Relation of nutrients and hormones in polycystic ovary syndrome1–3

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ABSTRACT
Background: Insulin resistance, infertility, and hirsutism, common characteristics of polycystic ovary syndrome (PCOS), improve with even modest weight loss. Optimal dietary treatment for PCOS is not known.

Objective: We compared the effects of acute protein administration with those of glucose challenges on hormones related to obesity and insulin resistance (ie, cortisol and insulin), hirsutism [ie, dehyd tropeandosterone (DHEA) and androstenedione], and hunger (ie, ghrelin).

Design: Patients with PCOS (n = 28; aged 26 ± 2 y) were tested with a 5-h oral-glucose-tolerance test (OGTT) and a euvo lemic, euenergetic protein challenge.

Results: Glucose ingestion caused larger fluctuations in blood glucose and more hyperinsulinemia than did protein (P < 0.01, overall treatment-by-time interaction). During the protein challenge, cortisol and DHEA declined over 5 h. During OGTT, cortisol and DHEA increased after the third hour and began to show significant divergence from protein from the fourth hour (P ≤ 0.01). During OGTT, 18 patients who had a blood glucose nadir of <69 mg/dL had elevated cortisol (baseline: 10.4 ± 0.4; nadir: 5.9 ± 0.1; peak: 12.7 ± 0.9 µg/dL) and DHEA (baseline: 15.6 ± 1.3; nadir: 11.2 ± 1.0; peak: 24.6 ± 1.6 ng/mL) (P < 0.01), whereas the remaining 10 patients with a glucose nadir of 76 ± 2 mg/dL had no increase in adrenal steroids. Both glucose and protein suppressed ghrelin (from 935 ± 57 to 777 ± 51 pg/mL and from 948 ± 60 to 816 ± 61 pg/mL, respectively). After glucose ingestion, ghrelin returned to baseline by 4 h and increased to 1094 ± 135 pg/mL at 5 h. After the protein challenge, ghrelin remained below the baseline (872 ± 60 pg/mL) even at 5 h. The overall treatment effect was highly significant (P < 0.0001).

Conclusions: Glucose ingestion caused significantly more hyperinsulinemia than did protein, and it stimulated cortisol and DHEA. Protein intake suppressed ghrelin significantly longer than did glucose, which suggested a prolonged sati etogenic effect. These findings provide mechanistic support for increasing protein intake and restricting the simple sugar intake in a PCOS diet. Am J Clin Nutr 2007;85:688–94.

KEY WORDS Polycystic ovary syndrome, PCOS, whey protein, adrenal steroids, ghrelin

INTRODUCTION
Polycystic ovary syndrome (PCOS) affects 6% of women; in the United States, ≈6.8 million women have PCOS. The cardinal features of PCOS are androgen excess, ovarian dysfunction, and infertility (1). Most patients with PCOS are obese and insulin resistant; almost 50% of them meet the criteria of the metabolic syndrome (2, 3) as defined by the National Cholesterol Education Program Adult Treatment Panel III (4). Their risk of type 2 diabetes is significantly increased (1). Gestational diabetes may also be more common in PCOS (5–7), although the evidence is not conclusive (8).

It is important to recognize that even modest amounts of weight loss improve all of the manifestations of PCOS: weight loss decreases insulin resistance, serum androgen concentrations, ovarian size, and the number of ovarian cysts; it increases ovulation and fertility; and it improves the concentrations of plasma lipids (9–11). Despite the importance of weight loss, the optimal dietary treatment for PCOS is not known. High-protein diets are being promoted (12) because of their beneficial effects on satiety (13, 14), lean body mass (15–17), weight maintenance (18, 19), and lipid markers (10). High-fat diets are being used to reduce insulin response (20).

These desirable outcomes may partly be due to concomitant decreases in dietary carbohydrates, glycemic index, and glycemic load (21–23). Unfortunately, the mechanisms underlying the differential effects of nutrients are not known. Thus, the overall aim of this research was to compare the acute hormonal effects of eucaloric, euvo lemic glucose with those of protein ingestion, with a long-term goal of defining the optimal dietary treatment strategies for persons with PCOS. We focused on the hormones influencing clinical features of PCOS. These hormones included insulin, adrenal steroids, cortisol—which causes insulin resistance, dyslipidemia, central obesity, and hypertension (24)—and dehyd roepiandosterone (DHEA) and androstenedione—which constitute the substrates for peripheral testosterone synthesis (25). The hunger signal ghrelin was

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measured to compare the potential effects of glucose with those of protein on satiety (26, 27).

