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DEHYDROEPIANDROSTERONE SULFATE AND INSULIN RESISTANCE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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Abstract

Objective—We tested the hypothesis that increasing DHEAS levels is associated with improved insulin resistance in patients with PCOS.

Design—Cross-sectional cohort analysis.

Setting—Academic medical center.

Patients—352 women with PCOS.

Interventions—Patients presenting for evaluation of symptoms related to androgen excess were evaluated physically and biochemically through laboratory analysis.

Main Outcome Measures—Circulating DHEAS, total testosterone (TT), free testosterone (FT), sex hormone binding globulin (SHBG), and 17-hydroxyprogesterone (HP) levels, and calculated homeostasis model assessment of insulin resistance (HOMA-IR).

Results—Bivariate analysis indicated that all parameters were associated with HOMA-IR, except HP and age, and confirmed a negative correlation between DHEAS and HOMA-IR. Multivariate analysis indicated that increases in DHEAS, SHBG, HP, and age were associated with decreasing HOMA-IR, while increases in FT, BMI, and WHR were associated with increasing HOMA-IR. In decreasing order of importance, the following variables predicted insulin resistance: Body mass index (BMI) > waist-hip ratio (WHR) > age > DHEAS > FT > SHBG > HP.

Conclusions—DHEAS is negatively correlated to insulin resistance in PCOS, and in our model ranked just behind other well-established predictors including BMI, WHR, and age. Whether this is

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due to a direct beneficial effect on insulin action by adrenal androgens such as DHEA, or whether DHEAS simply reflects the circulating levels of hyperinsulinemia, remains to be determined.

Keywords

Polycystic Ovary Syndrome; PCOS; dehydroepiandrosterone sulfate; DHEAS; insulin resistance; adrenal androgens

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) affects 5–7% of reproductive aged women (1–4). A significant proportion of women with PCOS demonstrate variable degrees of measurable insulin resistance. A recent study reported the prevalence of insulin resistance to be approximately 64% in PCOS (5). The insulin resistance of PCOS results in hyperinsulinemia which, at least in part, stimulates androgen secretion by ovarian theca cells (6–8), and decreases the hepatic synthesis of sex hormone binding globulin (SHBG) (6).

The effect of insulin on the secretion of adrenal androgens, including dehydroepiandrosterone sulfate (DHEA) and its sulfated form, DHEAS, is less clear. In one study, the acute response of DHEAS levels to a physiologic rise in insulin via administration of a 75 gram glucose load in obese and non-obese women with and without PCOS was studied, concluding that acute increases in insulin within the physiologic range did not effect DHEAS levels in any patient group, and thus likely does not play a significant role in the regulation of circulating DHEAS in PCOS or euandrogenic women (9). In contrast, another study evaluated the effect of insulin on adrenal tissue in vitro, and found that in general, insulin increased the production of DHEAS and suppressed DHEA production, although the responses were variable among the adrenal tissue donors (10).

In turn, it is possible that DHEA or DHEAS is associated with improvements glucose production, utilization, and insulin action. Studies have shown that DHEA suppresses the activity and expression of glucose -6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK) decreasing gluconeogenesis (11). DHEA has also been shown to increase glucose uptake in the hepatocytes (as shown with increased uptake of 2-deoxyglucose) and has been reported to increase insulin binding to its own receptor (11,12). Clinically, a negative correlation between DHEAS and insulin resistance in obese females with type 2 diabetes mellitus (DM), but not in non-DM females, has been reported (13). Low DHEAS levels have been associated with coronary artery disease in men (14–16). Although the mechanism underlying this association is unclear, a study of a Japanese population found that a decrease of serum DHEAS levels over a period of time is significantly associated with the development of DM in men (17), suggesting a complex interaction between DHEAS and insulin and the development of cardiovascular disease and DM.

DHEAS levels have also been shown to decrease with age, as does insulin action (18–21). Therefore, decreasing DHEAS levels over time have been postulated to be associated with the age-related increases in insulin resistance. Additionally, postulations have been made that supplementation with oral DHEA which is then converted to DHEAS in the GI tract (namely the small intestine and liver) may actually help with the prevention and treatment of insulin resistance and coronary artery disease (22). Studies have shown improved glucose tolerance and insulin sensitivity with DHEAS supplementation in diabetic rodents (23). The application of these studies in humans may be limited, however, as rodents biologically have very low circulating levels of DHEA and DHEAS, and supplementation was much more supraphysiologic than could be obtained in humans (22).

