Metabolic dysfunction in obese Hispanic women with PCOS

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Abstract

Study question: Are certain ethnic groups with PCOS at increased risk of metabolic disorders?

Summary answer: Obese Hispanic women with PCOS are at increased risk of metabolic disorders compared to age- and BMI-matched obese non-Hispanic white women with PCOS in the United States.

What is known already: Ethnic differences in body composition and metabolic risk are well established. Polycystic ovary syndrome (PCOS) is a common disorder in reproductive age women and is associated with high rates of insulin resistance, glucose intolerance and dyslipidemia.

Study design, size, duration: A cross-sectional observational study was performed at an Academic Medical Center on 60 reproductive age women with PCOS in the United States.

Participants/materials, setting, methods: Fasting blood was obtained from 17 Hispanic, 22 non-Hispanic black and 21 non-Hispanic white women with PCOS who were similar in age and BMI. Anthropometric parameters, insulin, lipid and lipoprotein levels by nuclear magnetic resonance were compared between the 3 groups.

Main results and the role of chance: Age and BMI were similar between the groups (P=0.52 for age and P=0.60 for BMI). Hispanic women with PCOS had higher waist to hip ratio (WHR) (P=0.02), HOMA-IR (P=0.03), and a more atherogenic lipid and lipoprotein profile consisting of lower HDL (P=0.02), higher LDL particle number (P=0.02), higher VLDL particle size (P=0.03) and lower LDL (P=0.03) and HDL particle size (P=0.005) compared to non-Hispanic white women. The differences in HDL, HOMA-IR, VLDL and LDL size did not persist after adjustment for WHR while differences in LDL particle number (P=0.04) and HDL size (P=0.01) persisted.

Limitations, reason for caution: The sample size for the 3 groups was small but the findings were still significant. The women were mostly obese so the ethnic differences in metabolic disorders may not apply to non-obese women with PCOS.

Wider implications of the findings: Independent of BMI, obese reproductive age Hispanic women with PCOS in the United States had greater degree of abdominal obesity, insulin resistance and dyslipidemia. Hispanic women with PCOS may benefit from more focused management of metabolic parameters.

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Introduction

Dyslipidemia is one of the most frequent metabolic abnormalities in women with polycystic ovary syndrome (PCOS). Women with PCOS have been shown to have higher triglyceride and LDL cholesterol and lower HDL cholesterol compared to control women of similar ethnicity, age and BMI (1-4). In addition, using nuclear magnetic resonance (NMR) technique, our group has demonstrated that reproductive age women with PCOS have a more atherogenic lipoprotein profile consisting of higher VLDL and LDL particle number and significantly lower HDL size and borderline lower LDL size compared to control women of similar age and BMI (5). Other investigators using different techniques have reported similar findings, although NMR is the gold standard technique for assessment of lipoprotein particle number and size (6-8). These adverse alterations are not always fully apparent on conventional lipid assay (9) but are strongly associated with insulin resistance (9) and cardiovascular disease (10-13). These atherogenic alterations are also likely related to increased accumulation of intra-abdominal fat (14).

Ethnic differences in insulin sensitivity and body composition are well recognized. Greater degrees of insulin resistance and abdominal obesity have been reported among Hispanic Americans compared to other ethnicities in the United States (15-17). Hispanic women have been shown to have lower insulin sensitivity (18) and higher prevalence of metabolic syndrome (19), type 2 diabetes, and cardiovascular disease risk factors compared to non-Hispanic white women (20). There is a suggestion that the prevalence of PCOS is higher among Hispanic women compared to women of other ethnicities although the prevalence in this study was determined by self-report (21). Furthermore, Hispanic women with PCOS have been shown to have higher degree of insulin resistance compared to other ethnic groups (22) although this

finding has not been universal (23). If metabolic dysregulation is more severe among Hispanic women with PCOS compared to other ethnic groups, these women will benefit from more intense monitoring of metabolic parameters.

In this study, we examined for differences in body composition, insulin sensitivity and lipid and lipoprotein profile by NMR between obese women with PCOS among the following racial/ethnic groups in the United States: Hispanic, non-Hispanic white and non-Hispanic black. Identification of groups of women with PCOS at higher risk for metabolic and cardiovascular disease is important since these groups may require closer metabolic monitoring.

