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Prevalence and Predictors of the Metabolic Syndrome in Women with Polycystic Ovary Syndrome

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Context: Polycystic ovary syndrome (PCOS) and the metabolic syndrome have many features in common and may share the same pathogenesis.

Objective: This study was performed to determine the prevalence and predictors of the metabolic syndrome in PCOS.

Design: The clinical, hormonal, and oral glucose tolerance test results were analyzed in 394 PCOS women who were screened for participation in a multicenter trial to evaluate the effects of troglitazone on ovulation and hirsutism.

Setting: A multicenter clinical trial is presented.

Patients or Other Participants: The subjects were women with PCOS who had or lacked the metabolic syndrome.

Main Outcome Measures: Waist circumference, fasting glucose, high-density lipoprotein cholesterol and triglyceride concentrations, and blood pressure were the main outcome measures.

Results: Twenty-six (6.6%) subjects had diabetes; among the 368 nondiabetics, the prevalence for individual components comprising the metabolic syndrome were: waist circumference greater than 88 cm in 80%, high-density lipoprotein cholesterol less than 50 mg/dl in 66%, triglycerides greater than or equal to 150 mg/dl in 32%, blood pressure greater than or equal to 130/85 mm Hg in 21%, and fasting glucose concentrations greater than or equal to 110 mg/dl in 5%. Three or more of these individual criteria were present in 123 (33.4%) subjects overall. The prevalence of the metabolic syndrome did not differ significantly between racial/ethnic groups. The prevalence of the metabolic syndrome from lowest to highest quartile of free testosterone concentration was 19.8, 31.3, 46.9, and 35.0%, respectively [$P = 0.056$ adjusted for body mass index (BMI)]. None of the 52 women with a BMI less than 27.0 kg/m^2 had the metabolic syndrome; those in the top BMI quartile were 13.7 times more likely (95% confidence interval, 5.7–33.0) to have the metabolic syndrome compared with those in the lowest quartile. Thirty-eight percent of those with the metabolic syndrome had impaired glucose tolerance compared with 19% without the metabolic syndrome ($P < 0.001$).

Conclusions: The metabolic syndrome and its individual components are common in PCOS, particularly among women with the highest insulin levels and BMI. Hyperinsulinemia is a likely common pathogenetic factor for both PCOS and the metabolic syndrome. (***J Clin Endocrinol Metab* 91: 48–53, 2006**)

POLYCYSTIC OVARY SYNDROME (PCOS) is a common condition affecting approximately 5–8% of reproductive aged women in the United States (1). It is characterized by chronic anovulation and hyperandrogenism with variable clinical manifestations that include oligomenorrhea, infertility, hirsutism, and acne (2, 3). Although these manifestations typically provide the impetus to seek medical evaluation, it is the associated complications of PCOS, namely obesity, dyslipidemia, insulin resistance, and less commonly, hypertension that may be more important determinants of overall, long-term health in this population (4–7).

Many of the anthropometric and metabolic abnormalities of PCOS overlap with components of the metabolic syndrome, a clustering of both lipid and nonlipid risk factors that identify individuals at increased risk for coronary heart disease and type 2 diabetes mellitus (8–13). These risk factors include central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hypertension, and elevated fasting plasma glucose concentrations (8).

The present analysis was undertaken to determine both the prevalence and predictors of the metabolic syndrome in a large cohort of women with PCOS defined by uniform criteria. To accomplish this, analyses were performed on data derived from a geographically and ethnically diverse group

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Abbreviations: BMI, Body mass index; CI, confidence interval; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; PCOS, polycystic ovary syndrome.

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of women with PCOS who participated in a large multicenter national trial (14).

Subjects and Methods

Subjects

Anthropometric and metabolic measures were available for 410 women with PCOS who participated in a multicenter study designed to evaluate the effects of troglitazone on ovulation and hirsutism, as previously reported (14). A diagnosis of PCOS required: 1) the presence of chronic ovulatory dysfunction, defined as intermenstrual intervals of 45 d or more or a total of eight or fewer menses per year; 2) hyperandrogenemia, defined as a serum-free testosterone concentration greater than 21.8 pmol/liter, the upper limit of normal defined by the central laboratory used for this study; and 3) the exclusion of other disorders such as nonclassical congenital adrenal hyperplasia, thyroid dysfunction, and hyperprolactinemia.