Given these data, we have hypothesized that increasing DHEAS levels are associated with improved insulin resistance in PCOS. To test this hypothesis, we undertook a cross-sectional cohort analysis of 352 women with PCOS. We should note that while the measurement of insulin resistance can be achieved by dynamic tests such as the euglycemic clamp and the frequently sampled intravenous glucose tolerance test, surrogate measures assessing the basal degree of insulin resistance, such as the homeostasis model assessment (HOMA-IR), are more feasible for use in larger epidemiologic studies such as those undertaken in the present study (24).

MATERIALS AND METHODS

Subjects

Three hundred and fifty-two women with PCOS presenting for evaluation of symptoms potentially related to androgen excess between October 1987 and June 2002 were included. Their data was obtained during the first three visits and maintained in a computerized database (Alpha Four v. 6.0; Alpha Software, Burlington, MA). None of the subjects were premenarchal or postmenopausal, had undergone prior hysterectomy, bilateral oophorectomy or natural menopause, or had been previously diagnosed or were receiving hormonal treatment for at least three months prior to their evaluation. IRB approval was obtained for this study. Dr. Azziz is a consultant for Merck & Co., Pfizer, Procter & Gamble, and Quest Diagnostics.

PCOS was diagnosed by conventional means as described by the National Institute of Child Health and Human Development (NICHD) in April 1990 (25); these criteria were included in the more recent criteria proposed by the European Society for Reproductive Medicine and the American Society for Reproductive Medicine (ASHRE/ASRM) in 2003 (26,27), and by a task force of the Androgen Excess Society in 2006 (28). In brief, PCOS was defined by i) the presence of hyperandrogenemia or clinical hyperandrogenism, ii) oligo-ovulation, and iii) the exclusion of other disorders (25).

Ovulatory dysfunction was defined as a history of intermenstrual intervals greater than 35 days or less than 26 days, or 8 or fewer menstrual cycles in a year, or by a day 22–24 progesterone (P4) levels less than 4 ng/mL in patients with vaginal bleeding intervals of 27–34 days. Clinical hyperandrogenism was defined by hirsutism with a modified Ferriman-Gallwey (mFG) score of greater than 6 (29). Hyperandrogenemia was defined by an androgen value exceeding the 95th percentile of 98 race-matched eumenorrheic control women from the same population as previously reported, including a total testosterone (TT) >88 ng/dL, a free testosterone (FT) > 0.66 ng/dL, or a DHEAS >2750 ng/mL (30). PCOS was diagnosed only after other disorders had been excluded including hyperprolactinemia, thyroid disorders, 21-hydroxylase-deficient non-classical adrenal hyperplasia, Cushing's syndrome and iridizing androgen-secreting neoplasms.

On physical exam, in addition the height, weight, and mFG score, the waist was measured at the narrowest portion of the torso approximately midway between the lower costal margin and the iliac crest, and the hip circumference was measured over the widest portion of the gluteal and greater trochanteric region. The body mass index (BMI) and waist-to-hip ratio (WHR) were then calculated.

Laboratory Analysis

A 30-cc sample of blood was drawn and analyzed for FT and TT, SHBG, and DHEAS; plasma samples were assessed for fasting insulin and glucose levels. The levels of DHEAS and HP were measured by a direct radioimmunoassay (RIA) using a commercially available kit (Diagnostic System Laboratories, Webster, TX). TT was measured by in-house method after

serum extraction, as previously reported (31). The activity of SHBG was determined by equilibrium dialysis and FT was calculated, as previously described (32). Plasma glucose measurements were performed using Ektachem DR slides (Johnson & Johnson Clinical Diagnostics, Rochester, NY), and insulin was measured by RIA (Diagnostic Systems Laboratories).