Changes in these hormones were compared by using the oral-glucose-tolerance test (OGTT) and a eucaloric, euvolemic whey protein challenge. OGTT was used because it is well standardized to identify insulin resistance, impaired glucose tolerance, and diabetes (28). Whey protein was used because it is considered a “fast protein” that does not coagulate in the stomach and that rapidly increases plasma concentrations of amino acids, exerts an insulinotropic effect, and reduces postprandial glycemia in healthy subjects and persons with type 2 diabetes (13, 29).

Although standard OGTT is conducted over 2 h, this test was extended to 5 h because, in a previous study in patients with PCOS, we observed that several participants experienced symptoms suggestive of hypoglycemia after a 2-h OGTT (30). Therefore, a 5-h OGTT was used to document postprandial hypoglycemia, if it occurred (31).

The 5-h testing also allowed us to determine the changes in ghrelin during a period that is similar to the usual interval between meals. Previously published reports showed changes in ghrelin in 2–3 h, which is a shorter time than the usual between-meal interval (32–34).

SUBJECTS AND METHODS

Subjects

Twenty-eight patients with PCOS aged 18–45 y and with a body mass index (in kg/m²) of 25–40 were recruited. All participants were examined by the principal investigator (SEK-K), who is the director of the PCOS program at the Medical Center of the University of California, Davis. The participants fulfilled the Rotterdam criteria for PCOS (35) by having ovarian dysfunction, as evidenced by amenorrhea (no periods for >6 mo) or oligomenorrhea (<8 periods/y, cycle length >45 d, or both), and clinical (hirsutism) or laboratory evidence for hyperandrogenemia (total testosterone >54 ng/dL or free testosterone >9.2 pg/mL). Ultrasound evaluation of the ovarian structure was not carried out because most ultrasound reports do not provide the detailed information required by the Rotterdam criteria (presence of ≥12 follicles in each ovary, with each follicle measuring 2–9 mm in diameter; increased ovarian volume > 10 mL; or a combination, although the subjective appearance of PCO is not adequate).

Adult-onset 21-hydroxylase deficiency was ruled out by measuring basal concentrations of 17-hydroxyprogesterone in the morning. Although this measurement is routinely made during the follicular phase of the cycle, most patients had oligomenorrhea or amenorrhea, and, thus, the follicular phase could not be defined. The mean basal concentration of 17-hydroxyprogesterone was 53.0 ± 3.4 ng/dL; the highest value was 106.0 ng/dL. Because all of the basal morning concentrations of 17-hydroxyprogesterone were <200 ng/dL, none of the participants required a cortisyn-stimulation test. Prolactinoma was ruled out by measuring the serum prolactin concentration, and androgen-secreting tumors were ruled out based on serum testosterone (36–38). Cushing’s disease was ruled out clinically because the Rotterdam criteria require biochemical testing only when there is clinical suspicion. Patients were excluded if they used oral contraceptives, antiandrogen medications, insulin sensitizers, d-chiro inositol, or any other medications or supplements that affect weight or insulin sensitivity during the preceding 2 mo; have impaired glucose tolerance, diabetes mellitus, untreated hypothyroidism, and any other systemic illness such as renal, hepatic, and gastrointestinal disease; smoke; or drink > 2 alcoholic drinks/wk.

Written informed consent was obtained from all subjects. The study protocol was approved by the Human Subjects Committee of the University of California, Davis.