Other exclusionary criteria included unresolved medical conditions, hysterectomy, and/or oophorectomy, established type 1 or type 2 diabetes mellitus, significant cardiovascular disease, active cancer within the past 5 yr, and participation in another investigational study within the past 30 d. The use of medications known or suspected to affect reproductive or metabolic function within 60 d of study entry was prohibited. This study was approved by and conducted according to the guidelines of the institutional review boards of each of the participating centers. All subjects provided written informed consent.

Each subject had height and weight recorded at the initial visit. While in the supine position, waist circumference was measured at the level of the umbilicus and hip circumference was measured at the level of the pubic symphysis. Blood pressure was measured three times in the same arm after the patient was seated and at rest for a minimum of 15 min. The systolic and diastolic measurements reported represent the mean of the three readings.

Fasting laboratory studies and oral glucose tolerance test

After a 12-h overnight fast, each subject had an oral glucose tolerance test. Glucose and insulin levels were measured at −10 and 0 min and at 30, 60, 90, and 120 min after the oral ingestion of 75 g of dextrose. Fasting blood samples were also obtained for measurement of total testosterone, free testosterone, total cholesterol, HDL cholesterol, and triglycerides. The low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula.

Laboratory analysis

Serum-free testosterone was determined using equilibrium dialysis against a buffer containing tritium-labeled testosterone. Total serum testosterone was measured by RIA after extraction with hexane-ethyl acetate and column chromatography. These assays were performed by Endocrine Sciences, Inc. (Calabasas Hills, CA). Glucose levels were measured by the hexokinase method (747-200; Hitachi, Hialeah, FL), and insulin levels were measured by RIA. Lipid analyses were performed by Medical Research Laboratories, Inc. (Highland Heights, KY). Triglyceride levels were measured using the standard lipase, glycerokinase, glycerol-3-phosphate oxidase, and peroxidase method, and HDL cholesterol was determined by the precipitation and enzymatic method (Hitachi 747).

Statistical analyses

The Student's *t* test and ANOVA were used for between-group comparisons of continuous variables. Between-group differences of categorical variables were evaluated by χ^2 tests. The Cochran-Armitage trend test and logistic regression models were employed to examine the effect of various factors on the risk for the metabolic syndrome. Statistical significance for all analyses was defined as a two-tailed *P* value of less than 0.05. Results are expressed as mean ± SEM. Data analysis was performed using SPSS (SPSS, Inc., Chicago, IL), Stata Version 8 (Stata Corp., College Station, TX), and SAS (SAS Institute, Inc., Cary, NC).

Results

Prevalence of the metabolic syndrome

For the present analyses, complete data were available for 394 (96%) of the 410 women who entered the study. The subjects ranged in age from 18–41 yr; the range in body mass index (BMI) was 19–65 kg/m^2. Twenty-six (6.6%) subjects proved to be diabetic upon oral glucose tolerance testing and were excluded from all subsequent analyses to avoid the confounding effects of the diabetic state on measures that define the metabolic syndrome. Among the remaining 368 women, 123 (33.4%) met criteria for the metabolic syndrome. The prevalence of the metabolic syndrome did not differ significantly between racial/ethnic groups and was evident in 34% of Caucasian, 26% of African-American, 31% of Hispanic, 50% of Asian, and 43% of women with mixed ancestral origin.

