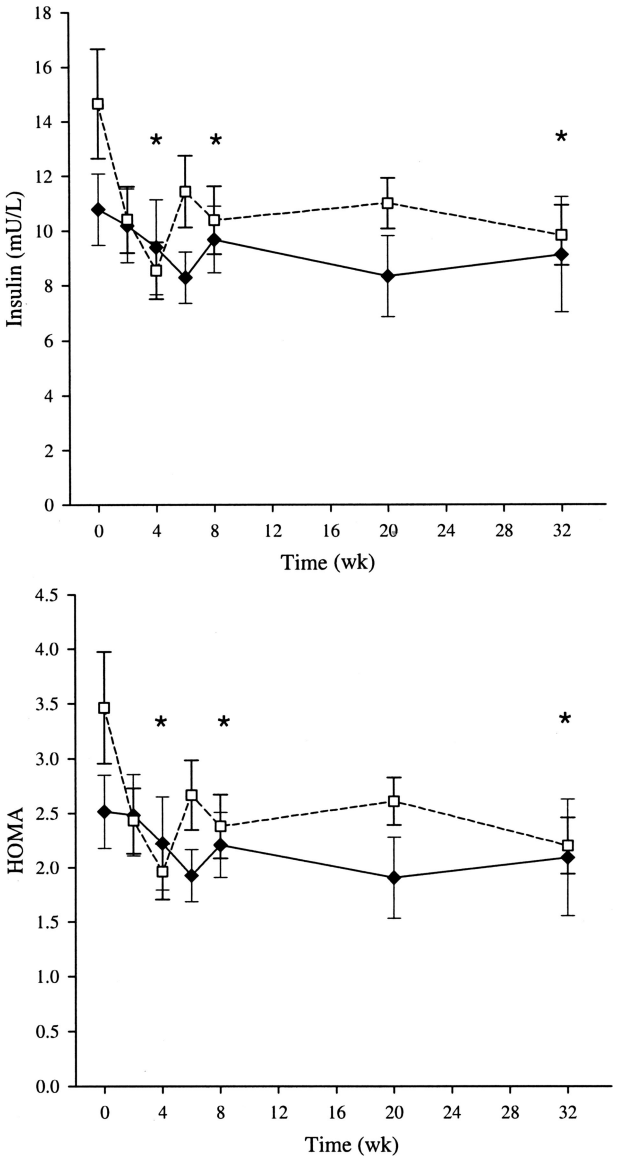

FIGURE 3. Mean (±SEM) concentrations of fasting insulin and homeostasis model assessment of insulin sensitivity (HOMA) before and after 8 wk of energy restriction with one dietary pattern (meal replacements; phase 1) and 24 wk of follow-up with either a fat-counting (FC; ♦) or carbohydrate-counting (CC; □) dietary protocol (phase 2). Phase 1 (weeks 0–8): $n = 16$ for FC and 18 for CC; phase 2 (weeks 8–32): $n = 9$ for FC and 14 for CC. *Significant effect of time relative to week 0 for all treatments combined, $P < 0.05$. The time × diet interaction was not significant for any variable.

Fasting blood pressure, lipids, C-reactive protein, ghrelin, and insulin and glucose homeostasis

No time × diet interaction was observed for any metabolic variables. In phase 1, significant decreases in total cholesterol (2.6 ± 3.3%; $P < 0.001$), triacylglycerols (12.9 ± 5.2%; $P = 0.005$), LDL cholesterol (12.1 ± 3.3%; $P < 0.001$), and HDL cholesterol (9.5 ± 3.5%; $P < 0.001$) occurred. In phase 2, increases in these variables were observed so that they did not differ significantly between study commencement and completion. In phase 1, fasting ghrelin increased (7.5 ± 3.6%; $P = 0.013$) and CRP decreased (9.6 ± 8.2%; $P = 0.018$) significantly, but, at study completion, they did not differ significantly from the values at study commencement (Table 4).