Oral-glucose-tolerance and protein challenge tests

The OGTT and protein challenge test studies were performed at the General Clinical Research Center of the University of California, Davis. The subjects were following their habitual diets and were weight stable. Their average carbohydrate intake was 255 g/d before testing. The studies were initiated between 0700 and 0800, after an overnight fast. An intravenous catheter was placed in the forearm. The OGTT and the protein challenge test were performed 7–10 d apart, in random order. For the OGTT, the participants ingested 75 g glucose (Glucola; Alleghance Healthcare Corp, McGaw Park, IL) at 0 min. For the protein challenge, they ingested 75 g 98% pure, intact whey protein isolate containing no carbohydrate (Glanbia Foods, Twin Falls, ID). The glucose and the protein drinks were euvolemic and eucaloric. The blood samples were obtained at baseline and every 30 min thereafter for 5 h. The subjects remained supine in bed throughout the testing to avoid confounding effects of physical activity on blood glucose. The samples for glucose were collected in sodium fluoride–containing tubes on ice. Other samples were collected in either serum separation tubes or tubes containing EDTA or heparin. The nursing staffers who collected the samples and the laboratory personnel who carried out the assays were blinded. Before data analysis, a glucose concentration <69 mg/dL was defined as hypoglycemia.

Laboratory assays

Glucose was measured with the use of the hexokinase method in a clinical chemistry analyzer (Poly-Chem System, Cortlandt Manor, NY). Insulin and total ghrelin concentrations were measured with the use of radioimmunoassay kits (Linco Research Inc, St Charles, MO); the CVs were 8.2% and 7%, respectively. Cortisol, DHEA, and androstenedione were measured with the use of radioimmunoassay kits (Diagnostic System Laboratories, Webster, TX); the CVs were 5.3%, 7.8%, and 4.3%, respectively.

Statistical analysis

Statistical analysis was programmed with the R 2.1.1 language and environment (The R Foundation for Statistical Computing, Auckland University, Auckland, New Zealand; Internet: http://www.r-project.org/). Data were presented as means ± SEs, and P < 0.05 was considered significant. Linear mixed models with random intercept were used as a primary tool for the statistical analysis. The random intercept was shared by measurement on the same subject to take into account the subject-specific effect and to adjust for correlated error structure of observations. Time was treated as a categorical factor to allow enough flexibility in reproducing the complex longitudinal patterns observed in marker measurements. Interaction terms of type of challenge (glucose compared with protein) with time were introduced to address the effect at each particular time point as well as overall. Symbolically, the model can be represented in the form of Marker ~ intercept + main effect (time) + interaction effect (time × treatment)/subject, where intercept models mean marker
value at time zero before treatment is applied. Main effect (time) models the mean marker response over time under the OGTT challenge. Interaction effect (time × treatment) models the difference in mean marker response by time point between protein challenge and OGTT. All terms are adjusted for the subject-specific effect that contributes to between-subject variability of measurements and a correlation of measurements over time. Validity of the model was assessed with the use of residual plots. Testing for treatment differences was done for every time point as well as overall; the latter testing involved testing all coefficients in the treatment by block of time. A model-based analysis that is resistant to type I error inflation resulting from multiple comparisons was used. All model-based hypothesis testing was based on the so-called Wald test, which is equivalent to the likelihood ratio test for large samples. Akaike information criterion was monitored to prevent inflated type I error and over-fitting.

As a descriptive analysis, the area under the curve (AUC) summary measure was computed for each subject. A paired t test was used to assess the treatment effect on the AUC. AUC summary measures were computed with the use of the Sympon quadrature method. In numeric computation of the AUC integrals, missing values were treated according to “last observation carried forward” principle. AUC analysis was performed for descriptive and interpretation purposes, and no adjustment was made for multicomparsions.

Baseline, lowest, and peak values for cortisol and DHEA were defined on the basis of the longitudinal trajectory of the marker in each subject. The baseline was the value obtained at 0 min before the administration of glucose or protein challenge; the nadir was the lowest value; the peak was the highest value after the nadir. These definitions were adopted before (and without the knowledge of the results of) the statistical analysis. A statistical linear mixed model was then applied to such clinically assessed measurements.

RESULTS

Clinical characteristics of the participants

The mean age was 26 ± 2 y, the weight was 97.5 ± 4.1 kg, and the body mass index was 35.9 ± 1.2. The mean serum concentrations were 0.84 ± 0.12 ng/mL for testosterone, 37.2 ± 6.5 nmol/L for sex hormone–binding globulin, and 215 ± 32 ng/mL for DHEA sulfate (DHEAS). (The reference values in 19 women with regular menstrual cycles were 0.27 ± 0.03 ng/mL for testosterone, 68.5 ± 6.6 mmol/L for sex hormone–binding globulin; and 116 ± 24 ng/mL for DHEAS.) The mean morning 17-hydroxyprogesterone concentration was 53.0 ± 3.4 ng/dL, and the highest value was 106.0 ng/dL.

