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Role of diet in the treatment of polycystic ovary syndrome

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Abstract

Objective—To determine whether eucaloric diets either enriched with monounsaturated fatty acids (MUFA; 17% energy) or low in carbohydrates (Low CHO; 43% energy) would increase insulin sensitivity (Si) and decrease circulating insulin concentrations, relative to a standard diet (STD; 56% CHO, 31% fat, 16% protein), among women with polycystic ovary syndrome (PCOS).

Design—Crossover.

Setting—Academic research environment.

Patient(s)—Healthy women with PCOS not on hormonal or insulin-sensitizing therapy.

Intervention(s)—Subjects consumed three, 16-day, eucaloric diets, each separated by a 3-week washout period. A frequently sampled, intravenous, glucose tolerance test was administered at baseline and following each diet.

Main Outcome Measure(s)—Fasting glucose, insulin, the acute insulin response to glucose (AIRg), Si, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), total testosterone (T), free T, A4, total cholesterol, high-density lipoprotein cholesterol (HDL-C), tryglycerides (TG), and free fatty acids (FFA).

Result(s)—Fasting insulin was lower following the Low CHO diet relative to the STD diet; AIRg was lower following the Low CHO diet relative to the MUFA diet. Fasting glucose, Si, and the circulating concentrations of reproductive hormones were not significantly affected by the intervention.

Conclusion(s)—A moderate reduction in dietary carbohydrate reduced the fasting and postchallenge insulin concentrations among women with PCOS, which, over time, may improve reproductive/endocrine outcomes.

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Keywords

Polycystic ovary syndrome; hyperandrogenism; low-carbohydrate diet; monounsaturated fat; insulin resistance; β-cell function

Polycystic ovary syndrome (PCOS) is an endocrine disorder found in approximately 6.5% of reproductive-age women (1), and is commonly associated with obesity, menstrual irregularity, infertility, insulin resistance (IR), and clinical hyperandrogenism and/or hyperandrogenemia. Although the pathogenesis of PCOS remains unclear, evidence points to the role of IR and the associated hyperinsulinemia as possible contributing factors. Insulin inhibits the hepatic production of sex hormone-binding globulin (SHBG) (2–4) and insulin-like growth factor binding protein-I (IGFBP-I) (5), and stimulates ovarian P450c17α activity and androgen production (6, 7). Insulin resistance has been identified in the majority of lean and obese PCOS subjects, although obesity appears to exacerbate both IR and hyperinsulinemia.

Treatment for PCOS subjects typically includes insulin-lowering drugs, anti-androgen therapy, oral contraceptives, and the implementation of lifestyle changes, including weight loss if necessary. Weight loss, accompanied by an increase in insulin sensitivity (Si), has proven to be a successful treatment for the metabolic and hormonal abnormalities characteristic of the PCOS population (8–10). Weight loss has also proven to be an effective treatment for type 2 diabetes mellitus (T2DM; 11–13), a disease that shares similar clinical and metabolic features with PCOS, including generalized and abdominal obesity, IR, hyperinsulinemia, dyslipidemia, and an increased risk for the development of cardiovascular disease.

Current dietary recommendations for subjects with T2DM reflect earlier observations regarding the beneficial effects of high monounsaturated fatty acid (MUFA) and low carbohydrate (CHO) diets, and the potential detrimental effects of high CHO diets (14–18). Treatment of T2DM subjects with high MUFA diets significantly improved serum concentrations of glucose, insulin, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) (14–16), and improved Si as assessed by the euglycemic hyperinsulinemic clamp (14). Similarly, a 2-week Low CHO and high-protein diet demonstrated an improvement in the glucose, insulin, and lipid profiles of T2DM men (17). Alternatively, treatment of T2DM subjects with a high CHO diet (60% CHO) for 15 days was observed to significantly increase mean very low-density lipoprotein cholesterol (VLDL-C) concentrations and significantly decrease mean HDL-C concentrations (18).

To date, only two studies have examined the effect of diet composition in women with PCOS. Moran and colleagues studied the impact of high and low protein diets in 28 PCOS subjects treated with a hypocaloric diet for 12 weeks followed by weight maintenance for an additional 4 weeks (19). Women on the high protein diet did not differ from those on the low protein diet with respect to concentrations of circulating lipids, insulin, glucose, or hormones, although the postprandial glucose response was reduced in women receiving the high protein diet. Similarly, implementation of a 3-month eucaloric polyunsaturated fatty acid (PUFA)-rich diet did not alter the endocrine profile of 17 women with PCOS (20). However, the only intervention in this study was the provision of walnuts. Although a significant weight loss with treatment was reported, fasting glucose and the glucose response to an oral glucose challenge increased significantly. Thus, although it appears that diet composition may alter the metabolic profile of subjects with PCOS, the optimal diet has not yet been determined.