In phase 1, significant decreases in fasting glucose (1.8 ± 1.0%; $P = 0.02$) and systolic blood pressure (6.6 ± 1.4%; $P < 0.001$) were seen that were maintained in phase 2, so that a net decrease in fasting glucose (2.9 ± 1.2%; $P = 0.046$) and systolic blood pressure (6.6 ± 2.2%; $P = 0.002$) occurred. No change in diastolic blood pressure or 2-h OGTT glucose occurred in phase 1 or phase 2 (Table 4). At week 0, 33 (76.7%) of 43 subjects had normal glucose tolerance; at week 8, 91.1% of subjects had normal glucose tolerance; and, at week 32, 87.0% of subjects had normal glucose tolerance ($P = 0.003$ for change over time). At week 0, 20.9% of subjects met the criteria for the metabolic syndrome as compared with 5.9% at week 8 and 4.3% at week 34 ($P = 0.085$ for change over time).

Insulin homeostasis, reproductive hormones, and menstrual cyclicity

No differences were observed between the diet groups with respect to changes in insulin. In phase 1 of the study, fasting insulin (2.8 ± 1.1 mU/L; $P = 0.003$) and HOMA (0.7 ± 0.3; $P = 0.005$) decreased significantly (**Figure 3**). This decrease occurred by week 4 for insulin (3.9 ± 1.2 mU/L; $P = 0.013$) and HOMA (0.9 ± 0.3; $P = 0.02$), corresponding to a weight loss of 3.8 ± 0.3 kg. These decreases were maintained for phase 2 of the study so that a net decrease in insulin (3.5 ± 1.6 mU/L or 11.9 ± 10.7%; $P = 0.044$) and HOMA (0.9 ± 0.4; $P = 0.033$) occurred. During phase 1, reductions in testosterone (0.3 ± 0.7 nmol/L; $P = 0.019$), FAI (3.1 ± 6; $P = 0.001$) and free testosterone (10.7 ± 3.3 pmol/L; $P = 0.001$) and significant increases in SHBG (3.2 ± 1.8 nmol/L; $P = 0.020$) occurred (**Figure 4**). These decreases in FAI (2.4 ± 40.2; $P = 0.022$) and free testosterone (8.8 ± 2.6 pmol/L; $P = 0.001$) occurred during weeks 0–2 for and corresponded with a weight loss of 2.4 ± 1.0 kg. In phase 2, the decrease in testosterone was sustained (0.4 ± 0.1 nmol/L;