Changes in plasma glucose and insulin

Twenty-eight subjects completed the 5-h OGTT, and 23 subjects completed both the 5-h OGTT and the protein challenge test (Figure 1). The order of the tests was randomized, and no effect of the treatment order on test results was observed. Protein challenge did not significantly affect plasma glucose (baseline: 97 ± 2 mg/dL; peak at 30 min: 103 ± 3 mg/dL; nadir at 240 min: 91 ± 2 mg/dL; P = 0.30–0.75 when glucose concentrations at different time points were compared with the baseline concentration). During the OGTT, plasma glucose concentrations were higher during the first 3 h but below the baseline afterward (baseline: 98 ± 2 mg/dL; peak at 60 min: 156 ± 8 mg/dL; nadir at 240 min: 76 ± 2 mg/dL). Except t = 0 (no treatment at this point) and t = 180 min (crossing point), a significant treatment effect was observed at all time points (P < 0.0001). Although whey protein also increased insulin secretion (as is consistent with the known stimulatory effects of amino acids), plasma insulin concentrations were significantly higher after glucose ingestion. For example, the peak insulin concentrations were 132.1 ± 12.5 μU/mL at 30 min after glucose ingestion and 97.2 ± 12.2 μU/mL at 60 min after protein (P < 0.001). Overall, a highly significant difference was observed in insulin concentrations by treatment (P < 0.0001, model-based). However, treatment effects were not significant; comparisons of insulin concentrations at different time points showed no significant treatment effect. As seen in Figure 1, it was evident that the insulin response during the first 2.5 h was responsible for the overall significance; when glucose concentrations were above the baseline; the glucose group had significantly higher insulin concentrations than did the protein group. Because of the crossing curves, overall comparison of insulin AUC showed no significant difference: some of the
Changes in androstenedione also showed similar trends. During the OGTT, the average androstenedione values were $1.77 \pm 0.20, 1.46 \pm 0.10, 1.39 \pm 0.13, 1.56 \pm 0.11, 1.58 \pm 0.12$, and $1.64 \pm 0.10$ ng/mL at 0 min and 1, 2, 3, 4, and 5 h, respectively. During the protein challenge test, these values were $1.53 \pm 0.16, 1.23 \pm 0.10, 1.18 \pm 0.14, 1.24 \pm 0.13, 1.32 \pm 0.15$, and $1.40 \pm 0.13$ ng/mL, respectively. The protein challenge showed consistently lower concentrations of androstenedione than did OGTT. However, the overall treatment effect was not significant ($P = 0.221$, model-based).

Next, we examined whether the increases in adrenal steroids were related to the changes in plasma glucose. Before data analysis, we defined the hypoglycemic group as subjects with a glucose nadir of $<69$ mg/dL during OGTT. We contrasted baseline and peak measurements against the nadir and introduced an interaction term to allow testing for the peak response. The hypoglycemic group ($n = 18$) had larger increases in cortisol and DHEA than did the nonhypoglycemic group ($n = 10$). Cortisol concentrations were $10.1 \pm 0.5 \mu$g/dL at baseline, $5.9 \pm 0.1 \mu$g/dL at nadir, and $12.7 \pm 0.9 \mu$g/dL at peak in the hypoglycemic group and $10.4 \pm 0.4 \mu$g/dL at baseline, $6.1 \pm 0.1 \mu$g/dL at nadir, and $7.8 \pm 1.0 \mu$g/dL at peak in the nonhypoglycemic group ($P < 0.01$). The DHEA concentrations were $15.6 \pm 1.3$ ng/mL at baseline, $11.2 \pm 1.0$ ng/mL at nadir, and $24.6 \pm 1.6$ ng/mL at peak in the hypoglycemic group and $13.2 \pm 3.3$ ng/mL at baseline, $9.1 \pm 1.2$ ng/mL at nadir, and $11.9 \pm 1.9$ ng/mL at peak in the nonhypoglycemic group ($P < 0.01$). The hypoglycemic group also had a greater increase in androstenedione from the nadir to the peak than did the nonhypoglycemic group ($P = 0.06$).