Characteristics of women with and without the metabolic syndrome

As shown in Table 1, women with and without the metabolic syndrome were similar in age (29.2 ± 0.5 *vs.* 28.1 ± 0.4 yr) and did not differ significantly in their levels of either total (0.62 ± 0.03 *vs.* 0.63 ± 0.02 ng/ml) or free (41.8 ± 1.6 *vs.* 37.8 ± 1.3 pmol/liter) testosterone, although this was marginally significant ($P = 0.063$). As expected, compared with women who did not meet criteria for the metabolic syndrome, those with the metabolic syndrome had a significantly higher BMI (40.4 ± 0.7 *vs.* 33.8 ± 0.5 kg/m^2), waist circumference (112.7 ± 1.5 *vs.* 97.9 ± 1.2 cm), waist to hip ratio (0.91 ± 0.01 *vs.* 0.86 ± 0.01), systolic (123.6 ± 1.2 *vs.* 111.5 ± 0.8 mm Hg) and diastolic (78.3 ± 0.8 *vs.* 71.6 ± 0.6 mm Hg) blood pressures. In addition, the fasting glucose (95.3 ± 0.9 *vs.* 90.2 ± 0.5 mg/dl) and insulin (32.2 ± 2.5 *vs.* 17.3 ± 0.8 μU/ml) concentrations were significantly higher in those with the metabolic syndrome. Finally, SHBG levels were significantly lower in PCOS women with the metabolic syndrome compared with those PCOS women without the metabolic syndrome (32.8 ± 1.4 *vs.* 43.8 ± 1.4 nM; $P < 0.05$).

TABLE 1. Comparison of PCOS women with and without the metabolic syndrome

	With metabolic syndrome	Without metabolic syndrome
No. (%) of subjects	123 (33.4)	245 (66.6)
Age (yr)	29.2 ± 0.5	28.1 ± 0.4
BMI (kg/m^2)	40.4 ± 0.7	33.8 ± 0.5[a]
Waist circumference (cm)	112.7 ± 1.5	97.9 ± 1.2[a]
Waist to hip ratio	0.91 ± 0.01	0.86 ± 0.01[a]
Systolic blood pressure (mm Hg)	123.6 ± 1.2	111.5 ± 0.8[a]
Diastolic blood pressure (mm Hg)	78.3 ± 0.8	71.6 ± 0.6[a]
Fasting glucose (mg/dl)	95.3 ± 0.9	90.2 ± 0.5[a]
Fasting insulin (μU/ml)	32.2 ± 2.5	17.3 ± 0.8[a]
Total cholesterol (mg/dl)	202.7 ± 3.0	183.1 ± 2.2[a]
HDL cholesterol (mg/dl)	38.4 ± 0.7	50.7 ± 0.8[a]
Triglycerides (mg/dl)	203.7 ± 8.0	103.8 ± 2.5[a]
LDL cholesterol (mg/dl)	125.0 ± 2.8	111.6 ± 2.0[a]
Total testosterone (ng/ml)	0.62 ± 0.03	0.63 ± 0.02
SHBG (nM)	32.8 ± 1.4	43.8 ± 1.4[a]
Free testosterone (pmol/liter)	41.8 ± 1.6	37.8 ± 1.3

Data are mean ± SEM.
[a] $P < 0.001$.

After adjustment for the effects of either BMI or the degree of insulin resistance, however, this difference was no longer significant.

In eight subjects with the metabolic syndrome, the triglyceride level exceeded 400 mg/dl, thus precluding use of the Friedewald formula for calculation of LDL levels. Even with the elimination of these subjects, those with the metabolic syndrome had levels of total cholesterol (202.7 ± 3.0 *vs.* 183.1 ± 2.2 mg/dl), triglycerides (203.7 ± 8 *vs.* 103.8 ± 2.5 mg/dl), and LDL cholesterol (125.0 ± 2.8 *vs.* 111.6 ± 2.0 mg/dl) that were significantly higher than those in women without the metabolic syndrome. Finally, HDL cholesterol levels were significantly lower in women who met criteria for the metabolic syndrome (38.4 ± 0.7 *vs.* 50.7 ± 0.8 mg/dl).

Prevalence of individual components of the metabolic syndrome (Table 2)

Within the entire cohort of subjects, the waist circumference exceeded 88 cm in 80%, HDL cholesterol was less than 50 mg/dl in 66%, triglycerides were 150 mg/dl or greater in 32%, whereas blood pressure was 130/85 mm Hg or greater in 21% and fasting glucose concentrations were 110 mg/dl or greater in 5%.

