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Cardiovascular disease in PCOS is related to severe insulin resistance, not mild.

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The current analysis was initiated to determine whether BMI, serum testosterone levels or magnitude of insulin sensitivity as measured by a gold standard, which predicts the CVD risk in women with PCOS.

A retrospective data-base query was performed to identify patients with PCOS. These patients had on the same day a quantitative measurement of insulin-mediated glucose disposal, a determination of blood pressure, and blood drawn for measurement of serum lipid/lipoprotein and androgen concentrations.

The patients in this study with PCOS were oligovulatory with clinical or biochemical evidence of hyperandrogenism. They had no evidence of thyroid abnormalities ($0.39 < \text{TSH} < 4.0 \mu\text{IU/ml}$); hyperprolactinemia (am fasting prolactin $< 26 \text{ ng/ml}$); hypothalamic pituitary dysfunction or ovarian failure ($1.4 < \text{FSH} < 20 \text{ mIU/ml}$ and estradiol $> 20 \text{ pg/ml}$); ovarian and adrenal androgen-secreting tumors and non-classical congenital adrenal hyperplasia. Subjects were excluded from analysis if they had diabetes mellitus, participated in another research study in the last 30 days, and used hormones or other medications which may affect serum lipids, reproductive or metabolic function within sixty days of study. Exclusion of medications included insulin sensitizing agents, oral hyperglycemics, insulin, anti hypertensives, and oral contraceptives or other steroids.

Insulin-mediated glucose disposal was quantified by a modification of the insulin suppression test (IST) as originally described and validated by our research group (1–3).

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Height and weight were determined with subjects in light clothing and without shoes. Blood pressure was measured on the patients left arm after sitting for at least five minutes. Three measurements one minute apart were averaged to provide a mean systolic and diastolic blood pressure measurement.

Lipid and lipoprotein concentrations were measured in fresh plasma less than 4 hours after being collected. Lipoproteins were analyzed on the Beckman LX 20 analyzer (Beckman Instruments, Fullerton, California). Total cholesterol was determined by a timed endpoint enzymatic method with intra-assay coefficient of variation (CV) of 3% and inter assay CV of 2.5%. Triglycerides (TG) concentration was determined by timed endpoint enzymatic method with intra assay CV of 3% and inter assay CV of 3.5 %. High density lipoprotein cholesterol (HDL-C) concentrations was determined by detergent and timed endpoint enzymatic method with intra assay CV of 3% and inter assay CV of 4.5 %. Low-density lipoprotein cholesterol (LDL-C) concentration was determined by detergent and timed endpoint enzymatic method intra assay CV of 2% and inter assay CV of 3.5 %. Non-HDL-C was calculated by subtracting HDL-C concentration from total cholesterol concentration.

Total testosterone (T) and SHBG were determined by standard clinical EIA at ARUP Laboratories (Salt Lake City, UT, USA), and free T was calculated by that laboratory using the Sodergard equation (17). The intra- assay and inter-assay CV for total T were 3 and 8% respectively. These measurements were available on 45 individuals studied the day of the IST. Thirty-one patients did not have total and free serum T concentrations determined in the Sanford Clinical Laboratory, but had referred to Stanford with values for androgens determined in a variety of outside laboratories. Consequently, the values in these 30 subjects were not included in this analysis.

All statistical analyses were done using the statistical package for social sciences 11.0 (SPSS Inc., Chicago, IL). Continuous variables were evaluated for normal distribution using the Kolmogorov-Smirnov test. All variables tested were normally distributed. Results are reported as mean value $\pm$ standard deviation (SD). In addition to the analysis of continuous variables, the 75 patients were divided into quartiles on the basis of their SSPG concentrations. Demographics, serum androgen levels, blood pressure, and logarithmic conversion of lipid levels for each of these four groups was compared by one way ANOVA and Games-Howel post hoc tests.