Characteristics of the hypoglycemic group were that these 18 subjects were significantly less obese (94.1 $\pm 5.0$ kg) and had significantly lower fasting plasma glucose (91 $\pm 2$ mg/dL) than did the remaining 10 subjects (weight: 106.8 $\pm 4.1$ kg, $P = 0.07$; fasting glucose 106 $\pm 4$ mg/dL, $P < 0.001$). No difference was observed between fasting insulin concentrations in the 2 groups.

Changes in plasma ghrelin

Both protein and glucose ingestions suppressed ghrelin (from $935 \pm 57$ to $777 \pm 51$ pg/mL and from $948 \pm 60$ to $816 \pm 61$ pg/mL, respectively). After glucose ingestion, ghrelin returned to baseline by 4 h and increased to $1094 \pm 135$ pg/mL at 5 h. After the protein challenge, ghrelin remained below the baseline even at 5 h ($872 \pm 60$ pg/mL) (Figure 3). Significant treatment differences were found during the 3–5-h period, and the overall treatment effect was highly significant ($P < 0.0001$). The ghrelin response during OGTT was not related to the presence or absence of hypoglycemia (data not shown).

DISCUSSION

This study showed that glucose ingestion caused larger fluctuations in blood glucose and more hyperinsulinemia than did the intact whey protein. Hyperinsulinemia contributes to obesity by stimulating lipoprotein lipase and fatty acid synthase. The lipoprotein lipase enzyme releases the fatty acids from the triacylglycerol-rich lipoproteins, and fatty acid synthase facilitates the storage of fatty acids as triacylglycerol in the adipose tissue. Simultaneously, insulin inhibits the hormone-sensitive lipase, thus interfering with the mobilization of the triacylglycerols stored in the adipose tissue. Hyperinsulinemia also contributes to the other endocrine abnormalities seen in PCOS: insulin
concentrations and DHEA occurred in all the subjects who had blood glucose
novel finding of our study was that the prompt increase in cortisol
injection of insulin to induce an adequate stress response. The
are stored in the intraabdominal fat depots, resulting in central
centrated consumption of sweet and fatty foods (45, 46). Cortisol
contributes to obesity by increasing caloric intake and pref-
erential consumption of sweet and fatty foods (45, 46). Cortisol
increases lipolysis in the adipose tissue and thereby raises the
increased counterregulatory hormones during asymptomatic hy-
diabetes and the report of Solter et al (43, 44) that showed in-
creased counterregulatory hormone secretion with plasma glu-
cose-tolerance test (– – –; n = 28) and protein challenge (––; n = 23).
Differences between responses to the 2 treatments are expressed through
treatment-by-time interaction effect. Overall, the interaction effect is highly
significant (P < 0.001). Key timepoint P values are shown on the graph. All
tests are based on the Wald test performed by using a linear mixed model
applied to all available data.

After ingesting glucose, two-thirds of the patients with PCOS had postprandial hypoglycemia and greater cortisol and DHEA
secretion. Although the protein challenge delivered an identical amount of calories and raised plasma insulin, it did not alter plasma glucose or stimulate adrenal steroids. It is well estab-
lished that hypoglycemia stimulates secretion of pituitary
ACTH, which, in turn, stimulates adrenal steroids (31). In fact,
hypoglycemia is used as endocrine testing to assess the integrity
of the hypothalamic-pituitary-adrenal axis. During this test, the
blood glucose concentration is lowered to <50 mg/dL by an
injection of insulin to induce an adequate stress response. The
novel finding of our study was that the prompt increase in cortisol and DHEA occurred in all the subjects who had blood glucose concentrations < 69 mg/dL during OGTT. This observation was similar to that of the report of Spyer et al (42) that showed increased counterregulatory hormone secretion with plasma glu-
cose concentrations < 67 mg/dL in patients with well-controlled diabetes and the report of Solter et al (43, 44) that showed increased counterregulatory hormones during asymptomatic hy-
poglycemia in obese subjects. The increase in serum cortisol can contribute to the progres-
sion of obesity, insulin resistance, and metabolic syndrome. Cor-
tisol contributes to obesity by increasing caloric intake and pref-
erential consumption of sweet and fatty foods (45, 46). Cortisol
increases lipolysis in the adipose tissue and thereby raises the
concentration of free fatty acids in the circulation. When accom-
panied by hyperinsulinemia, as seen in PCOS, these fatty acids are stored in the intraabdominal fat depots, resulting in central
obesity (47), and are used for triacylglycerol production in the liver, contributing to hyperlipidemia (48). Cortisol increases glu-
cose production by stimulating gluconeogenic enzymes in the
liver (49), and it causes insulin resistance in the muscle. In fact,
effects of cortisol in the muscle may be directly related to the
development of metabolic syndrome (50). Because ≈60% of
patients with PCOS are insulin resistant (51) and 46% of them
manifest the metabolic syndrome (3), nutrient-related postpran-
dial cortisol secretion may have significant consequences in
PCOS.