An elevated waist circumference was seen with significantly higher frequency in African-Americans compared with the rest of the sample ($P < 0.01$). There was also a significant association between increased triglycerides and race ($P = 0.018$) with African-Americans having the lowest prevalence (22%).

Positive and negative predictive values for the individual components of the metabolic syndrome

Each individual component of the metabolic syndrome was assessed to determine its ability to predict the presence (positive predictive value) or absence (negative predictive value) of the requisite number of remaining components needed to establish the diagnosis of the metabolic syndrome (Table 3).

The presence of a fasting plasma glucose of 110 mg/dl or greater had the highest positive predictive value (84%) for the presence of the metabolic syndrome (Fig. 1A). However, only 19 subjects met this criterion. Elevated triglycerides, a much more common finding, also had a high-positive predictive value for the presence of the metabolic syndrome: 98 (83%) of the 118 women with a triglyceride level greater than or equal to 150 mg/dl had at least two additional components of the metabolic syndrome (Fig. 1B). Seventy-eight percent of those with a systolic blood pressure greater than or equal to 130 mm Hg (Fig. 1C) or diastolic blood pressure greater than or equal to 85 mm Hg (Fig. 1D) met criteria for the metabolic syndrome. By contrast, only 48% of women with an HDL cholesterol less than 50 mg/dl (Fig. 1E) and 41% of women with a waist circumference greater than 88 cm (Fig. 1F) met criteria for the metabolic syndrome.

TABLE 2. Prevalence (%) of individual components of the metabolic syndrome in PCOS women

Components of the metabolic syndrome	Caucasian	African-American	Other[a]	Overall
Waist circumference > 88 cm	79	94[b]	65	80
HDL cholesterol < 50 mg/dl	67	58	70	66
Triglycerides ≥ 150 mg/dl	32	22	52	32
Hypertension ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic	22	20	15	21
Fasting glucose ≥ 110 mg/dl	4	12	3	5

[a] Hispanic, Asian, and others of mixed ancestry.
[b] $P < 0.01$ compared to Caucasian and other groups.

Waist circumference (Fig. 1F), HDL cholesterol (Fig. 1E), and triglycerides (Fig. 1B) each had high-negative predictive values. Of the 74 women whose waist circumference was less than 88 cm, 71 (96%) did not meet criteria for the metabolic syndrome (Fig. 1F). Of the 125 women with an HDL more than 50 mg/dl, 118 (94%) did not meet criteria for the metabolic syndrome (Fig. 1E). Finally, of the 247 women with a triglyceride level less than 150 mg/dl, 223 (90%) did not meet criteria for the metabolic syndrome (Fig. 1B). The negative predictive values for hypertension (Fig. 1, C and D) and elevated fasting glucose (Fig. 1A) were 79 and 70%, respectively.

Family history of diabetes

Diabetes was present in a first-degree relative in 98 (28.5%) of the 344 women for whom this information was available. A family history of diabetes was present in 38 (33%) of the 115 women with the metabolic syndrome and 60 (26%) of the 229 women without the metabolic syndrome, a difference that was not statistically significant ($P = 0.16$ by χ^2). In contrast, women with a family history of diabetes exhibited a significantly greater number of individual components of the metabolic syndrome (2.37 ± 0.11 *vs.* 1.92 ± 0.08; $P < 0.01$).

Prevalence of impaired glucose tolerance (IGT)

The prevalence of IGT among those meeting criteria for the metabolic syndrome was twice that observed in those without the metabolic syndrome (38% *vs.* 19%; $P < 0.001$). Because women with type 2 diabetes were excluded from analysis, the prevalence of type 2 diabetes in relation to the presence or absence of the metabolic syndrome could not be determined.

Obesity and the metabolic syndrome

None of the 52 women with a BMI less than or equal to 27.0 kg/m^2 met criteria for the metabolic syndrome. Of the remaining 304 women whose BMI was greater than 27.0 kg/m^2, 121 (40%) had the metabolic syndrome. Women in the upper quartile of BMI were 13.7 times more likely [95% confidence interval (CI), 5.7–33.0] to have the metabolic syndrome compared with those in the lowest quartile.

