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Substituting Poly and Mono-unsaturated Fat for Dietary Carbohydrate Reduces Hyperinsulinemia in Women with Polycystic Ovary Syndrome

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Abstract

Objective: Hyperinsulinemia is a prevalent feature of Polycystic Ovary Syndrome (PCOS), contributing to metabolic and reproductive manifestations of the syndrome. Weight loss reduces hyperinsulinemia but weight regain is the norm, thus preventing long-term benefits. In the absence of weight loss, replacement of dietary carbohydrate (CHO) with mono/polyunsaturated fat reduces ambient insulin concentrations in non-PCOS subjects. The current study evaluated whether this dietary intervention could ameliorate hyperinsulinemia in women with PCOS.

Design/Setting/Patients: Obese women with PCOS (BMI 39 ± 7 kg/m2) and insulin resistance completed a crossover study (Stanford University Clinical Research Center) comparing two isocaloric diets, prepared by research dietitians, containing 60% CHO/25% fat versus 40% CHO/45% fat (both 15% protein and ≤ 7% saturated fat). After 3 weeks on each diet, day-long glucose, insulin, and fasting lipid/lipoproteins were measured.

Results: Day-long glucose did not differ according to diet. Day-long insulin concentrations were substantially (30%) and significantly lower on the low-CHO/higher fat diet. Beneficial changes in lipid profile were also observed.

Conclusions: Replacement of dietary CHO with mono/polyunsaturated fat yields clinically important reductions in day-long insulin concentrations, without adversely affecting lipid profile in obese, insulin-resistant women with PCOS. This simple and safe dietary intervention may constitute an important treatment for PCOS.

Keywords: Insulin; Insulin-resistant; Diet; Carbohydrate; Obesity

Abbreviation:

PCOS: Polycystic Ovary Syndrome

Introduction

Polycystic Ovary Syndrome (PCOS), present in 6-10% of reproductive-aged women, is the most common endocrinopathy in this population and contributes to decreased fertility [1-4], dyslipidemia [5,6], and markedly increased risk of type 2 diabetes [7,8]. It is now understood that approximately 75% of these patients are insulin resistant (IR) and/or hyperinsulinemic [9], and are even more IR than BMI-matched non-PCOS controls [10]. High insulin concentrations are considered to play a major role in the pathophysiology of PCOS, contributing to both hyperandrogenism and oligomenorrhea/infertility [10]. Elevated insulin concentrations contribute to hirsutism and anovulation by augmenting LH secretion by the pituitary gland [11], reducing synthesis of SHBG by the liver [12], and acting synergistically with LH on ovarian theca cells to stimulate testosterone synthesis [1]. Hyperinsulinemia and insulin resistance also potentiate the maladaptive cardiac risk profile [13] that occurs in PCOS, including fasting and postprandial hypertriglyceridemia [14], decreased high density lipoprotein cholesterol (HDL-C) [14], increased plasma plasminogen activator inhibitor [9], decreased fibrinolytic capacity [15], low-grade systemic inflammation [16], endothelial dysfunction [17], and increased risk for atherosclerotic disease [18]. Thus, lowering ambient insulin concentrations in women with PCOS may have multiple beneficial effects.

Lowering insulin concentrations with metformin [19,20], thiazolidinediones [21,22], and dietary weight loss [23] have been associated with decreased androgen concentrations, increased ovulation and pregnancy, and decreased plasma triglycerides in insulin resistant women with PCOS. While metformin is frequently used to treat PCOS, it is not a true insulin sensitizer, and thiazolidinediones, while effective in reducing insulin resistance and ambient insulin concentrations [21], cause weight gain, may increase risk of cardiovascular events [24], potentiate osteoporosis [25], fluid retention [26], and are not approved for use in pregnancy. Dietary weight loss, the first line intervention, is safe and can reduce ambient insulin concentrations by 30% [23], but is infrequently sustained [27], and thus long-term benefits are rarely realized.