To control for the effects of interactions as a cause of significant relationships between age, BMI, serum androgen levels and SSPG levels with the CVD risk factors measured, data were analyzed by partial correlation for relationships while controlling for the other factors. The analysis was performed to determine whether SSPG concentration, age, BMI and serum androgen levels were significant predictors of abnormalities while controlling for the effect of the other variables. Statistical significance was accepted as a two sided $p < 0.05$. Approval from the Stanford University Institutional Review Board had been obtained for collection and analysis of this data. All subjects signed an informed consent document for participation in this research and collection and analysis of the data.

Table 1 presents the demographic and metabolic characteristics of the study population. In an effort to assess the independent association of obesity (BMI), androgen excess (total and free T), and insulin resistance (SSPG concentration) on the CVD risk factors measured, partial correlation coefficients were calculated, in which the relationship between any one of these and a given CVD risk factor was adjusted for differences in the other 3 variables plus age. The results of this analysis are shown in Table 2. The results in Table 2 emphasize the apparent central role played by differences in degree of insulin resistance. These data demonstrate that neither BMI nor total testosterone was significantly related to any of the CVD risk factors when adjusted for the other potential predictors. When controlling for the other variables, BMI, serum total testosterone, serum free testosterone, patient age and magnitude of insulin resistance, it is primarily magnitude of insulin resistance which is associated with 6 of 7 CVD risk factors. Although a significant relationship does exist between serum free testosterone and non-HDL-c ($p=0.03$) and triglyceride levels ($p=0.001$).

Table 3 compares the values of CVD risk factors as a function of the degree of insulin resistance (SSPG concentration) present in each quartile. In general, the higher the SSPG concentrations, the worse the individual CVD risk factors, with the exception of significant increases in total or LDL-C concentrations. It is worth noting that the mean CVD risk profile in the 50 % most insulin sensitive women is well within what would be considered to be normal limits.

Obesity had no independent relationship to any of the CVD risk factors measured; neither MetS components nor concentrations of total cholesterol, LDL-C, or non-HDL-C. However, insulin resistance, as assessed by direct measure of insulin-mediated glucose disposal, was independently associated with all of the CVD risk factors measured, both MetS and non-MetS, with the exception of a relationship with HDL-C ($r=-0.29$, $p=0.07$). As shown in Table 3, in most cases, the more insulin resistant (the higher the SSPG concentration), the more adverse the value of the individual CVD risk factor. The two exceptions to this generalization are total cholesterol and LDL-C concentrations, and this is consistent with the fact that neither of these variables is significantly related to degree of insulin resistance (4).

Not only was the measure of insulin resistance independently correlated with all of the metabolic components of the MetS but also the data in Table 3 demonstrate the dramatic difference in CVD risk association that exists in women with PCOS as a function of degree of insulin resistance. Thus, the 25 % of women who were most insulin sensitive (Quartile I) did not demonstrate any evidence of increased CVD risk, and comparisons with the 25 % of the most insulin resistant women (Quartile IV) are quite revealing. Thus, not all women with PCOS appear to be at increased CVD risk, but the subset who are also insulin resistant present a substantial clinical problem. Earlier studies did not directly measure insulin-mediated glucose disposal, and any adjustments for the role of insulin resistance were performed with surrogate estimates of insulin action. The 50% most insulin sensitive persons with PCOS as a group are not at increased risk of CVD. The relatively enormous degree of metabolic heterogeneity in women with PCOS illustrated in Table 3 leads to the obvious hypothesis that failure to unequivocally demonstrate an increase in incident CVD in women with PCOS is because a substantial portion of these individuals are not insulin resistant.