Fasting insulin levels and the metabolic syndrome

There was a significant ($P < 0.0001$) increasing trend in the proportion of women with the metabolic syndrome as related to the fasting insulin concentration; the prevalence of the metabolic syndrome from lowest to highest quartile of fasting insulin was 12.1, 25.3, 38.5, and 58.2%, respectively. This trend remained significant ($P = 0.001$) even after adjusting for BMI. Women in the highest quartile of fasting

TABLE 3. Positive and negative predictive values of each component of the metabolic syndrome (MS)

Components of the MS	No. of subjects with criterion	No. of subjects with criterion and at least three total criteria	Percentage of subjects with criterion who have MS (positive predictive value)	No. of subjects without criterion	No. of subjects without criterion and less than three total criteria	Percentage of subjects without criterion who do not have MS (negative predictive value)
Waist circumference > 88 cm	287	119	41	74	71	96
HDL cholesterol < 50 mg/dl	240	115	48	125	118	94
Triglycerides ≥ 150 mg/dl	118	98	83	247	223	90
Hypertension ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic	78	61	78	290	228	79
Fasting glucose ≥ 110 mg/dl	19	16	84	347	242	70

insulin, after adjusting for BMI, had a 5-fold greater chance (95% CI, 2.1–11.8) of having the metabolic syndrome than did women in the lowest quartile.

Free testosterone and the metabolic syndrome

The concentration of free testosterone was also significantly ($P = 0.005$) related to an increasing trend in the proportion of women with the metabolic syndrome. The prevalence of the metabolic syndrome from lowest to highest quartile of free testosterone was 19.8, 31.3, 46.9, and 35.0%, respectively. However, this trend did not remain statistically significant ($P = 0.056$) after adjusting for BMI.

Discussion

The metabolic syndrome is defined by both lipid and nonlipid criteria that identify individuals at increased risk for coronary heart disease and type 2 diabetes (8–13). Because women with PCOS have high rates of IGT and type 2 diabetes