We also observed increases in adrenal androgens during
OGTT. The increase seen in DHEA was larger than the increase in androstenodione. Similarly, Farah-Eways et al (52) reported that,
after ACTH stimulation, serum DHEA increased by 222%
and androstenodione increased by 31% in patients with PCOS,
whereas DHEA increased by 266% and androstenodione in-
creased by 68% in healthy control women. Although testosterone
is the main excessive androgen in PCOS, depending on patients’
ethnicity, 20–30% of patients with PCOS have high serum con-
centrations of DHEAS (25, 53). Brothers and sisters of the pa-
tients with PCOS also have higher plasma DHEAS concentra-
tions (54, 55). Thus, adrenals can be an important source of
androgens. Although the main adrenal androgens, DHEA and
androstenodione, have minimal direct biological effects, they
constitute the primary substrates for testosterone synthesis in the
peripheral tissues. In PCOS patients, DHEA secretion in re-
sponse to ACTH (56) and the conversion of adrenal androgens to
testosterone by 5α-reductase (57) are increased. It is not yet
known whether nutrient-related postprandial secretion of ad-
renal androgen can contribute to the hyperandrogenemia in
PCOS. Because testosterone has a long half-life, our study
was not designed to address this possibility, and a single
episode of a rise in adrenal steroids occurring during the last
2 h of the OGTT cannot be expected to influence plasma
testosterone concentrations.

Our observations related to ghrelin can be important to the
nutritional management of PCOS. The findings that protein in-
gestion suppressed ghrelin for a longer time than glucose and that
it did not cause a rebound increase are consistent with the recent
report of Blom et al (58) and suggest that protein intake may
prolong satiety. Previous reports indicated that protein intake
neither suppressed nor increased ghrelin concentrations (32–34).
Those studies compared the ingestion of glucose with that of
solid mixed meals or determined the ghrelin response during 2-3
h. We compared glucose and protein in equal weights, volumes,
and calories over a longer period. The protein-induced suppres-
sion of ghrelin was probably due to the increase in insulin. Insulin
is known to suppress ghrelin independent of the changes in glu-
cose concentrations (59, 60). Broglio et al (26) showed that both
oral glucose intake and intravenous insulin administration sup-
pressed ghrelin, although they had opposite effects on plasma
glucose. It is interesting that the same study showed that intra-
venous arginine did not suppress ghrelin, despite increasing in-
sulin. Therefore, the oral route may be necessary for protein-
induced suppression of ghrelin. Alternatively, the intrinsic
properties of proteins may be important. The protein used in this
study, whey protein, does not coagulate in the stomach, increases
plasma concentrations of amino acids rapidly, and may suppress
hunger more effectively (29).
In summary, oral glucose intake caused larger fluctuations in plasma glucose, increased hyperinsulinemia, and stimulated adrenal steroid secretion in patients with PCOS. In addition, glucose intake suppressed the hunger signal ghrelin for a shorter period of time than did protein intake. These acute challenge studies showed that nutrients have significantly different endocrine effects and that protein may be a preferred nutrient over glucose for patients with PCOS. The findings of these acute studies need to be validated with the use of natural foods and carbohydrate-enriched rather than protein-enriched diets. Further research is necessary to determine whether foods with high glycemic load contribute to the progression of obesity, insulin resistance, and hirsutism in obese women. A revision of the manuscript. None of the authors had a personal or financial conflict of interest.

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