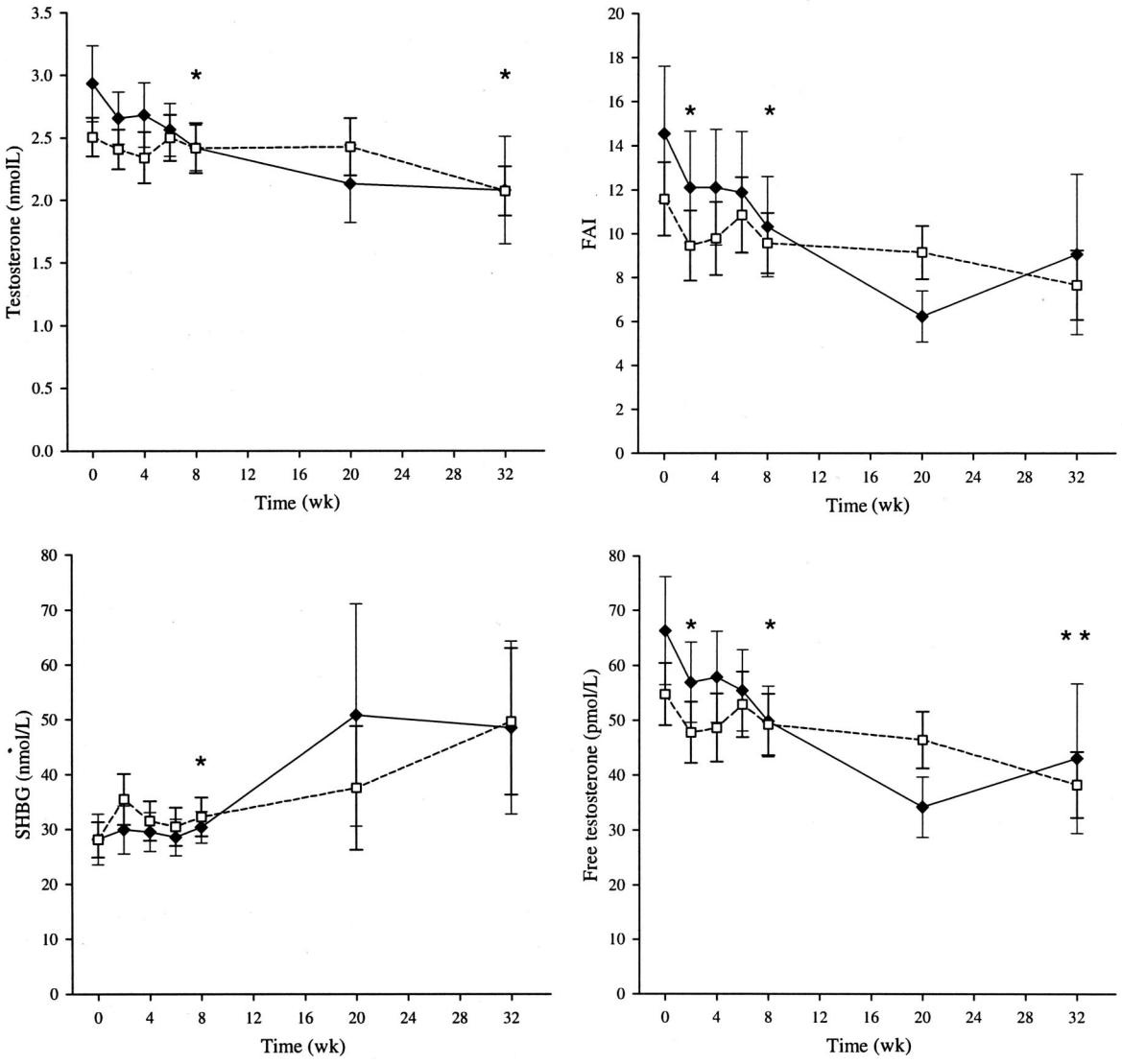

FIGURE 4. Mean (±SEM) fasting testosterone concentrations, sex hormone–binding globulin (SHBG) concentrations, free androgen index (FAI), and free testosterone concentrations before and after 8 wk of energy restriction with one dietary pattern (meal replacements; phase 1) and 24 wk of follow-up on either a fat-counting (FC; ♦) or carbohydrate-counting (CC; □) dietary protocol (phase 2). Phase 1 (weeks 0–8): $n = 16$ for FC and 18 for CC; phase 2 (weeks 8–32): $n = 7$ for FC and 11 for CC. *Significant effect of time relative to week 0 for all treatments combined, $P < 0.05$. **Trend for the effect of time relative to week 0 for all treatments combined, $P = 0.087$. The time × diet interaction was not significant for any variables.

$P = 0.013$), and there was a trend for the decrease in free testosterone to be sustained (8.8 ± 5.6 pmol/L; $P = 0.087$) so that a net decrease occurred from weeks 0–32. For SHBG and FAI, there was no difference between the values at study commencement and those at completion. When an intention-to-treat analysis was used for insulin, HOMA, testosterone, and free testosterone values, there was no difference in the results using either the baseline value carried forward or the last clinical value carried forward. Thus, a significant decrease in insulin, HOMA, testosterone, and free testosterone occurred during phase 1 (weeks 0–8) and was maintained during phase 2 (weeks 8–32) such that an overall decrease in insulin, HOMA, and testosterone occurred from weeks 0–32, and there was a trend for an overall decrease in free testosterone from weeks 0–32. No change was seen in 2-h insulin over the duration of the study (64.2 ± 11.5 mU/L at week 0).