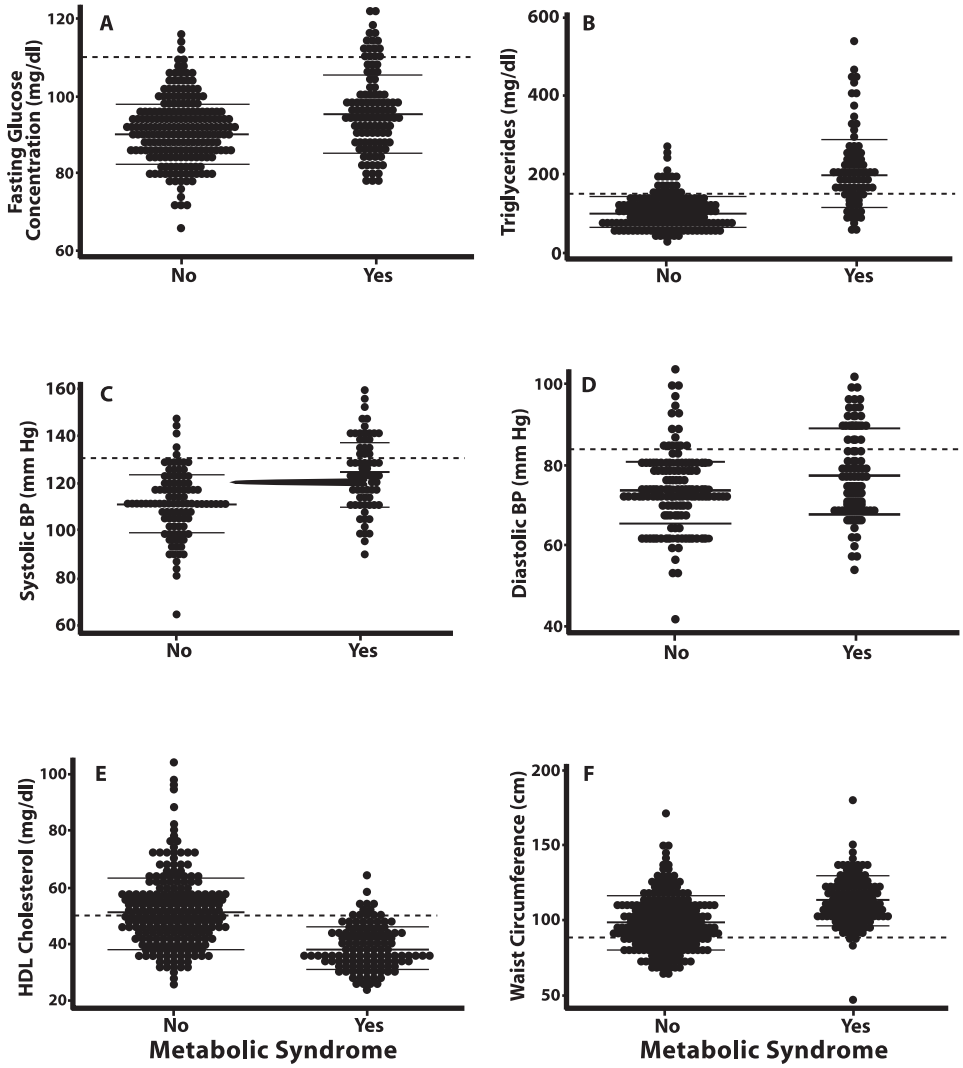

FIG. 1. Individual data plotted for fasting glucose (A), triglycerides (B), systolic blood pressure (C), diastolic blood pressure (D), HDL cholesterol (E), and waist circumference (F) in PCOS patients with and without the metabolic syndrome. The *dashed line* represents the threshold value for each criterion that comprises the metabolic syndrome. *Solid horizontal lines* through the data points represent the mean ± 1 SD.

(15, 16) as well as a substantial number of risk factors for cardiovascular disease (5), it has been generally assumed that many are also likely to meet criteria for the metabolic syndrome. However, it was not until recently that this link has been reported (17, 18).

We sought to identify factors that serve as predictors for the metabolic syndrome using data derived from a cohort of women of diverse geographic and racial/ethnic backgrounds who have been diagnosed with PCOS by uniform criteria (14). Our analyses were most notable for the finding that fully one third of nondiabetic women with PCOS have developed the metabolic syndrome well before the end of their fourth decade, and usually before the end of their third decade of life. This prevalence is markedly higher than the 6.7% prevalence of metabolic syndrome reported in women between the ages of 20 and 30 yr and the 15% prevalence reported in women between ages 30 and 40 yr from the Third National Health and Nutrition Examination Survey (NHANES III) (19), although it is important to note that the subjects who participated in the present study were self-selected and had substantially higher body weights than the cross-section of women participating in the NHANES survey. The prevalence of the metabolic syndrome in PCOS may be even higher than we report here since the present study population was not comprised of randomly selected women with PCOS, but rather of women with PCOS whose participation in a clinical trial could reflect a substantial degree of health-consciousness and, therefore, a lower prevalence of overweight and obesity. Although the prevalence of the metabolic syndrome observed in the present study population approaches that seen in women who are usually between the ages of 50 and 60 yr (19), it is important to note that there is substantial variation in the prevalence of metabolic syndrome in PCOS, depending upon the population studied and criteria used to define the metabolic syndrome (18, 20–22). For example, using National Cholesterol Education Program III criteria (8), the metabolic syndrome was evident in only 1.6% of Czech women with PCOS, a prevalence that did not differ from that observed in controls (20). On the other hand, Apridonidze *et al.* (18) reported a 23% prevalence of metabolic syndrome in PCOS using a modified version of the National Cholesterol Education Program III criteria (8) in which a BMI in excess of 32 kg/m^2 was used as a surrogate for a waist circumference greater than 88 cm.

We also found that the prevalence of the metabolic syndrome *per se* did not differ by ethnic/racial background. However, there were significant race-specific differences in the prevalence of individual components of the metabolic syndrome. African-American women had a significantly higher prevalence of an increased waist circumference compared with the remaining subjects, a finding consistent with the race-specific data derived from NHANES (23). An increased waist circumference is typically highly correlated with hyperinsulinemia and is thought to reflect an increase in the proportion of total body fat that is deposited in the visceral compartment compared with the sc space (24, 25). Women of African-American descent also had triglyceride levels that were lower than those observed in the other racial groups. Although this finding is consistent with previous reports (26), the cause for this difference is not known.