Given the limited information available for dietary treatment of women with PCOS, we designed an intervention protocol involving three, 16-day, eucaloric diets based upon diets previously shown to be successful in improving the glucose, insulin and lipid profiles in select T2DM populations (14–17). We hypothesized that eucaloric diets, which are either enriched with monounsaturated fatty acids (MUFA; 17% energy) or are low in carbohydrates (Low CHO; 43% energy), would increase Si and decrease circulating insulin concentrations, relative to a standard diet (STD; 56% CHO, 31% fat, 16% protein). The decrease in insulin concentrations following the Low CHO and MUFA diets would allow for an increase in the production of SHBG, decrease in free T, decrease in insulin-stimulated androgen synthesis, and an improvement in the lipid profile. To test these hypotheses, we prospectively studied 11 women with PCOS who received three, 16-day, eucaloric diets, each separated by a 3-week washout period. The results of this study would not only have an impact on the treatment of PCOS, but also may provide clues to dietary factors that may play a role in its development.

MATERIALS AND METHODS

We recruited nondiabetic subjects with PCOS who were not on hormonal or insulin-sensitizing therapy for at least 2 months. Subjects were excluded if they were postmenopausal, had a history of an eating disorder, were currently on a modified diet, were participating in extreme exercise (i.e., >30 min/day), or planned to move from the Birmingham area within the following 6 months. The presence of PCOS was defined by criteria arising from a National Institutes of Child Health and Human Development sponsored conference in 1990: [1] clinical evidence of hyperandrogenism and/or hyperandrogenemia, [2] oligo-ovulation, and [3] the exclusion of related disorders (21). We should note that we selected a subject population largely comprised of overweight and obese subjects so that the results would be applicable to the general PCOS population, which in the United States is approximately 70% obese (22). The study population consisted of five African-Americans, four Caucasians, one Asian, and one individual of Caribbean descent. The University of Alabama at Birmingham (UAB) Institutional Review Board approved this study for Human Use, and all subjects gave written informed consent.

Ovulatory dysfunction was defined as menstrual cycles >45 days in length or <8 cycles per year, or by a luteal-phase progesterone (P4) level <4 ng/mL in conjunction with a monophasic basal body temperature chart if menstrual cycles were less than 45 days in length. Hirsutism was defined as a modified Ferriman-Gallwey (F-G) score ≥6 (23, 24). For the purpose of this study, subjects were deemed hyperandrogenemic if the level of total testosterone (T), free T, or DHEAS exceeded the 95th percentile values of 100 normal, healthy, nonhirsute eumenorrheic female controls. Subjects were regarded as hyperandrogenemic if total T was >62.0 ng/dL, free T was >21.5 pmol/L, or androstenedione (A) was >2.52 ng/mL. Twenty-one hydroxylase deficient nonclassic adrenal hyperplasia was excluded by a basal follicular phase 17-hydroxyprogesterone (17-HP) level <2.0 ng/mL (25); hyperprolactinemia and hypothyroidism were excluded by normal levels of prolactin (PRL) and thyroid-stimulating hormone (TSH), respectively. Cushing's syndrome and androgenic tumors were excluded by appropriate testing, if suspected clinically.

Study Design

Before beginning the study, subjects completed a medical history form and underwent a brief physical exam, including hirsutism scoring. Before baseline testing, subjects were asked to consume 250 g of carbohydrate per day for 3 days. All metabolic tests, including the measurement of hormones and lipids and the frequently sampled intravenous glucose tolerance test (FSIGT), were performed at the UAB General Clinical Research Center

(GCRC) following a standard evening meal (or the last evening meal of the particular diet to which they had been assigned) and a 10–12-hour fast. Following the completion of baseline testing, subjects were assigned to one of three treatment regimens.

The assignment of diet regimen, and the order of diets within each regimen, was not randomized due to feasibility issues. The regimens varied with respect to diet order; in all cases, diets were administered for at least 16 days with a 3-week washout. Subjects assigned to Regimen 1 received the Low CHO diet, followed by the MUFA diet, and lastly, the STD diet. Subjects assigned to Regimen 2 received the Low CHO diet, followed by the STD diet, and lastly, the MUFA diet. Subjects assigned to Regimen 3 received the MUFA diet, followed by the Low CHO diet, and lastly, the STD diet.

Dietary Treatment

Because dietary guidelines have not been developed for women with PCOS, we based our diets on dietary treatments previously shown to be successful in improving the glucose, insulin, and lipid profiles in select T2DM populations. The STD diet was modeled after the 1986 American Diabetes Association (ADA) guidelines for the T2DM population (26). The Low CHO diet was developed based upon the reported changes in the lipid and glucose profiles following a 14-day Low CHO (17) and 15-day high CHO diet in subjects with T2DM (18). The high MUFA diet was developed based on the reported improvements in the insulin and lipid profile (14–16) of the T2DM population following a high MUFA diet. All subjects received between 2,000–2,300 kilocalories/day. All diets and snacks consisted of natural food items, were provided by the UAB GCRC Metabolic Kitchen, and were rotated on a 4-day cycle.