Among IR individuals without PCOS, isocaloric moderately-low CHO diets enriched in mono-and polyunsaturated fats have been shown to lower day-long insulin concentrations and reduce fasting and postprandial triglyceride concentrations [28,29]. There are very limited data on the use of this type of diet in women with PCOS, who, due to marked insulin resistance, stand to benefit from this macronutrient composition with dramatic insulin lowering. Two dietary weight loss

studies that substituted protein for CHO showed no difference according to macronutrients [30,31], but the effect of weight loss or substitution of protein for CHO may have overridden any benefit from CHO restriction per se in lowering insulin concentrations. Two eucaloric studies with crossover design comparing moderate variations in dietary CHO (55% vs 40%), with mono/polyunsaturated fat substitution, showed significant reduction in fasting insulin after 3-8 weeks [32,33]. Day-long insulin response to replacement of dietary CHO with fat in the eucaloric state has not yet been reported in women with PCOS. If moderate restriction in dietary CHO could ameliorate the pathologic manifestations of PCOS via reduction in hyperinsulinemia, this low-cost, safe treatment would have potential to become a first-line intervention in insulin-resistant women with PCOS, even in the absence of long term weight loss.

Subjects and Methods

The study group consisted of six healthy premenopausal female volunteers with PCOS who responded to an advertisement in the local newspaper. Potential volunteers were screened at the Clinical and Translational Research Unit (CTRU) with a medical history, physical examination, and basic laboratory measurements. PCOS was defined according to 1990 National Institute of Child Health and Human Development (NICHD) consensus criteria on the basis of oligomenorrhea or amenorrhea (≤ 8 menses/year or ≥ 5 days between bleeding episodes), clinical (hirsutism) or laboratory evidence of hyperandrogenism (serum testerosterone or calculated free testosterone above the upper limit of the normal reference range), and exclusion of pregnancy, hyperprolactinemia, thyroid dysfunction, and other hyperandrogenic disorders including Cushing's syndrome and congenital adrenal hyperplasia. Subjects were required to be premenopausal, overweight, nondiabetic, defined as fasting plasma glucose <126 mg/dL, and IR, defined by a Steady-State Plasma Glucose (SSPG) concentration >180 mg/dL (see below). Subjects were required to be free of major organ disease, weight stable for 3 or more months, and not taking weight loss or antidiabetic medications, and to be <40 yrs of age. All subjects gave written informed consent and the study protocol was approved by the Stanford Human Subjects Review Board.

Insulin sensitivity was quantified by the modified insulin suppression test as previously described [28,34] and validated [35]. Briefly, subjects are brought into the CTRU after an overnight fast, and intravenous catheters are placed in both arms. Somatostatin (250 μg/hr), insulin (25 mU/m2/min), and glucose (240 mg/m2/min) are then infused into one arm over 180 minutes. Blood samples are collected from the opposite arm at 10-minute intervals from 150 to 180 minutes when subjects have reached steady state for both insulin and glucose. The four values obtained from 150 to 180 minutes are averaged and considered to represent the SSPG and insulin SSPI concentrations. Since the glucose infusion rate is kept constant among all study subjects, and the SSPI is by design the same in all subjects, the SSPG value represents the relative efficacy of insulin in inducing disposal of a glucose load in each subject: a higher SSPG value is indicative of greater insulin resistance. Our lab has previously determined that an SSPG value of 180 mg/dL represents the cutoff point for the top 40% of the nondiabetic population [36], and this was therefore used as our definition of insulin resistance.

Subjects were assigned, in random order by using a random number generator, to one of two 3-week, eucaloric diets, varying in composition of CHO and mono/polyunsaturated fat, with a two week washout period between diets. One diet contained 40% CHO, 15% protein, and 45% fat, while the alternate diet contained 60% CHO, 15% protein, and 25% fat. Both diets contained ≤ 7% saturated fat, a ratio of polyunsaturated to monounsaturated fat of 1.0, 200 mg Cholesterol, and 20 g fiber. The CHO content of both diets consisted of starches and sugars, primarily from fruits and vegetables. The glycemic index and the ratio of complex to simple CHO were similar in both diets. The Harris-Benedict equation [37] was used to estimate each volunteer's basal energy expenditure, and an activity factor was added to estimate total daily caloric requirement (basal energy expenditure x 1.3-1.55, depending on each subject's level of physical activity). To enhance compliance with the macronutrient composition and eucaloric requirements of the diet, all food was prepared in the Stanford CTRU kitchen, and consisted of a 3-day menu rotation meeting the assigned macronutrient composition and calculated daily caloric requirements. Subjects were scheduled to visit the CTRU twice weekly to pick up their prepared meals and snacks, obtain body weight, return empty food containers and be interviewed to confirm complete consumption. All subjects consented to consume 100% of food provided, and to consume no other food or beverages except water, black tea or coffee or diet soda during the diet phases of the protocol.