Materials and Methods

Subjects

Sixty reproductive age women with PCOS were recruited for the study. Of these women, 17 were Hispanic, 22 were non-Hispanic blacks and 21 were non-Hispanic whites. Women with PCOS were recruited from advertisement at the University of Illinois or from endocrinology or reproductive endocrinology clinics who agreed to participate in the research. These women were recruited as part of our original study to assess for differences in lipid and lipoprotein profile between PCOS and control women (5). Eligible women were between 18 to 40 years of age who were free of chronic disease including diabetes and hypertension and reported a history of menstrual irregularity and clinical hyperandrogenism such as hirsutism, acne or androgenic alopecia. The diagnosis of PCOS was confirmed based on the NIH criteria and defined by presence of oligomenorrhea (<6 menses per year) and clinical and biochemical hyperandrogenism (24). Biochemical hyperandrogenism was established based on an elevated total or bioavailable testosterone levels. Levels were considered to be elevated if they were above the normal range in our assay (25). Thyroid hormone abnormalities, hyperprolactinemia

and non-classical congenital hyperplasia due to 21 hydroxylase deficiency were excluded by appropriate laboratory testing in all women with PCOS. All women with PCOS underwent a history and physical exam by a physician investigator that included detailed questions regarding their reproductive function and symptoms related to hyperandrogenism. All Women reported oligomenorrhea as defined by <6 menstrual cycles per year since menarche. Additionally, All women reported clinical symptoms consistent with hyperandrogenism and had elevated androgen levels to qualify for participation in the study. We do not report hirsutism scores such as Ferriman Gallwey scoring system since even though all of our patients complained of skin manifestations of hyperandrogenism including hirsutism, cosmetic removal of hair was common among women and interfered with the accuracy of this determination. None of the women with PCOS had received any oral contraceptive, other forms of hormonal contraception or fertility treatments for at least 3 months prior to their participation nor had they received progesterone for at least one month prior to their participation in the study. None of the women had ever received any insulin sensitizing agents or metformin.

Women were excluded from participation if they were pregnant or lactating, had any chronic disease including diabetes, hypertension, psychiatric disorder or any surgical procedure on their ovaries or uterus. None of the subjects were receiving any medication for treatment of dyslipidemia, diabetes or hypertension. Women were asked to complete standard questionnaires regarding alcohol and tobacco use and exercise habits. English was the primary language of all Hispanic participants who were mostly second or third generation of Central American background. Hispanic women were well acculturated into American lifestyle including dietary habits.

Ethical Approval

The study was approved by the institutional review board at the University of Illinois and all subjects signed written informed consent prior to the participation in the study.

Data Collection

All women were studied at the clinical research center at University of Illinois and underwent a history and physical exam by a physician investigator that included detailed menstrual and medical history as well as assessment for hirsutism and other signs of hyperandrogenism and insulin resistance. Standardized forms were used to obtain medical history including information on exercise habits, alcohol and tobacco use. Height, weight and waist measurements were determined on all subjects. Blood pressure was determined as average of 3 measurements following 30 minutes of rest at the clinical research center. A morning blood sample was obtained after an overnight fast from all subjects that included measurements of total and bioavailable testosterone, sex hormone binding globulin, lipid, and lipoprotein profile. A 2-hr oral glucose tolerance test was performed on all women with administration of 75 grams of oral glucola and determination of baseline and 2-hour glucose levels.

Laboratory Methods

All laboratory evaluations with the exception of lipoprotein profile and insulin were performed at Quest Diagnostics. Total testosterone was measured by turbulent flow liquid chromatography mass spectrometry that has an assay sensitivity of 0.034 nmol/L and no cross reactivity with 30 testosterone related compounds. Bioavailable testosterone was calculated based on constants for the binding of testosterone to SHBG and albumin. SHBG was measured by extraction, chromatography and radioimmunoassay and albumin was measured by spectrophotometry. Total and HDL cholesterol and triglyceride levels were determined by