Although all diets were similar in energy and protein, they differed concerning carbohydrate and fat content (Table 1). The MUFA and Low CHO diets were similar except that the Low CHO diet had a lower percentage of kilocalories from carbohydrate, and a higher percentage of kilocalories from fat, specifically PUFAs. We manipulated the MUFA content of the MUFA diet by providing containers of olive oil for the subjects, who were instructed to mix the oil into their entrees or use the oil as a salad dressing. We manipulated the carbohydrate and fat content of the Low CHO diet by reducing the amount of bread, rice, and noodles in the diet, providing reduced-carbohydrate bread in place of regular bread, and opting for higher PUFA-rich snacks such as sunflower seeds. This design enabled us to control for macronutrients and forms of fat, provided us with results independent of weight loss, and was feasible for the UAB GCRC Metabolic Kitchen.

In addition to controlling for macronutrient intake, we also attempted to design diets containing similar amounts of dietary constituents that could potentially influence our outcomes of interest. The dietary cholesterol content for all diets fell within the dietary guidelines set forth by the American Heart Association (AHA) (27). The intake of dietary fiber met the AHA recommendations (25–30 g/day) for both the STD and Low CHO diets, and fell just short in the MUFA diet (24 g/day) (28). Total fiber, soluble fiber, and trans fatty acid content were similar for all diets. Nutrient calculations were performed by a registered dietitian using the Nutrition Data System for Research (NDS-R) software version 4.04 (2001), developed by the Nutrition Coordinating Center, University of Minnesota in Minneapolis, Food and Nutrient Database 32 (29).

The diets were designed to be eucaloric, to avoid confounding due to weight loss, which is well documented as beneficial for the PCOS population (8–10). Kilocalorie requirements for weight maintenance were calculated using the Harris Benedict formula (30), which estimates basal energy expenditure, multiplied by an activity factor of 1.35. This formula and the activity factor have proven to be successful for estimating weight maintenance

energy requirements for relatively sedentary women in other studies utilizing the UAB GCRC. During each 16-day dietary treatment, subjects were weighed with minimal clothing and without shoes (Scaletronix digital scale) by the GCRC Metabolic Kitchen staff 2–3 times per week. On the 16th day of the dietary treatment, subjects reported to the GCRC for testing. A washout period of 3 weeks was scheduled between testing and the beginning of the next dietary treatment. During this time, subjects were advised to resume their normal eating habits, continue their usual exercise programs, and avoid taking any new medications without notifying the study personnel.

Dietary compliance was monitored through frequent weighing and the application of a 24-hour urine collection. The GCRC Metabolic Kitchen staff was instructed to contact the dietitian if any subject gained or lost in excess of 2.2 kilograms during the dietary treatment period. In addition, subjects were responsible for completing a 24-hour urine collection for assessment of urinary sodium just before their overnight GCRC admission. Results of the 24-hour urine collection are not reported here; the collection was used primarily as a psychological reminder to adhere to the intervention protocol.

Body Composition and Fat Distribution

Skin fold measurements were taken at 17 sites using skinfold calipers. Waist circumference was measured midway between the lateral lower ribs and the iliac crest using a steel measuring tape. Hip circumference was measured at the widest place over the buttocks. Total and regional (i.e., trunk and legs) body composition (i.e., fat mass and lean body mass) were measured by dual-energy X-ray absorptiometry (DXA) using a Prodigy (GE-Lunar, Madison, WI). All subjects were scanned in light clothing while lying flat on their backs with arms at their sides. One individual performed and analyzed all scans with ENCORE 2002 software version 6.10.029. Visceral (intraabdominal) and subcutaneous abdominal fat were analyzed by computed tomography (CT) scanning with a Light Speed instrument (General Electric, Milwaukee, WI) as previously described (31). A 5 mm scan at the level of the umbilicus (approximately the L4-L5 intervertebral space) was taken. One individual analyzed all scans for cross-sectional area (cm^2) of adipose tissue using the density contour program with Hounsfield units for adipose tissue set at −190 to −30. The test-retest reliability for visceral fat was assessed at 1.7% (31).

Frequently Sampled Intravenous Glucose Tolerance Test

After an overnight fast, a glucose dose of 300 mg/kg body weight was administered intravenously (IV), and insulin (0.02 U/kg) was administered as an iv bolus 20 minutes following the injection of glucose. Blood samples were collected 35 times over a period of approximately 4 hours. Glucose and insulin concentrations were analyzed, and values were entered into the MINMOD computer program (version 5.15; Richard N. Bergman, Ph.D., Department of Physiology and Biophysics, University of Southern California, Los Angeles) for determination of Si, the acute insulin response to glucose (AIRg), and the disposition index (DI = Si × AIRg) (32, 33). The AIRg is the incremental insulin area under the curve above basal from 0 to 10 minutes.