The data were split into those with baseline fasting insulin concentrations above and below the median (10.45 mU/L; baseline fasting insulin 17.8 ± 1.8 and 7.9 ± 0.4 mU/L, respectively; $P < 0.001$). At baseline, compared with the subjects with high insulin, the subjects with low insulin concentrations had significantly lower 2-h insulin (91.8 ± 20.0 and 36.7 ± 7.2 mU/L, respectively; $P = 0.015$), testosterone (3.1 ± 0.3 and 2.3 ± 0.2 nmol/L, respectively; $P = 0.023$), FAI (16.3 ± 2.9 and 9.7 ± 1.5, respectively; $P = 0.05$), and free testosterone (72.2 ± 8.9 and 48.2 ± 5.3 pmol/L, respectively; $P = 0.027$). From weeks 0–2, the subjects with high insulin showed a decrease in testosterone [0.4 ± 0.1 nmol/L ($P = 0.007$); time × insulin interaction, $P = 0.011$]; FAI [4.0 ± 0.1 ($P = 0.001$); time × insulin interaction, $P = 0.049$]; and free testosterone [14.4 ± 3.6 pmol/L ($P = 0.001$); time × insulin interaction, $P = 0.026$], and the subjects

with low insulin had no change. From weeks 0–4, the subjects with high insulin showed a decrease in testosterone [0.3 ± 0.1 nmol/L ($P = 0.004$); time × insulin interaction, $P = 0.023$] and free testosterone [9.1 ± 2.8 pmol/L ($P < 0.001$); time × insulin interaction, $P = 0.037$] and a trend for a decrease in FAI [2.3 ± 0.8 ($P < 0.001$); time × insulin interaction, $P = 0.056$], and the subjects with low insulin had no change.

Diet groups did not differ significantly in changes in reproductive hormones, ovulation, or menstrual cyclicity. No differences were seen in menstrual cyclicity improvements between subjects with baseline fasting insulin above or below the median. During phase 1, 15 of 33 subjects ovulated twice, 13 of 33 subjects ovulated once, and 5 of 33 subjects did not ovulate. Over the entire study, there was an improvement in menstrual cyclicity in 16 (57.1%) of 28 subjects. This improvement occurred through resumption of menses ($n = 1$) and ovulation ($n = 3$) in previously amennorrheic subjects and improvement in cycle length ($n = 12$) in other subjects. Two subjects (both in the FC diet group) became pregnant during phase 2; at the estimated time of conception, their weight losses were 6.5 and 11.8 kg.

DISCUSSION

Considerable research has been conducted on the effects of weight loss in improving abnormal reproductive and metabolic variables in women with PCOS (7, 8). We also showed here for the first time that meal replacements are an effective, nutritionally adequate short-term strategy for reducing weight and improving body composition, quality of life, and metabolic and reproductive variables. Meal replacements (with or without dietetic input) as part of a reduced-energy diet (4–6 MJ/d) are nutritionally adequate, and they produce weight loss comparable to or greater than that obtained with conventional reduced-energy diets (32). Women with PCOS also exhibit high dropout rates and poor compliance with dietary protocols, potentially because of greater difficulty with energy restriction due to lower satiety (13). Because they provide greater dietary flexibility and aid compliance with and adherence to a reduced-energy diet, meal replacements may be a preferred weight-loss strategy for some persons (32).

Only a subset of subjects (57.1%) had improved menstrual cyclicity after weight loss. We found no differences between responders and nonresponders, although we did not perform a complete gonadotrophic or insulin sensitivity assessment. Subjects with PCOS who show menstrual improvements after 4–6 mo of weight loss have greater decreases in fasting insulin, HOMA, insulin sensitivity (7, 8), lutenizing hormone, and central fat (8) and greater increases in lutenizing hormone and reductions in estradiol (38) than do subjects with PCOS who do not show menstrual improvements after weight loss. In 182 normogonadotropic, oligomenorrheic, infertile women undergoing ovulation induction with clomiphene citrate (39), elevated baseline FAI was the most important negative determinant of treatment response. It is currently unclear why reproductive function is restored with energy restriction or weight loss, how long it would take for the short-term hormonal changes to translate into improvements in reproductive function, and what the key triggering hormonal factor is.