spectrophotometry. The intra- and inter-assay coefficients of variation were 1.1 and 1.8% for total cholesterol respectively, 2.1 and 2.9% for HDL, 1.1 and 1.9% for triglyceride. The LDL cholesterol was calculated using the Freidewald equation (26). Plasma glucose was collected in a fluoride/oxalate tube and analyzed using spectrophotometry. The intra- and inter-assay coefficient of variation for this assay was 1.1 and 1.5%. Insulin was measured by a chemiluminescent sandwich immunoassay measuring to as low as 14 pmol/L. The inter- and intra-assay coefficient of variation for this assay was 4 and 5%. Lipoproteins were analyzed using NMR technology by LipoScience (Raleigh, NC). The intra- and inter-assay coefficient of variation were 1.4 and 3.1% for VLDL particle number, 2.4 and 2.1% for LDL particle number, 1.2 and 1.5% for HDL particle number, 0.8 and 1.8% for VLDL size, 0.5 and 0.4% for LDL size and 0.5 and 0.6% for HDL size (27).

Statistical Analyses

The homeostatic index of insulin resistance (HOMA IR) was calculated according to the following formula: [fasting glucose (mmol/L) X fasting insulin (μU/mL)] ÷ 22.5] (28). Continuous variables were presented by mean and standard deviations. Bioavailable testosterone, fasting and 2 hour insulin, and HOMA IR were LN-transformed prior to all analyses because of skewed distributions. All other variables were normally distributed based on histogram. Continuous variables were compared by general linear model for the overall comparison followed by Bonferroni analyses for comparisons of differences between various ethnic groups. These analyses were repeated after adjustment for WHR. Categorical variables were compared using chi-square statistics. Analyses were performed using the 18.0 PC package of SPSS statistical software (SPSS, Inc., Chicago, IL). A $P \leq 0.05$ was considered significant.

Results

Baseline clinical and laboratory characteristics of women with PCOS in each group is summarized in Table 1. There were no differences in age or BMI among the three groups of women (Table 1). Hispanic women had higher waist to hip ratio (WHR) compared to non-Hispanic white women (P=0.02, Table 1). There were no differences in blood pressure between the 3 groups (P=0.8, Table 1). Very few women in each group smoked (3 Hispanic, 1 non-Hispanic black and 3 non-Hispanic white) or consumed more than 3 alcoholic beverages per week (1 Hispanic, 1 non-Hispanic black and 3 non-Hispanic white); differences that were not significant between groups (P=0.6 and P=0.2 respectively, data not shown). Thirty-eight percent of non-Hispanic whites, 33% of non-Hispanic blacks and 28% of Hispanic women reported routine exercise of at least 30 minutes 3 times per week; differences that were not significant between groups (P=0.70, data not shown).

Total and bioavailable testosterone and DHEAS were not different between the three groups (Table 1) but SHBG levels were significantly higher in non-Hispanic white compared to Hispanic (p=0.04, Table 1) and non-Hispanic black women (P=0.03, Table 1). Women were excluded from research if they had a prior history of DM2. None of the subjects in the study had DM2 or impaired fasting glucose based on fasting blood glucose. Two Hispanic women and one non-Hispanic black woman had DM2 based on the 2-hr glucose value and five Hispanic women, five non-Hispanic black women and 4 non-Hispanic white women had IGT based on 2-hr glucose value. These differences were not statistically different. Hispanic women had higher HOMA IR (P=0.03, Table 1) and fasting insulin levels compared to non-Hispanic white women (P=0.04, Table 1). Similarly 2-hr insulin levels were higher in Hispanic women compared to non-Hispanic white women (P=0.002, Table 1). The differences in HOMA IR and fasting

insulin levels between Hispanic and non-Hispanic white women with PCOS became borderline significant after adjustment for WHR (P=0.05 for HOMA IR and P=0.06 for fasting insulin, Table 1). However, the difference in 2-hr insulin remained significant even after adjustment for WHR (P=0.01, Table 1).