Biochemical Assays

Serum samples from the FSIGT were analyzed for glucose concentration by the glucose oxidase method (Analox, Lunenburg, MA). Insulin was assayed in duplicate 100 uL aliquots by double-antibody RIA with reagents obtained from Linco Research Inc. (St. Charles, MO); assay sensitivity was 2.9 uIU/mL, mean intraassay coefficient of variation (CV) was 4.0%, and mean interassay CV was 3.5%.

Fasting sera were analyzed for concentrations of SHBG, DHEA-S, T, A, PRL, TSH, 17-HP, LH, FSH, total cholesterol, HDL-C, TG, and free fatty acids (FFA). Measurement of SHBG was obtained after sera were diluted 1:101 and assayed in duplicate 25 uL aliquots using an immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX); assay sensitivity was 6.5 nmol/L, intraassay CV was 7.5%, and interassay CV was 6.5%. A spreadsheet-based program acquired from Stephen J. Winters (Department of Medicine, University of Louisville; Louisville, Kentucky), founded on the method of Södergard et al. (34), was used for the calculation of free T (pM/L). This algorithm is based upon the concentrations of total T, albumin, and SHBG, the binding capacity of SHBG, and the association constants of T for albumin and SHBG. The DHEA-S, T, A4, PRL, TSH, and 17-HP were measured by direct RIA, using commercially available kits (DHEA-S, T and TSH from Diagnostic Products Corp., Los Angeles, CA; A4, PRL, and 17-HP from Diagnostic Systems Laboratories, Webster, TX). LH and FSH were measured by immunoradiometric assay (kits acquired from Diagnostic Products Corp., Los Angeles, CA). The intra- and interassay CVs for the DHEA-S assay were 8.1% and 4.2%; for T, they were 2.5% and 5.7%; for A4, they were 5.2% and 8.0%; for PRL, they were 6.7% and 5.4%, for TSH, they were 1.4% and 2.8%, and for 17-HP, they were 1.4% and 2.1%. Intraassay CVs for the LH and FSH assays were 2.6% and 3.5%, respectively, and the interassay CVs were 2.6% and 7.6%, respectively.

Triglyceride and cholesterol were measured enzymatically, using commercially available kits from Johnson & Johnson Clinical Diagnostics (Rochester, NY) and HDL-C was separated using a dextran sulfate and magnesium chloride precipitation. The FFA were assayed with “NEFA-C” reagents acquired from Wako Diagnostics (Richmond, VA). The assay was modified to accommodate a reduced sample volume (10 μL), and use of a microplate reader for measurement of optical density at 550 nm. Mean intra- and interassay CVs for FFA were 7.4% and 3.7%, respectively. The Friedewald formula was used to calculate low-density lipoprotein cholesterol (LDL-C) when TG concentrations <400 (35). Two subjects had TG concentrations >400; LDL-C was not available on these subjects.

Sample Size and Power Calculations

Sample size for this study was based on published data regarding changes in insulin area under the curve and SHBG with troglitazone treatment among women with PCOS (36). Thus, sample size was not necessarily adequate for detecting changes in all outcomes of interest. For example, a sample size of 11 had 50% power to detect as significant the observed difference in change in serum TG of 50 mg/dL between Low-CHO and STD diets.

Data Analysis

Descriptive statistics for dietary and biochemical variables are presented as mean ± SD. Mixed models repeated measures analysis, assuming an unstructured covariance matrix, was used to examine differences among visits (baseline, MUFA, STD, Low CHO), and differences among changes from baseline with treatment for the MUFA, STD, and Low CHO diets. The Tukey post hoc test was used to determine the specific differences between pairs of means following the visits, and pairs of mean changes. Pearson partial correlation analyses were used to determine the relationships between body composition measures and metabolic outcomes after adjustment for race (African-American, Caucasian), which contributes to variance in body fat distribution, Si, and AIRg (37, 38); thus, only African-American and Caucasian subjects were included in the correlation analyses (n = 9). To ensure normality of distribution, metabolic variables were log transformed before analysis. All statistical tests were two-tailed and were performed using a significance level of 5%. All statistical analyses were performed using the SAS software package (version 9.0; SAS Institute, Inc., Cary, NC).

RESULTS

Population Demographics

We recruited 15 subjects with PCOS, ages 19 – 42 years old, with a body mass index (BMI) of 24–37 kg/m^2. Four subjects did not complete the study; two subjects had scheduling conflicts, one wanted to become pregnant, and one chose to resume taking oral contraceptives. Descriptive statistics of the 11 subjects comprising the study population are given in Table 2. No subject presented with clinical evidence of acanthosis nigricans. Two of the subjects were classified as current smokers. One subject reported smoking >10 cigarettes per day for 16 years, and the other reported smoking 6–10 cigarettes per day for 21 years.