The HOMA-IR value was calculated, using fasting plasma glucose and insulin concentrations, as follows (33):

$$\text{HOMA} - \text{IR} = \frac{(\text{fasting glucose in mmol/L}) \times (\text{fasting insulin in } \mu\text{IU/mL})}{22.5}$$

Statistical Analysis

Nine potential predictors of insulin resistance were considered including DHEAS, TT, FT, BMI, WHR, SHBG, HP, age, and race. For all of the predictors except BMI, WHR, age, and race, the data distribution was much better approximated by a Gaussian curve on the LOG scale. Thus, for those 5 potential predictors (DHEAS, TT, FT, SHBG, HP), both the original variable and its base 10 log was considered. The log values were found to be much more linearly related to log HOMA-IR and were therefore used as candidates in the regression analyses.

Bivariate associations between the base 10 log of each continuous variable and log HOMA-IR were assessed using both the parametric Pearson correlations and the non parametric rank based Spearman correlations. The simultaneous relation of all 9 potential predictors with HOMA-IR was evaluated using both backward step-down linear regression (using the log scale variables except BMI, WHR, age and race) and by regression tree methods (CART-classification and regression tree). For the multivariate analysis, a significance of $p < 0.16$ retention criterion was used to keep a variable in the model. Mean log HOMA-IR differences across race was assessed with one way analysis of variance.

RESULTS

In the bivariate analysis of the eight continuous variables, all parameters were found to be significantly related to HOMA-IR except HP and age using both Pearson and Spearman correlations (Table 1). As hypothesized, a negative correlation between DHEAS and HOMA-IR was confirmed divaricately (Figure 1). Regarding race, White women were found to have a significantly higher mean HOMA-IR than Black women, despite the absence of difference in BMI between White and Black women.

Our multivariate modeling found that all variables, except TT and race, were simultaneously significantly related to the HOMA-IR value. Higher DHEAS, SHBG, HP and age were associated with a lower HOMA-IR value, while higher FT, BMI, and WHR values were associated with a higher HOMA-IR value. Multivariately, there was no significant difference across the races. The following equation was derived via multivariate regression analysis to predict a patient's HOMA-IR:

$$\begin{aligned} \text{Log HOMA} - \text{IR} = & 1.601 + .0184 \log FT - 0.153 \log DHEAS + 0.0129 \log BMI + 1.335 \log WHR - 0.267 \log SHBG \\ & - 0.079 \log HP - 0.006 \log age \end{aligned}$$

These seven factors (FT, DHEAS, BMI, WHR, SHBG, HP, and age) together accounted for 39% of the variation in log HOMA-IR.

The regression coefficients in the model provide the average rate of change in log HOMA-IR for a one unit change in a given variable, controlling for the other variables. For example, for every one unit increase in log SHBG (which corresponds to a 10 fold increase in SHBG), log HOMA IR decreases by 0.267 log units on average, corresponding to a reduction in HOMA-IR by a factor of $10^{-0.267}$, or 0.540, assuming all other variables are held constant. Thus, for a 10 fold increase in SHBG, HOMA-IR is only 54% as large. Similarly, holding all other variables constant, a one unit increase in log DHEAS is associated with an average reduction in HOMA-IR by a factor of $10^{-0.153}$, or 0.70; thus, for a 10-fold increase in DHEAS, HOMA-IR is only 70% as large.

The regression coefficients of the continuous variables were then standardized to rate of change per standard deviation, which allows the variables to be ordered by importance (Table 2). For example, a one standard deviation change in BMI is associated with a 0.122 unit increase in log HOMA-IR corresponding to a 1.33 fold increase in HOMA-IR, in its original scale. Note that DHEAS was negatively correlated to insulin resistance in patients with PCOS, and in our model ranked just behind other well-established predictors of insulin resistance, including BMI, WHR, and age.

DISCUSSION

We hypothesized that DHEAS levels are negatively correlated to insulin resistance in patients with PCOS. This was confirmed in both our bivariate and multivariate models. Our multivariate regression analysis indicates that, in decreasing order of importance, the following factors all significantly affect HOMA-IR: BMI>WHR>age>DHEAS>FT>SHBG>HP. Given these data, likely a complex interaction between adrenal and possibly ovarian steroidogenesis, body fat content and distribution, and age determines the degree of insulin resistance in PCOS. Whether the inverse relationship of DHEAS levels and insulin resistance is due to a direct beneficial effect on insulin action by adrenal androgens such as DHEA, or whether DHEAS simply reflects the circulating levels of hyperinsulinemia, remains to be determined.