Each defining criterion was evaluated for its value to either confirm (positive predictive value) or exclude (negative predictive value) the full metabolic syndrome (Table 3 and Fig. 1). For example, a waist circumference below the threshold of 88 cm was a relatively rare occurrence, but was highly predictive of the absence of the metabolic syndrome. In contrast, a fasting HDL cholesterol level less than 50 mg/dl was seen in over half of the cohort, but its presence was only 48% predictive of the metabolic syndrome. Conversely, an elevated fasting glucose concentration was highly predictive of the metabolic syndrome, but its practical utility appears to be diminished by the fact that only 5% of subjects had this finding.

We next examined whether factors known to enhance risk for type 2 diabetes also influenced the risk for metabolic syndrome in PCOS. One third of women with the metabolic syndrome had a first degree-relative with type 2 diabetes, whereas 26% of those without the metabolic syndrome had a diabetic first-degree relative, a difference that was not significant. Of note, however, was the finding that women with a family history of diabetes had a significantly greater number of individual components of the metabolic syndrome (2.37 ± 0.11 *vs.* 1.92 ± 0.08; $P < 0.01$). IGT, a precursor to type 2 diabetes, was evident in 38% of women with the metabolic syndrome compared with a prevalence of 19% in women without the metabolic syndrome.

Although insulin levels *per se* are not used to diagnose either PCOS or the metabolic syndrome, it is generally acknowledged that insulin resistance and compensatory hyperinsulinemia are key pathogenetic factors in the pathogenesis of these disorders. As such, it might be expected that women with both PCOS and metabolic syndrome would have higher insulin levels than those who have PCOS alone. In fact, fasting insulin concentrations were nearly twice as high (32.2 ± 2.5 *vs.* 17.3 ± 0.8 μU/ml; $P < 0.001$) in the PCOS women with the metabolic syndrome compared with women without metabolic syndrome. There was also a significant ($P < 0.0001$) increasing trend in the proportion of women with the metabolic syndrome as a function of the fasting insulin concentration: the prevalence of the metabolic syndrome from lowest to highest quartile of fasting insulin was 12.1, 25.3, 38.5, and 58.2%, respectively, and women in the highest quartile of fasting insulin had a 5-fold greater chance (95% CI, 2.1–11.8) of having the metabolic syndrome than did women in the lowest quartile after adjustment for the effect of body weight/obesity.

Obesity, a key determinant of insulin concentrations, appeared to have an independent effect on risk for the metabolic syndrome: women in the highest quartile of BMI had nearly a 14-fold increased chance of having the metabolic syndrome compared with women in the lowest quartile of BMI and none of the 52 women whose BMI was less than 27.0 kg/m^2 met criteria for the metabolic syndrome.

Finally, it is of interest that SHBG levels were significantly lower in PCOS women with the metabolic syndrome compared with those PCOS women without the metabolic syndrome (32.8 ± 1.4 *vs.* 43.8 ± 1.4 nM; $P < 0.05$). However, after adjustment for the effects of either BMI or the degree of insulin resistance, this difference was no longer significant. We interpret this to indicate that variation in SHBG levels

results largely from the effects of insulin resistance/hyperinsulinemia upon hepatic SHBG production. Thus, a low level of SHBG may serve as another marker of insulin resistance, a key factor in the pathogenesis of metabolic syndrome.

In summary, the metabolic syndrome is evident at an early age in women with PCOS, irrespective of race and ethnicity. Hyperinsulinemia, a central factor in the pathogenesis of PCOS, also appears to be a critical link between PCOS and the metabolic syndrome. Strategies designed to attenuate insulin resistance have proved to be of benefit in the treatment of both syndromes; whether such strategies will lead to a reduction in risk of developing cardiovascular disease and type 2 diabetes remains to be determined.

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