At the end of each dietary phase subjects were admitted to the CTRU for determination of their day-long plasma glucose and insulin concentrations in response to breakfast and lunch in an 8-hour meal profile test. During this test, they were given test meals congruent with their assigned diet, containing as percent of total calories, 15% protein, and either 40% CHO and 45% fat, or 60% CHO and 25% fat. Test meals were given at 8 AM and noon (20% and 40% of calculated daily caloric requirement, respectively), and blood was drawn at hourly intervals before and after the test meals from 8 AM to 4 PM. For statistical analyses, day-long insulin and glucose concentrations were calculated via the trapezoidal method as the area under the curve (AUC) of the values for the nine time points. Fasting blood was obtained for measurement of lipid and lipoprotein concentrations as previously described [38-40]. After completion of the first diet, subjects entered a 2-week washout phase, following which they began the second study diet. After 3 weeks on the second diet they again completed the metabolic testing described above.

Data are presented as a mean + standard deviation (SD). Paired Student's t-tests were used to compare the metabolic response at the end of each dietary period versus baseline values. Triglycerides were log-transformed for statistical analysis. P-values <0.05 were considered statistically significant.

Results

The study subjects had a mean ± SD age of 30 ± 7 yrs, BMI 39 ± 7 kg/m2, and were all Caucasian. Mean SSPG was 268 ± 15 mg/dL, consistent with insulin resistance. Body weight was NS different at the completion of each dietary phase, as shown in Table 1.

Also shown in Table 1 are the area under the curve glucose (AUC glucose) and insulin (AUC insulin) obtained during the 8-hr meal profile, and fasting plasma total cholesterol, triglyceride, HDL-C, and LDL-C (cholesterol) concentrations at the completion of each dietary phase. AUC glucose did not differ significantly according to diet.

However, AUC insulin concentrations were 30% lower on the low-CHO/fat-enriched diet (450 ± 140 vs 644 ± 174 μU/mL 8h, p=0.02), with significant differences at several individual time points (hours 1, 4,5,6).

Fasting plasma total cholesterol, triglyceride, and HDL-C concentrations did not differ significantly between diets, and LDL-C was significantly lower on the low-CHO/fat-enriched diet. AUC insulin concentrations by the hour are shown in Figure 1, which clearly demonstrates greater excursions in insulin following both breakfast and lunch on the higher CHO diet.

Variable	Dietary phase[a]		Difference	P[b]
	40% CHO	60% CHO		
Weight (kg)	103.5 ± 18.9	103.9 ± 18.8	0.4 ± 0.5	0.1
AUCglucose (mg/dL)	4101 ± 1326	3621 ± 891	480 ± 1289	0.4
AUCinsulin (uU/mL)	450 ± 140	644 ± 174	194 ± 148	0.02
Cholesterol (mg/dL)	175 ± 32	195 ± 44	20 ± 29	0.14
Triglyceride (mg/dL)	134 ± 73	198 ± 221	64 ± 162	0.37
HDL-C (mg/dL)	40 ± 7	41 ± 7	1 ± 5	0.75
LDL-C (mg/dL)	108 ± 21	116 ± 17	12 ± 60	<0.05

Table 1: Dietary-induced changes in weight and metabolic variables in six obese women with polycystic ovary syndrome. Note: Data are means ± SD. AUC=area under the curve; HDL-C=high density lipoprotein-cholesterol; LDL-C=low density lipoprotein-cholesterol. [a]All measurements were made at the end of each dietary phase. [b]Paired Student's t-tests were used to compare the metabolic response at the end of each dietary period. P-values < 0.05 were considered statistically significant.

Discussion

The results of this study suggest that replacement of dietary CHO with mono-and polyunsaturated fat may represent an important dietary intervention for women with PCOS. Results show clearly that in the absence of weight loss, reducing dietary CHO from 60-40%, with substitution of mono/polyunsaturated fat and no change in protein yields substantial and statistically-significant reductions in hyperinsulinemia in subjects with PCOS. Lowering ambient insulin concentrations is important because hyperinsulinemia has been linked to adverse sequelae of the syndrome such as anovulation/infertility, hyperandrogenism/hirsutism, and adverse lipid profile.