Subjects with high baseline insulin concentrations had maximal improvements in reproductive hormones after acute energy restriction (weeks 2–4). However, no differences in menstrual cyclicity were observed between subjects with higher or with lower baseline insulin; this lack of difference was also observed in women who have PCOS with or without IR and who are undergoing 12-mo treatment with metformin or an energy-reduced diet (40). It may be that only short-term energy restriction is needed to improve reproductive function, a change that likely occurs through reductions in insulin-stimulated androgen production (4). However, reproductive improvements have been reported after 4–6 wk (7, 41) or 3–5 mo (7, 9) of energy restriction. Weight loss may be more important than acute energy restriction in sustaining improvements, or a specific decrease in weight or insulin (depending on the initial weight or IR) may be needed to improve reproductive function. However, not all women with PCOS have IR (42), although those who do are more severely affected clinically (43). Moreover, responders to a 6-mo weight-loss program had significant reductions in estradiol and increases in LH secretion after 7 d of acute energy restriction (38), which suggests that other hormonal responses to energy restriction may precede improvements in follicular function.

The aim of the long-term intervention was to compare the effect of 2 education strategies moderately restricting fat or carbohydrate on maintenance of weight and reproductive and metabolic improvements. We achieved a moderately restricted fat or carbohydrate intake for 3 mo of weight maintenance, and no differential effects of diet group on changes in weight or body composition were observed. Severe carbohydrate restriction (20–30 g/d) results in greater weight loss than a does structured reduced fat intake over 6 mo (15, 16), potentially because of the simplicity of the education strategy, the restriction of food choices, or greater proportional dietary protein intake (15) with its resultant changes in satiety (44) and lean mass maintenance (45). We may not have restricted carbohydrate sufficiently to achieve significant increases in protein intake or decreases in food choices, so as to aid in reducing energy intake. Weight loss also is typically not maintained after 12 mo with a low-carbohydrate diet (16, 46), which raises compliance and sustainability issues similar to those seen with other weight-maintenance regimens. With respect to the effect of modulating GI or GL on weight loss, greater reductions in BMI (26, 47) and fat mass (26) were reported for an ad libitum low-GI diet than for an energy-restricted diet over a 4- (47) or 12- (26) mo treatment of obese children and adolescents. In the current study, we observed no differences in GI, GL, or weight loss between the CC and FC groups. A larger reduction in GL, through greater reduction in GI or carbohydrate amount, may be needed to translate the acute satiating effects of low-GI foods into significant clinical practice. The role of GI or GL in weight maintenance is also unclear. When used in conjunction with a 12-mo program of low fat and reduced energy but increased physical activity, advice on reducing dietary GI did not have any additional effect on weight loss (7.6 kg) or regain (4.6 kg) in 56 overweight persons (25).

At study completion, the subjects following both dietary strategies maintained a weight loss of 4.7 kg. Equivalent sustained reductions in waist circumference, insulin, HOMA, and testosterone occurred with both diets, likely because of the similar weight maintenance and possibly the similar GI, GL, and protein intake. The weight loss seen in the current study is a clinically relevant weight loss that is associated with a reduced prevalence of diabetes (10) and the metabolic syndrome (48) in the general population and improved fertility outcomes in PCOS (9). This sustained weight loss could potentially be due to the reduced GL load compared with baseline, although we observed no relation

between GI, GL, and weight loss. Alternatively, the decrease in REE observed during weight loss (49) may predispose subjects to regain weight. We observed a partial return of REE to baseline at study completion, which may have aided weight maintenance. Indeed, an increase in REE was reported in conjunction with sustained weight maintenance achieved by following a program of post-weight-loss physical activity (50). Given the lack of concomitant change in TFFM in weight maintenance, the mechanism for this effect is unclear and requires further exploration.

The monthly follow-up or physical activity advice may also have aided weight maintenance and dietary compliance (51, 52). However, in the last 3 mo of weight maintenance, subjects did not adhere to their daily allocated fat or carbohydrate intake, energy intake increased insignificantly, and some metabolic variables returned to baseline, which indicated a lessening of dietary compliance. Energy intake, weight regain, and the number of study dropouts may have increased further with a longer period of weight maintenance. In previous weight-loss studies in women with PCOS, structured individualized dietary and exercise protocols accompanied by input from dietitians, exercise professionals, and psychiatrists were successful in achieving weight loss [6.3 kg at 24 wk (9) or 2.6–6.3 kg at 48 wk (19)] and sustained improvements in ovulation and fertility. Incorporation of a more structured physical activity protocol, behavioral treatment, group support, and increasing intensity or frequency of follow-up and dietary counseling would likely increase long-term compliance (11, 51) and may outweigh the effects of modifying dietary composition. This could also be a more relevant approach in patients with PCOS if appetite regulation is impaired.