Non-Hispanic white women had significantly higher HDL cholesterol compared to Hispanic women (P=0.02, Figure 1). There were no differences between groups in LDL cholesterol (P=0.80 data not shown). There were no differences between groups in triglyceride levels (P=0.06, Figure 1). LDL particle number (LDL-PN) was highest in Hispanic (1386 ± 514 nmol/L) compared to non-Hispanic black (1146 ± 458 nmol/L) and non-Hispanic white women (936 ± 290 nmol/L) and this difference achieved statistical significance between Hispanic and non-Hispanic white women (P=0.02, Figure 1). The difference in LDL particle number between Hispanic and non-Hispanic white women persisted after adjustment for WHR (P=0.04, Figure 1). VLDL size (VLDL-S) was highest in Hispanic women (52 ± 8 nm) compared to non-Hispanic black (48 ± 7 nm) and non-Hispanic white women (45 ± 5 nm) and this difference achieved statistical significance between Hispanic and non-Hispanic white women (P=0.03, Figure 1). LDL size (LDL-S) was lowest in Hispanic (20.5 ± 0.7 nm) compared to non-Hispanic black (20.9 ± 0.9 nm) and non-Hispanic white women (21.3 ± 0.8 nm) and this difference achieved statistical significance between Hispanic and non-Hispanic white women (P=0.03, Figure 1). The differences in VLDL-S and LDL-S did not persist after adjustment for WHR (P=0.15 and P=0.14 respectively, Figure 1). HDL size (HDL-S) was lowest in Hispanic (8.8 ± 0.3 nm) compared to non-Hispanic black (9.0 ± 0.4 nm) and non-Hispanic white women (9.3 ± 0.4 nm) and this difference achieved statistical significance between Hispanic and non-Hispanic white

women (P=0.005, Figure 1). The difference for HDL-S between Hispanic and non-Hispanic white women remained significant even after adjustment for WHR (P=0.01, Table 1).

Discussion

Our Results demonstrate that independent of BMI, there are ethnic differences in abdominal obesity, insulin sensitivity and lipid and lipoprotein levels among young obese reproductive age women with PCOS in the United States. Obese Hispanic women with PCOS had the highest waist to hip ratio (WHR) and this difference achieved statistical significance in comparison to obese non-Hispanic white women. Consistent with this finding, obese Hispanic women with PCOS had greater degree of insulin resistance as determined by higher HOMA IR, fasting and 2 hour insulin and lower SHBG; differences that achieved statistical significance in comparison to obese non-Hispanic white women. In addition to higher degree of insulin resistance, obese Hispanic women with PCOS had the lowest HDL cholesterol, highest LDL-PN and VLDL-S and lowest LDL-S and HDL-S; differences that became significant between Hispanic and similarly obese non-Hispanic white women. Many of these differences did not persist after adjustment for WHR suggesting that abdominal obesity predisposes to these adverse alterations in insulin sensitivity and lipid and lipoprotein parameters. However, the increase in LDL-PN and the decrease in HDL-S in Hispanic women persisted even after adjustment for abdominal obesity suggesting that additional unmeasured factors are responsible. These changes in lipid and lipoprotein profile are highly atherogenic and predispose to cardiovascular disease (9-11).

Lower HDL cholesterol levels have been reported in women with PCOS compared to reproductively normal women (1, 3, 4) and the finding from this study indicates that the levels are further reduced in obese Hispanic women with this condition. We have previously shown

that women with PCOS have higher LDL particle number and smaller more dense LDL and smaller HDL particles compared to ethnicity, age and BMI matched control women (5). This study demonstrates a further significant increase in LDL particle number and a reduction in HDL and LDL particle size in Hispanic women with PCOS compared to non-Hispanic white women with PCOS of similar BMI. HDL cholesterol is atheroprotective primarily by its role in reverse cholesterol transport that involves removal of cholesterol from macrophages in the vessel wall back to the liver (29). Smaller HDL particles are less effective in reverse cholesterol transport and hence are less atheroprotective (9, 30). Prospective studies of large cohorts have demonstrated that increased LDL particle number especially of dense small particles is a strong predictor of development of cardiovascular disease independent of LDL concentration (10). The increase in LDL-PN and the decrease in HDL-S and LDL-S in obese Hispanic women appear to be independent of abdominal obesity and place these women at increased risk for cardiovascular disorders compared to other ethnic groups.