Indeed, the 30% reduction in ambient insulin concentrations observed on the 40% CHO/45% fat/15% protein diet is comparable to insulin lowering achieved with thiazolidinedione treatment in PCOS, which has been demonstrated to reduce hyperandrogenism, increase ovulation/pregnancy, and improve metabolic profile in PCOS [21]. Due to side effects [25,26] cost and concern about adverse effects on fetal skeletal development, alternative treatments to reduce hyperinsulinemia in PCOS are needed. Metformin, which has little effect on ambient insulin concentrations, produces modest decreases in fasting plasma glucose, and triglyceride concentrations, and restores ovulation in some women with PCOS [41-43]. Lifestyle interventions are preferable to pharmacological interventions for the metabolic complications of PCOS due to decreased cost and increased safety, and are considered first-line in PCOS treatment.

The best-studied lifestyle intervention in PCOS is dietary weight loss, which in non-PCOS humans can lower day-long insulin concentrations up to 30%, reduce hypertriglyceridemia and subclinical inflammation, and improve endothelial dysfunction [44,45]. In women with PCOS, dietary weight loss of 7.7 kg has been shown to improve insulin resistance, restore ovulation and improve conception, as well as ameliorate hyperandrogenism, hirsutism, and dyslipidemia [23]. These effects may be mediated by reduction of hyperinsulinemia. Indeed in one study, the degree to which dietary weight loss lowered ambient insulin concentrations correlated with ovulation frequency [30]. Unfortunately, maintenance of weight loss is difficult and recidivism is the rule rather than the exception. Thus, manipulating macronutrient composition without a need for sustained weight loss is an attractive dietary option for long-term management of PCOS.

Surprisingly, despite a plethora of randomized controlled trials showing metabolic benefits of eucaloric CHO reduction in non-PCOS patients, studies adequately addressing this topic in PCOS have not been done. In non-PCOS healthy individuals with or without type 2 diabetes, substitution of dietary CHO with mono/polyunsaturated fats (with protein held constant) significantly reduces day-long insulin and triglyceride concentrations [46,47], and in diabetics, reduces plasma glucose concentration. One of three crossover eucaloric studies quantifying insulin resistance with euglycemic clamp showed improvement in insulin sensitivity on the monounsaturated fat-enriched, moderately-low CHO (40%) diet [48]. Further support for the metabolic benefits of dietary CHO restriction in non-PCOS patients is found in long-term weight loss studies of differing macronutrient composition, in which lower-CHO diets, after controlling for amount of weight loss, yielded greater triglyceride and hemoglobin A1c lowering and less reduction in HDL-C [28,48-53].

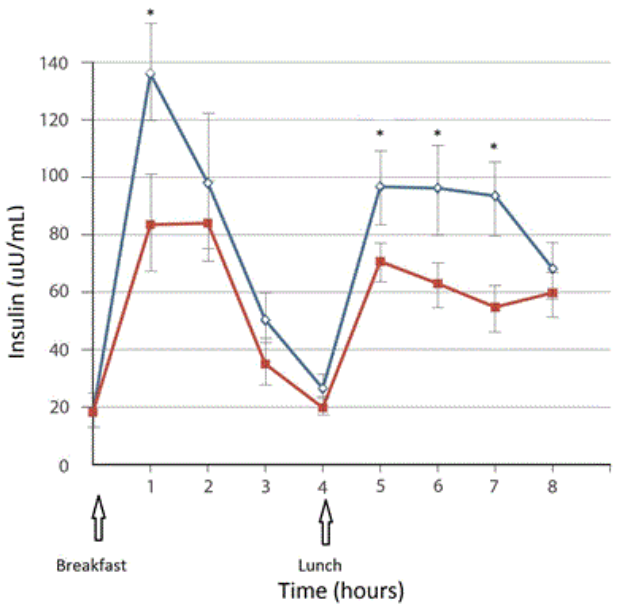

Figure 1: Plasma insulin concentrations during standardized meal profiles (congruent with assigned dietary phase) administered over eight hours in subjects on the 60% (open diamonds) carbohydrate and 40% carbohydrate diets (solid diamonds). Breakfast was administered at time 0 hrs and lunch at time 4 hrs, indicated by arrows. *Indicates p<0.05 for individual time points. Overall p<0.02 for comparison of insulin area-under-the curve (AUC) according to dietary phase.