In conclusion, we have shown for the first time that the use of twice-daily meal replacements was an effective and nutritionally adequate strategy for achieving weight loss and gaining associated hormonal and clinical benefits in overweight women with PCOS. Acute energy restriction improved reproductive hormonal variables in a study subset, which implied that long-term weight loss may not be needed for fertility improvements in all women with PCOS. We showed for the first time that advice on fat or carbohydrate restriction with moderate targets had no differential effect on weight maintenance and reproductive and metabolic variables in PCOS patients. However, it is possible that more stringent fat or carbohydrate targets may be more effective in achieving the dietary macronutrient restriction so that differential effects on weight and energy intake can be observed. Monthly support may have been important in facilitating weight maintenance and sustaining metabolic and hormonal improvements in conjunction with an improvement in menstrual function in 57% of the subjects. Both these dietary approaches may be useful additional strategies for women with PCOS, and they afford a degree of choice, depending on preference or short-term metabolic imperative.

We gratefully acknowledge Anne McGuffin, Kathryn Bastiaans, and Julia Weaver for coordinating the trial; Grant Brinkworth for assisting in the energy expenditure measurements; Jennifer Keogh for assisting in the dietary intervention; Rosemary McArthur, Ruth Pinches, Sue Davies, and Deborah Roffe for nursing expertise; and Alan Gilmore, Mark Mano, Cherie Keatch, and Candita Sullivan for assisting with the biochemical assays.

LM, MN, PMC, GAW, and RJN conceived of and designed the study and contributed to data analysis and manuscript writing. LM coordinated the study, collected the data, wrote the manuscript, and contributed to designing and implementing the study dietary protocol. MN and GW contributed to designing the study dietary protocol, and GW contributed to implementing the study dietary protocol. None of the authors had a personal or financial conflict of interest.

REFERENCES

1. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998;83:3078–82.
2. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–9.
3. Tarkun I, Arslan BC, Canturk Z, Turemen E, Sahin T, Duman C. Endothelial dysfunction in young women with polycystic ovary syndrome: relationship with insulin resistance and low-grade chronic inflammation. J Clin Endocrinol Metab 2004;89:5592–6.
4. Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ. Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. J Clin Endocrinol Metab 1986;62:904–10.
5. Plymate SR, Matej LA, Jones RE, Friedl KE. Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. J Clin Endocrinol Metab 1988;67:460–4.
6. Kiddy DS, Sharp PS, White DM, et al. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. Clin Endocrinol (Oxf) 1990;32:213–20.
7. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:812–9.
8. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999;84:1470–4.
9. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod 1998;13:1502–5.
10. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
11. Ayyad C, Andersen T. Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obes Rev 2000;1:113–9.
12. Robinson S, Chan SP, Spacey S, Anyaoku V, Johnston DG, Franks S. Postprandial thermogenesis is reduced in polycystic ovary syndrome and is associated with increased insulin resistance. Clin Endocrinol (Oxf) 1992;36:537–43.
13. Moran LJ, Noakes M, Clifton PM, et al. Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. J Clin Endocrinol Metab 2004;89:3337–44.
14. Hirschberg AL, Naessen S, Stridsberg M, Bystrom B, Holtet J. Impaired cholecystokinin secretion and disturbed appetite regulation in women with polycystic ovary syndrome. Gynecol Endocrinol 2004;19:79–87.
15. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 2003;88:1617–23.
16. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–90.
17. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–81.
18. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 2004;140:769–77.
19. Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertil Steril 2004;82:421–9.
20. Opperman AM, Venter CS, Oosthuizen W, Thompson RL, Vorster HH.