Subjects consumed each dietary treatment for a period of at least 16 days. In two cases, treatment was extended to 17 and 19 days due to illness (fever) and phlebotomy complications. Two subjects completed diet order regimen 1, four subjects completed diet order regimen 2, and 5 subjects completed diet order regimen 3. Mean weight change for all subjects during the MUFA, Low CHO, and STD diets was −0.1 (± 0.9 kg), −0.9 (± 1.4 kg), and −0.1 (± 1.0 kg), respectively. Recorded weights were missing for one subject during the STD diet (n = 10).

Endocrine and Metabolic Characteristics at Baseline and Following Each Dietary Intervention

Dietary treatment significantly affected concentrations of fasting insulin, cholesterol, FFA, and AIRg, but circulating concentrations of the reproductive hormones were not significantly affected by the intervention. Fasting insulin following the Low CHO diet tended to be lower than that at baseline (P=.05; Table 3) and following the STD diet (P=.07). The AIRg following the Low CHO diet tended to be lower than AIRg following the MUFA diet (P=.09). Neither DI nor Si differed with treatment. Total cholesterol differed with treatment (P<.05), tending to be lower following the Low CHO diet relative to the STD diet (P=.05). A significant treatment effect occurred for FFA (P<.05); concentrations of FFA were significantly lower at baseline compared with concentrations following the MUFA and Low CHO diets (P<.05 for both). Baseline concentrations of Total T, free T, DHEAS, SHBG, LH, and FSH were not significantly different from their respective concentrations following any of the treatments.

Change from Baseline in Endocrine and Metabolic Measures

Dietary treatment resulted in changes in concentrations of fasting insulin, AIRg, cholesterol, free T, and A from their respective baseline measures (P≤.05; Table 4). The decreases in fasting insulin and cholesterol were greater following the Low CHO diet than following the STD diet (P<.05 for both). The change in AIRg following the Low CHO diet (−189.1 ± 499.9 uIU/mL × 10 min) tended to differ from that following the MUFA diet (91.2 ± 548.4 uIU/mL × 10 min; P=.05). The change in A4 following the STD diet (−0.1 ± 0.4 ng/mL) differed significantly from that following the MUFA diet (0.1 ± 0.4 ng/mL; P<.05). In addition, the change in mean body weight during the Low CHO dietary intervention was significantly greater than that for the MUFA dietary intervention (P<.05), and tended to be greater than that for the STD dietary intervention (P=.07).

Changes in fasting insulin following the MUFA and Low CHO dietary treatments were significantly correlated with changes in the lipid profile. Following the MUFA diet, the decrease in fasting insulin was associated with the decrease in TG (r = 0.71, P<.05). Following the Low CHO diet, the decrease in fasting insulin was associated with the

increase in FFA (r = −0.65, $P<.05$). The association between the decrease in fasting insulin and the decrease in TG following the STD diet approached significance (r = 0.58, $P=.06$).

Correlation Coefficients among Endocrine and Metabolic Outcomes

Free T was inversely associated with Si at baseline ($P= .09$), and following the MUFA ($P<.05$), STD ($P<.05$), and Low CHO ($P=.09$) diets. Significant correlations were observed between SHBG and Si at baseline ($P<.05$) and following the Low CHO ($P<.05$) diet, and a similar trend was observed following the MUFA and STD diet. In addition, an inverse relationship between SHBG and fasting insulin was detected following the STD and Low CHO diets ($P<.05$ for both). Positive relationships were observed between TG, cholesterol, and FFA, and fasting insulin, following the MUFA and STD diets. Neither HDL-C nor LDL-C was related to Si, fasting insulin, or AIRg.

Correlation Coefficients between Body Composition and Metabolic Characteristics

At baseline, abdominal skinfold was significantly related to fasting insulin ($P<.05$) and AIRg ($P<.05$). The sum of four skinfolds was significantly related to fasting insulin ($P<.05$), and the positive association with AIRg approached significance ($P=.09$). Abdominal skinfold was inversely related to insulin sensitivity ($P<.05$), as was the sum of four skinfolds ($P<.05$).

DISCUSSION

The primary purpose of this study was to determine whether eucaloric diets enriched in MUFA or reduced in carbohydrate, relative to a “standard” ADA diet, could improve the androgen profile and/or insulin sensitivity in women with PCOS. Our major finding was that dietary intervention had a significant impact on our outcomes of interest, such that the Low CHO diet tended to decrease fasting insulin and AIRg in the PCOS population. Because elevated insulin is thought to contribute to the endocrine abnormalities in PCOS, a reduction in insulin would be expected to ultimately result in an improved endocrine profile.

Adherence to the Low CHO diet for a period of 16 days influenced fasting insulin and AIRg. In contrast, there was no treatment affect on Si, DI, or fasting glucose, although the lowest glucose concentrations were observed following the Low CHO diet. It is possible that the short length of the dietary intervention was insufficient with respect to change in Si; thus, a longer dietary intervention may be necessary to show effects on Si. The decrease in both fasting insulin and AIRg in response to the Low CHO diet may have been a direct result of the lower carbohydrate content of the Low CHO diet, which would result in lower insulin secretion. Nuttall et al. demonstrated in healthy men and women that insulin secretion following a meal is governed by the amount of carbohydrate consumed (39). However, we cannot rule out the possibility that changes in insulin clearance contributed to changes in AIRg with treatment.