Studies to address the potential benefits of moderate CHO restriction in PCOS in the absence of weight loss are limited to two small crossover studies, 2-8 weeks in duration, in which, similar to our study, mono- and polyunsaturated fats replaced dietary CHO (40 versus 55% CHO with protein held constant at 15 or 18%) [32,33]. Both showed significant reductions in fasting insulin following the lower CHO dietary phase, but day-long insulin was not measured. One further showed that free androgens decreased in association with degree of insulin lowering [32]. In contrast, two weight loss studies in which dietary CHO was replaced with protein showed no difference in insulin AUC response between dietary interventions, possibly due to overriding benefit of weight loss or insulin-stimulation by dietary protein. One weight loss study of 45 women randomized to a diet with either 55% or 40% carbohydrate for 16 weeks further showed that free androgen index and HDL-C improved to a greater degree on the lower CHO diet [30]. Our results extend those of the prior studies by demonstrating clinically-important reductions in day-long insulin in the absence of weight loss with a moderately-lower CHO diet enriched in mono- and polyunsaturated fat. This diet was associated with a favorable lipid profile and while we did not measure ovulation or androgens, we would expect these measures to improve with longer utilization based on prior studies demonstrating correlations between insulin lowering and these measures. In our subjects, glucoses were normal, and did not change significantly as a function of diet, but in PCOS patients with type 2 diabetes, a lower CHO diet might reduce glycemic levels as well, based on studies in non-PCOS type 2 diabetic patients [47].

It is important to note that in the current study, the increase in dietary fat did not increase in total or LDL-C. In fact, LDL-C was significantly reduced on the higher fat/lower CHO diet. In the current study, which included only 6 subjects, this finding must be interpreted with caution. Prior studies in the eucaloric state have shown that higher fat/lower CHO diets are associated with increased total LDL-C [54]. Differential findings in our study versus others may be due to strict control of saturated fat, maintained at <7% in the current study in which meals were prepared by study dietitians, whereas in other studies of longer duration and home preparation of meals, subjects may have increased consumption of saturated fat. In studies in non-PCOS individuals, substitution of dietary CHO with mono and polyunsaturated fats leads to reduction in triglyceride and apolipoprotein B (Apo B) concentrations, reduction in small dense LDL mass, lowering of total: HDL cholesterol ratio, and increased LDL particle diameter [55]. Indeed, this change in lipid profile would have been expected in the current study: while the magnitude of decrease in fasting plasma triglyceride concentration on the higher fat/lower CHO diet was substantial, the typical variability observed with triglyceride concentrations coupled with the small sample size likely contributed to lack of statistical significance. Future studies on diet in PCOS comparing CHO and fat substitutions will require larger subject numbers and would benefit from day-long triglyceride measurement and analysis of Apo B and LDL particle size.

Reproductive manifestations of PCOS including ovulation, serum androgens, and clinical hirsutism, were not assessed in the current study due to its small size and relatively short duration. Given the positive results in reduction of day-long insulin concentrations, however, a longer and larger trial, powered to detect changes in free androgen and ovulation frequency would be of great interest, since hyperinsulinemia potentiates androgen production by theca cells and reduction in sex hormone binding globulin concentrations [1], and augments adrenal androgen production [56]. Indeed, prior studies in PCOS have shown ovulation induction by other interventions that reduce insulin concentrations such as weight loss and/or thiazolidinedione treatment [21-23]. Further research is indicated to verify whether reduction of ambient day-long insulin concentrations by replacing dietary CHO with mono- and polyunsaturated fat is capable of long-term clinical metabolic and reproductive benefits in women with PCOS.

Conclusion

We have highlighted a potential dietary intervention that in the absence of weight loss produces clinically-meaningful reductions in ambient insulin concentrations in women with PCOS. Specifically, moderate reductions in dietary CHO to 40% of total daily calories with replacement by mono and polyunsaturated fat to comprise 45% of total daily calories may be considered a relatively non-insulinogenic diet in IR women with PCOS. This can be accomplished in the absence of adverse changes in lipid/lipoproteins. Given the high recidivism rates following dietary weight loss, it is useful to identify a non-extreme diet that is amenable to long-term use and yields health benefits in the absence of sustained weight loss. While further studies are indicated to determine whether long-term adoption of this diet can improve hyperinsulinemia-related clinical sequelae of PCOS, given the clear benefit, low cost, relative ease of use, and lack of side effects, the current data suggest that this diet should be considered a first line therapeutic intervention for hyperinsulinemic women with PCOS.

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NCT00186459.

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