Meta-analysis of the health effects of using the glycaemic index in meal-planning. Br J Nutr 2004;92:367–81.
21. Frost G, Leeds A, Trew G, Margara R, Dornhorst A. Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet. Metabolism 1998;47:1245–51.
22. Bouche C, Rizkalla SW, Luo J, et al. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. Diabetes Care 2002;25:822–8.
23. Holt S, Brand J, Soveny C, Hansky J. Relationship of satiety to post-prandial glycaemic, insulin and cholecystokinin responses. Appetite 1992;18:129–41.
24. Alfenas RC, Mattes RD. Influence of glycemic index/load on glycemic response, appetite, and food intake in healthy humans. Diabetes Care 2005;28:2123–9.
25. Carels RA, Darby LA, Douglass OM, Cacciapaglia HM, Rydin S. Education on the glycemic index of foods fails to improve treatment outcomes in a behavioral weight loss program. Eat Behav 2005;6:145–50.
26. Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced-glycemic load diet in the treatment of adolescent obesity. Arch Pediatr Adolesc Med 2003;157:773–9.
27. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
28. Luscombe-Marsh ND, Noakes M, Wittert GA, Keogh JB, Foster P, Clifton PM. Carbohydrate-restricted diets high in either monounsaturated fat or protein are equally effective at promoting fat loss and improving blood lipids. Am J Clin Nutr 2005;81:762–72.
29. Bouchard C, Tremblay A, Leblanc C, Lortie G, Savard R, Theriault G. A method to assess energy expenditure in children and adults. Am J Clin Nutr 1983;37:461–7.
30. Stunkard AJ, Messick S. The Three-Factor Eating Questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 1985;29:71–83.
31. Cronin L, Guyatt G, Griffith L, et al. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab 1998;83:1976–87.
32. Noakes M, Foster PR, Keogh JB, Clifton PM. Meal replacements are as effective as structured weight-loss diets for treating obesity in adults with features of metabolic syndrome. J Nutr 2004;134:1894–9.
33. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
34. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72.
35. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27(suppl):S5–10.
36. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
37. National Health and Medical Research Council. Recommended Dietary Intakes for use in Australia. Canberra, Australia: Australian Government Publishing Service, 1991.
38. Van Dam EW, Roelfsema F, Veldhuis JD, et al. Retention of estradiol negative feedback relationship to LH predicts ovulation in response to caloric restriction and weight loss in obese patients with polycystic ovary syndrome. Am J Physiol Endocrinol Metab 2004;286:E615–20.
39. Imani B, Eijkemans MJ, de Jong FH, et al. Free androgen index and leptin are the most prominent endocrine predictors of ovarian response during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. J Clin Endocrinol Metab 2000;85:676–82.
40. Goldenberg N, Glueck CJ, Loftspring M, Sherman A, Wang P. Metformin-diet benefits in women with polycystic ovary syndrome in the bottom and top quintiles for insulin resistance. Metabolism 2005;54:113–21.
41. Kiddy DS, Hamilton-Fairley D, Seppala M, et al. Diet-induced changes in sex hormone binding globulin and free testosterone in women with normal or polycystic ovaries: correlation with serum insulin and insulin-like growth factor-I. Clin Endocrinol (Oxf) 1989;31:757–63.
42. Dale PO, Tanbo T, Vaaler S, Abyholm T. Body weight, hyperinsulinemia, and gonadotropin levels in the polycystic ovarian syndrome: evidence of two distinct populations. Fertil Steril 1992;58:487–91.
43. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril 2005;83:1454–60.
44. Latner JD, Schwartz M. The effects of a high-carbohydrate, high-protein or balanced lunch upon later food intake and hunger ratings. Appetite 1999;33:119–28.
45. Lejeune MP, Kovacs EM, Westerterp-Plantenga MS. Additional protein intake limits weight regain after weight loss in humans. Br J Nutr 2005;93:281–9.
46. Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778–85.
47. Spieth LE, Harnish JD, Lenders CM, et al. A low-glycemic index diet in the treatment of pediatric obesity. Arch Pediatr Adolesc Med 2000;154:947–51.
48. Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 2005;142:611–9.
49. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med 1995;332:621–8.
50. Villanova N, Pasqui F, Burzacchini S, et al. A physical activity program to reinforce weight maintenance following a behavior program in overweight/obese subjects. Int J Obes (Lond) 2006;30:697–703.
51. Heshka S, Anderson JW, Atkinson RL, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. JAMA 2003;289:1792–8.
52. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr 2005;82(suppl):222S–5S.