Although the Low CHO diet had a relatively high PUFA content (17%), it is unlikely that this component would have affected insulin secretion. A high PUFA diet previously has been observed to increase fasting glucose and AUC glucose among women with PCOS (20). However, we did not see an elevation in glucose following this intervention arm. The difference between studies may have been due to the higher MUFA or fiber content of our diet.

We hypothesized that a eucaloric diet enriched with MUFA or low in carbohydrate would decrease insulin concentrations, and this in turn, would decrease androgen concentrations. Free T concentrations are reported to decline significantly in PCOS subjects following weight loss and the accompanying decrease in insulin concentrations (40). In the present

study, we did not observe a “treatment” effect on free T; however, free T was lower following the Low CHO diet, and there was a trend for the change in free T from baseline to differ among treatments (P=.05). Perhaps with a greater sample size, free T may have differed significantly among treatments. In addition, we observed a significant difference in the change in A4 from baseline to that following the MUFA and STD diets. Synthesis of A4 is stimulated by insulin in the ovarian stroma of women with hyperandrogenism (6), and circulating concentrations of A4 are reported to correlate with basal insulin concentrations in PCOS subjects (41). In the present study, however, change in A4 did not parallel change in insulin.

Despite significant changes in insulin with treatment, we did not observe treatment effects on LH, FSH, total T, or DHEA-S. We did not expect several of these hormones to change with treatment. For example, LH concentrations are not correlated with insulin concentrations (42), and therefore may not be affected by a decrease in insulin. In a previous study involving subjects with PCOS, reduction in insulin associated with moderate weight loss did not alter A or DHEA-S (9). However, T synthesis is stimulated by insulin in the ovarian stroma of hyperandrogenic women (6), and circulating concentrations are significantly correlated with basal insulin concentrations in PCOS subjects (41). Perhaps the modest reduction in insulin in the present study was insufficient to alter T.

The intervention had several effects on the lipid profile. Although an overall treatment effect was not detected for TG, mean circulating TG concentrations were lowest following the Low CHO diet. Triglycerides significantly increase in response to eucaloric High CHO diets (55%–60% energy) within 2 weeks (16, 43). Therefore, if the diets used in the present study affected TG, our 16-day intervention should have been of sufficient duration to detect a change. Likewise, there was no treatment effect on HDL-C. The results of this study agree with a previous report that HDL-C concentrations do not change significantly following a 2-week low CHO eucaloric diet (17).

Significant associations between measures of Si, fasting insulin, and various hormones and lipids were observed at baseline and following each dietary intervention. Cross-sectionally, SHBG was inversely related to both free T and fasting insulin at all visits. These relationships were expected, given that SHBG binds to T with high affinity, thereby reducing circulating concentrations of free T (44). The inverse association between SHBG and insulin reflects the negative influence of insulin on SHBG synthesis (45, 46). Similarly, Si was positively associated with SHBG at all visits, which implies that subjects with greater Si had lower insulin, and consequently higher SHBG.

During the course of the intervention, the decrease in fasting insulin that occurred across all dietary treatments was associated with a decrease in TG. Because insulin stimulates hepatic TG synthesis (47), it is likely that the intervention reduced circulating TG by decreasing circulating insulin. These results suggest that dietary intervention to lower insulin among the PCOS subject population may reduce risk for cardiovascular disease. The decrease in insulin also was associated with an elevation in FFA, which presumably reflected the attenuation of the antilipolytic effect of insulin (48). However, because TG also decreased in conjunction with the decrease in insulin, it appears that the additional FFA were not directed toward TG synthesis. Thus, the decrease in fasting insulin observed with the dietary interventions was associated, in general, with an improved metabolic profile.

Correlation analyses indicated that anthropometric measures were associated with fasting insulin, AIRg, and Si. Abdominal skinfold was positively associated with fasting insulin and AIRg, and inversely associated with Si. The sum of four skinfolds, including the subscapular, suprailiac, bicep, and the tricep skinfold, also exhibited a positive association

with fasting insulin and AIRg, and an inverse association with Si. In contrast, neither total body fat by DXA nor abdominal fat by CT scan was correlated with insulin outcome variables. These results suggest that subcutaneous fat distribution, assessed using multiple sites, is associated with metabolic abnormalities within this population.

The major strength of the present study was the utilization of three carefully controlled dietary interventions. The use of eucaloric diets limited the degree to which changes in body weight affected the outcomes. Limitations of the study included the small sample size, the potential effect of diet treatment order, the short intervention period, absence of information on the menstrual cycles, and absence of assessment of dietary intake before baseline testing and during the washout periods. Furthermore, change in body weight was not entered as a covariate in any of the statistical models due to limitations related to sample size and power.