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Table 1

Demographic and metabolic characteristics of the PCOS population

Variable	Mean $\pm$ SD N=75	Range
Age (Years)	30 $\pm$ 6	18 – 44
BMI (kg/m ²)	34.5 $\pm$ 9.0	18.5 – 69.4
Total T (ng/dl) *	48 $\pm$ 18	15–91
Free T (ng/dl) *	9.9 $\pm$ 4.9	1.3–21.3
SSPG (mg/dl)	188 $\pm$ 87	46–323
SBP (mm Hg)	121 $\pm$ 18	87–184
DBP (mm Hg)	71 $\pm$ 12	49–110
Total cholesterol (mg/dl)	185 $\pm$ 35	124–277
LDL-C (mg/dl)	116 $\pm$ 32	62–207
HDL-C (mg/dl)	49 $\pm$ 15	29–129
Non-HDL-C (mg/dl)	136 $\pm$ 38	55–224
Triglycerides (mg/dl)	116 $\pm$ 69	26–339

*
n=45

SBP= systolic blood pressure, DBP =diastolic blood pressure, LDL-C= low density lipoprotein cholesterol, HDL_C = high density lipoprotein cholesterol, BMI= body mass index, T= testosterone.

Table 2

Partial correlation coefficients between obesity (BMI), Androgens (total and free Testosterone), and insulin resistance (SSPG concentration) and the coronary vascular disease risk factors measured. Individual relationships have been adjusted for the values of the other 3 variables and age.

	BMI	Total T	FREE T	SSPG
SBP	$r=0.13$ $p=0.42$	$r=0.02$ $p=0.93$	$r=-0.10$ $p=0.54$	$r=0.42$ $p=0.008$
DBP	$r=-0.04$ $p=0.81$	$r=0.08$ $p=0.64$	$r=0.001$ $p=0.99$	$r=0.43$ $p=0.007$
Total cholesterol	$r=-0.29$ $p=0.07$	$r=0.19$ $p=0.25$	$r=0.24$ $p=0.14$	$r=0.40$ $p=0.01$
LDL-C	$r=-0.16$ $p=0.35$	$r=0.08$ $p=0.62$	$r=0.10$ $p=0.55$	$r=0.35$ $p=0.03$
HDL-C	$r=0.06$ $p=0.71$	$r=-0.13$ $p=0.41$	$r=-0.27$ $p=0.09$	$r=-0.29$ $p=0.07$
Non-HDL-C	$r=-0.30$ $p=0.06$	$r=0.23$ $p=0.15$	$r=0.34$ $p=0.03$	$r=0.49$ $p=0.002$
Triglycerides	$r=-0.21$ $p=0.21$	$r=0.26$ $p=0.10$	$r=0.50$ $p=0.001$	$r=0.56$ $p=0.0001$

SBP= systolic blood pressure, DBP =diastolic blood pressure, LDL-C= low density lipoprotein cholesterol, HDL_C = high density lipoprotein cholesterol, BMI= body mass index, T= serum testosterone, SSPG= steady state plasma glucose

Table 3

Change in CVD risk factors associated with increasing magnitude of insulin resistance

SSPG Quartile	I (46–107mg/dl)	II (108–191 mg/dl)	III (197–270 mg/dl)	IV (271–312 mg/dl)	p
SBP (mm Hg)	113 ± 3	111 ± 2	121 ± 5	137 ± 4	0.0001
DBP (mm Hg)	67 ± 3	66 ± 2	72 ± 2	79 ± 3	0.0001
Total cholesterol (mg/dl)	172 ± 6	182 ± 9	193 ± 9	191 ± 7	0.21
LDL-C (mg/dl)	103 ± 4	108 ± 9	126 ± 8	121 ± 8	0.12
HDL-C (mg/dl)	57 ± 4	51 ± 2	46 ± 5	40 ± 2	0.0001
Non-HDL-C (mg/dl)	116 ± 5	131 ± 10	148 ± 10	152 ± 7	0.012
Triglycerides (mg/dl)	79 ± 9	92 ± 18	128 ± 14	204 ± 46	0.0001

SBP= systolic blood pressure, DBP =diastolic blood pressure, LDL-C= low density lipoprotein cholesterol, HDL_C = high density lipoprotein cholesterol, SSPG= steady state plasma glucose level.