Our study is novel in its evaluation of DHEAS and insulin resistance in PCOS. Our findings are similar to the previously described negative correlation between DHEAS and insulin resistance in obese type 2 DM females (13). Most studies seem to indicate that DHEAS levels decrease with age, corresponding to an increase in insulin resistance as one ages (18–21). This negative correlation between age and DHEAS levels has been described in PCOS patients (34), and was also demonstrated in our PCOS cohort. However, in our study, age was actually negatively correlated to insulin resistance. The difference may be attributed to less severe disease in a woman who first presents for evaluation of PCOS an older rather than younger age.

The negative correlation between DHEAS and insulin resistance could be due to several different mechanisms. DHEA may directly affect insulin action. For example, DHEA decreases gluconeogenesis by suppressing the activity and expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK) (11). DHEA increases glucose uptake in hepatocytes (as shown by the increased uptake of 2-deoxyglucose) and increases insulin binding to its own receptor (11,12). Conversely, elevated circulating levels of glucose or insulin may cause a decrease in DHEAS levels, potentially by glucose or insulin action on the adrenal gland itself (35). Glucose-mediated glucose disposal, or the ability of glucose to control its own production and uptake, has been suggested as a possible mechanism of excess androgens in PCOS (34).

Because this is a cross-sectional study, we were only able to examine the DHEAS level and HOMA-IR at one time-point. A greater effect of DHEAS on insulin resistance and potentially

frank diabetes in PCOS may be found by studying the change in DHEAS over time (17). HOMA-IR has been shown to correlate well to insulin-mediated glucose disposal as assessed by the glucose clamp technique, and is thus a valuable predictor of insulin resistance, although it may be a less accurate measure of insulin action in patients with PCOS (33,36). Therefore, the calculated HOMA-IR in our patient population may not accurately estimate the actual levels of insulin resistance in our patients.

We conclude that DHEAS is negatively correlated to insulin resistance in PCOS. DHEAS, along with BMI, WHR, age, FT, SHBG, and HP all plays a role in determining the degree of insulin resistance in PCOS, as determined by the HOMA-IR measure. The mechanism by which DHEAS affects insulin resistance in PCOS is unknown. Additionally, DHEAS levels, or changes in DHEAS levels over time, could have an important prognostic value in the PCOS patient. Finally, DHEAS is part of a complex process involving adrenal and ovarian steroidogenesis, body fat content and distribution, and age, as demonstrated by our multivariate analysis, and elucidation of the underlying mechanisms will require further study.

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Figure 1.
Graph depicting the relationship of DHEAS and HOMA-IR (bivariate fit of log HOMA-IR by log DHEAS).

Table 1

Correlation of insulin resistance, as measured by HOMA-IR, with various features of PCOS

Variable	Pearson Correlation		Spearman Correlation	
	coefficient	p value	coefficient	p value
Age	0.036	0.4370	0.039	0.4616
BMI	0.500	< 0.0001	0.505	< 0.0001
WHR	0.499	< 0.0001	0.525	< 0.0001
log TT	0.112	0.0139	0.173	0.0011
log FT	0.245	< 0.0001	0.274	< 0.0001
log SHBG	−0.210	0.0011	−0.189	0.0004
log HP	−0.041	0.6631	−0.027	0.6193
log DHEAS	−0.224	< 0.0001	−0.238	< 0.0001

HOMA-IR is the homeostasis model assessment to estimate insulin resistance, BMI is body mass index, WHR is waist to hip ratio, TT is total testosterone, FT is free testosterone, SHBG is sex hormone-binding globulin, and HP is 17-hydroxyprogesterone.

Table 2

Rate of change per standard deviation (SD) in insulin resistance in PCOS, as measured by HOMA-IR, in order of importance

Variable	Standard rate of change per SD	% change per SD
BMI	0.122	+33%
WHR	0.104	+27%
Age	-0.046	-10%
log DHEAS	-0.042	-9%
log FT	0.038	+9%
log SHBG	-0.035	-8%
log HP	-0.024	-5%

HOMA-IR is the homeostasis model assessment to estimate insulin resistance, BMI is body mass index, WHR is waist to hip ratio, FT is free testosterone, SHBG is sex hormone-binding globulin, and HP is 17-hydroxyprogesterone. For example, with a BMI increase of one standard deviation, the insulin resistance, as measured by HOMA-IR, increases by 33%.