The significant results observed in the present study contrast with the lack of effect on metabolic or endocrine outcomes of a previous study among obese women with PCOS involving 1-month hypocaloric high protein or high carbohydrate diets (49). Differences between studies may relate to the energy balance status of the subjects (i.e., weight-maintenance vs. weight loss); to the degree of dietary control (i.e., provision of food in the present study); or to the inclusion of a control diet in the present study. However, it is also possible that the small decrease in body weight following the Low CHO diet in the present study reflected a state of negative energy balance and contributed to the observed reduction in fasting insulin. Additionally, the subjects of the present study had a lower mean BMI, perhaps indicating that they were more sensitive to dietary manipulation than the obese women in the earlier study.

In summary, results from this study suggest that a eucaloric Low CHO diet, which was relatively low in carbohydrate (43%) and cholesterol, high in fiber, and comprised of 45% fat (18% monounsaturated fat and <8% saturated fat), improved the metabolic profile of women with PCOS within 16 days. This information may allow clinicians to modify treatment regimens to allow for dietary management. In addition, utilizing this Low CHO diet in conjunction with a reduced calorie, weight loss regimen may produce additional favorable results in overweight and obese PCOS subjects.

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TABLE 1

Average dietary composition of standard, MUFA, and Low CHO diets from 4-day menu.

Macronutrients	STD	MUFA	Low CHO
Energy (kcals)	2,000	2,006	2,014
CHO (% kcals)	56	55	43
Protein (% kcals)	16	15	15
Total fat (% kcals)	31	33	45
SFA (% kcals)	7	7	8
PUFA (% kcals)	10	6	17
MUFA (% kcals)	13	17	18
Cholesterol (mg)	115	108	83
Trans FA (g)	3	5	4
Total fiber (g)	27	24	29

Note: STD = standard diet; CHO = carbohydrate; SFA = saturated fatty acids; PUFA = polyunsaturated fatty acids; MUFA = monounsaturated fatty acids; Trans FA = trans fatty acids.

TABLE 2

Descriptive characteristics of the PCOS population (n = 11).

	Mean ± SD	Range
Age (y)	33 ± 6	20–38
BMI (kg/m^2)	30.0 ± 3.7	23.3–35.5
Weight (kg)	80.5 ± 9.7	63.6–94.0
mF-G score[a]	11 ± 8	3–30
Waist circumference (cm)	92.9 ± 10.2	71.5–106.2
Hip circumference (cm)	107.0 ± 7.4	96.0–112.3
WHR	0.87 ± 0.08	0.70–0.97
Abdominal skinfold (mm)	32.6 ± 11.4	17.0–50.0
Saggital diameter (cm)	26.3 ± 3.4	20.2–30.7
Sum of 4 skinfolds (mm)[b]	106.8 ± 29.3	66.0–146.0
Fat mass (kg)	32.7 ± 8.7	20.6–43.7
Trunk fat mass (kg)	17.2 ± 5.2	9.5–25.7
IAAT (cm^2)	111.4 ± 52.5	42.2–202.8
SAAT (cm^2)	382.9 ± 134.4	216.5–582.4

Note: PCOS = polycystic ovary syndrome; BMI = body mass index; WHR = waist-to-hip ratio; IAAT = intraabdominal adipose tissue; SAAT = subcutaneous abdominal adipose tissue.

[a] mF-G score is the hirsutism score assessed by the modified Ferriman-Gallwey method (Hatch, et al. [23]).

[b] Sum of 4 skinfolds = biceps + triceps + subscapular + suprailiac.

TABLE 3

Metabolic characteristics of the PCOS population at baseline and following each diet (mean ± SD).