An additional finding of this study is the higher levels of SHBG among non-Hispanic white women with PCOS compared to Hispanic and non-Hispanic black women of similar BMI. Despite differences in SHBG, bioavailable testosterone levels did not differ between the groups. SHBG is an independent predictor of DM2 among all ethnicities (31) and reduced SHBG levels is a good surrogate for insulin resistance (32, 33). Lower SHBG levels among non-white women indicates that these women are more insulin resistant compared to non-Hispanic white women and is consistent with the results of HOMA IR and fasting and 2-hr insulin that also indicates higher degree of insulin resistance in Hispanic women. Interestingly, among a large group of obese premenopausal women without PCOS who had participated in the Diabetes Prevention Program, SHBG levels were not different between Hispanics, non-Hispanic white or black

women (34). In this study unlike ours, waist circumference was not different between the ethnic/racial groups. Abdominal obesity consisting of increased subcutaneous and visceral depots has been shown to be a feature of PCOS independent of overall obesity (35-37), and our data indicates that Hispanic women with this condition are more severely affected. There is data for strong associations between waist circumference and risk for insulin resistance and type 2 diabetes in Hispanic populations (38). Our group and others have shown that among both diabetic as well as non-diabetic cohorts, the lipoprotein abnormalities such as increase in VLDL and LDL particle number and reduction in LDL and HDL size correlate best with visceral fat rather than overall adiposity (39, 40).

Our study has a number of limitations. The sample size in each group was small and our findings require confirmation in larger studies. However, despite this limitation, there were significant differences in metabolic parameters between the three ethnic/racial groups of similar age and BMI. The differences in insulin resistance and lipid and lipoprotein parameters between Hispanic and non-Hispanic women with PCOS might be independent of PCOS and related to ethnic differences in these measures (15-17). Hispanics have been shown to have greater degree of insulin resistance and metabolic and cardiovascular risk factors independent of gender (18-20). An additional limitation is inclusion of mostly obese women thus the observed ethnic differences in metabolic parameters and lipid and lipoprotein profile may not apply to normal weight or overweight women with PCOS. We did not obtain a dietary history from our subjects and it is possible that dietary differences could account for the differences in metabolic parameters although women were similar in terms of exercise habits and their alcohol and tobacco use. Additionally, our data in Hispanic women may only apply to the Hispanic population in the United States and likely will not be reflective of native population throughout

Latin America who are different in terms of lifestyle, dietary habits, prevalence of obesity, metabolic dysfunction and even ethnic makeup (41). However, several aspects of our study are unique. To our knowledge simultaneous assessment of metabolic function in women with PCOS belonging to the three main ethnic groups in the United States is lacking especially since women in our study were similar in terms of age and BMI and were diagnosed with PCOS based on NIH criteria. Previous assessments of lipoprotein profile in women has not included the gold standard technique of NMR that provides a much more accurate, detailed and simultaneous assessments of VLDL, LDL and HDL particle size and number.

In summary, data on ethnic differences in insulin sensitivity and metabolic disorders in PCOS is sparse (22, 42) and contradictory (23). Our study is unique since we were able to simultaneously study women with PCOS from three ethnic/racial groups in the United States and compare their metabolic and cardiovascular risk factors. Our findings on lipoprotein parameters are also unique since we utilized the gold standard technique of NMR to obtain information on lipoprotein particle number and size which are superior predictors of atherosclerosis in comparisons to measures obtained from conventional lipid assays (10, 11). Our results indicate that obese reproductive age women of Hispanic with PCOS have higher degrees of abdominal obesity, insulin resistance and lipid and lipoprotein abnormalities compared to non-Hispanic white women with this condition in the United States. These findings require confirmation by larger studies but indicate that obese reproductive age Hispanic women with PCOS in the United States are at high risk for metabolic complications and may benefit from more focused monitoring of metabolic parameters.

Author's roles

All authors provided substantial contributions to conception and design, acquisition and/or analysis and interpretation of data, drafting and revising of the manuscript and provided final approval of the version to be published.

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Conflict of interest

None of the authors report any conflict of interest.

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Figure 1. Data are presented as mean ± standard error. *P<0.05 compared to non-Hispanic white; †P<0.01 compared to non-Hispanic white; §P=0.06 compared to non-Hispanic white; ‡after adjustment for WHR compared to non-Hispanic white.