	Baseline	MUFA	STD	Low CHO	Model *P*
I_o (μIU/mL)	20.6 ± 7.8[a]	17.8 ± 7.5	17.5 ± 7.2[a]	14.3 ± 8.2[a]	.03
G_o (mg/dL)	87.2 ± 6.6	83.0 ± 4.0	84.7 ± 7.3	80.5 ± 5.4	.10
Si ($\times 10^{-4}$ min^{-1}/(uIU/mL))	1.9 ± 1.7	1.9 ± 1.6	1.9 ± 1.7	2.1 ± 1.9	.94
AIRg (uIU/mL × 10 minutes)	1234.7 ± 1036.4	1325.8 ± 890.6[a]	1096.4 ± 781.3	1045.6 ± 876.8[a]	.04
Disposition index	1406.4 ± 869.8	1544.2 ± 858.1	1516.4 ± 1987.5	1412.3 ± 939.4	.50
TG (mg/dL)	157.0 ± 161.8	185.6 ± 225.0	188.6 ± 230.4	138.2 ± 151.1	.19
FFA (mEq/L)	0.5 ± 0.1[b]	0.7 ± 0.2[b]	0.6 ± 0.3	0.7 ± 0.2[b]	.01
Cholesterol (mg/dL)	166.7 ± 47.8	164.4 ± 59.5	165.4 ± 54.1[a]	148.6 ± 47.1[a]	.01
HDL-C (mg/dL)	37.6 ± 10.3	33.8 ± 7.5	35.2 ± 12.5	33.1 ± 7.5	.27
LDL-C (mg/dL)[c]	94.8 ± 29.6	92.7 ± 40.0	91.2 ± 32.9	85.1 ± 33.8	.23
T (ng/dL)	59.4 ± 48.5	59.0 ± 43.5	55.2 ± 42.9	56.2 ± 32.6	.74
Free T (pM/L)	37.3 ± 41.5	39.1 ± 33.1	35.7 ± 34.5	34.0 ± 24.5	.10
A (ng/mL)	1.5 ± 0.5	1.6 ± 0.4	1.4 ± 0.4	1.4 ± 0.5	.07
DHEAS (ug/dL)	157.6 ± 102.2	153.1 ± 85.6	144.1 ± 84.5	171.4 ± 123.5	.26
SHBG (nmol/L)	71.8 ± 29.5	58.8 ± 26.9	63.7 ± 28.7	68.9 ± 34.8	.11
LH (mlU/mL)	3.4 ± 2.1	5.1 ± 2.7	4.5 ± 2.5	6.4 ± 4.7	.18
FSH (mlU/mL)	3.4 ± 1.6	4.7 ± 1.3	3.8 ± 1.3	4.8 ± 1.5	.12

Note: PCOS = polycystic ovary syndrome; MUFA = monounsaturated fatty acids; STD = standard diet; CHO = carbohydrates; I_O = fasting insulin; G_O = fasting glucose; Si = insulin sensitivity; AIRg = acute insulin response to glucose; TG = triglycerides; FFA = free fatty acids; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; T = total testosterone; A_4 = androstenedione; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

[a] *P*=.05–.09 between groups with like symbol.

[b] *P*<.05 among groups with like symbol.

[c] n = 9.

TABLE 4

Change from baseline in metabolic characteristics (mean ± SD).

	MUFA	STD	Low CHO	*P* value
I_o (μIU/mL)	−2.8 ± 5.1	−3.1 ± 6.1[b]	−6.3 ± 9.3[b]	.05
G_o (mg/dL)	−4.2 ± 6.8	−2.5 ± 5.8	−6.7 ± 8.2	.28
Si ($\times 10^{-4}$ min^{-1}/(ulU/mL))	−0.1 ± 0.7	−0.0 ± 1.1	0.1 ± 0.8	.84
AIRg (ulU/mL × 10 minutes)	91.2 ± 548.4[a]	−138.3 ± 479.9	−189.1 ± 499.9[a]	.04
Disposition index	137.8 ± 461.0	110.0 ± 1821.3	6.0 ± 918.6	.38
TG (mg/dL)	28.6 ± 105.2	31.6 ± 76.0	−18.8 ± 73.2	.11
FFA (mEq/L)	0.2 ± 0.2	0.1 ± 0.2	0.2 ± 0.2	.12
Cholesterol (mg/dL)	−2.4 ± 22.1	−1.4 ± 14.5[b]	−18.1 ± 25.7[b]	.03
HDL-C (mg/dL)	−3.7 ± 9.9	−2.4 ± 7.4	−4.5 ± 7.7	.78
LDL-C (mg/dL)[c]	−2.1 ± 13.8	−3.6 ± 9.1	−9.7 ± 14.6	.22
T (ng/dL)	−0.3 ± 18.1	−4.2 ± 16.9	−3.2 ± 26.0	.55
Free T (pM/L)	1.8 ± 12.8	−1.6 ± 15.4	−3.3 ± 18.7	.05
A (ng/mL)	0.1 ± 0.4[b]	−0.1 ± 0.4[b]	−0.1 ± 0.3	.03
DHEAS (ug/dL)	−4.5 ± 68.0	−13.5 ± 25.0	13.8 ± 38.8	.17
SHBG (nmol/L)	−13.0 ± 16.8	−8.1 ± 14.9	−2.9 ± 9.7	.42
LH (mlU/mL)	1.7 ± 2.2	1.1 ± 2.5	3.1 ± 5.4	.38
FSH (mlU/mL)	1.3 ± 1.5	0.3 ± 1.4	1.4 ± 1.9	.09

I_O = fasting insulin; G_O = fasting glucose; Si = insulin sensitivity; AIRg = acute insulin response to glucose; TG = triglycerides; FFA = free fatty acids; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; T = total testesterone; A_4 = androstenedione; DHEAS = dehydroepiandrsterone sulfate; SHBG = sex hormone binding globulin; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

[a] P=.05–.09 between groups by post-hoc analysis.

[b] P<.05 between groups by post hoc analysis.

[c] n = 9.