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The association of urinary albumin excretion and metabolic complications in polycystic ovary syndrome

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ABSTRACT

Objective: This study was planned to screen polycystic ovary syndrome (PCOS) women for albuminuria and to evaluate the association between urinary albumin excretion (UAE) and metabolic disturbances of PCOS. In addition, this is the first study in the literature evaluating the association between UAE and carotid intima–media thickness (CIMT) in PCOS cases.

Study design: The study population consisted of 65 PCOS women. The study was prospectively designed and performed in a university hospital. The diagnosis of PCOS was made according to the Rotterdam criteria: exclusion criteria were hyperprolactinemia, thyroid dysfunction, adrenal dysfunction, diabetes mellitus, hypertension, and pregnancy. Blood samples were collected in the follicular phase of a menstrual cycle and serum samples were analyzed for fasting glucose, insulin, and hormone and lipid profiles. Twenty-four hour urine specimens were collected for the detection of UAE. CIMT was estimated by visual assessment of the distance between the lumen–intima and intima–adventitia interfaces.

Results: The mean age and BMI were 23 years and 23 kg/m^2, respectively. The median UAE was 7 mg/day (range: 0.3–154 mg/day). The median UAE as micrograms of albumin per milligram of creatinine (uACR) was 5.6 (0.28–159). Regarding the uACR cutoff value (>6.93 μg/mg), significantly higher levels of triglycerides, 17 OH-progesterone, insulin resistance (HOMA index > 2.1) and increased CIMT were present in these cases. Microalbuminuria (uACR > 25 μg/mg) was present in 6.2%. In the regression analyses serum HDL-C levels were found to be independent predictor for uACR > 2 μg/mg (OR: 0.85) and estradiol levels were the independent predicting factor for uACR > 6.93 μg/mg even after adjustments for age and BMI were performed (OR:1.02).

Conclusions: UAE, expressed as uACR > 6.93 μg/mg, seems to be an associated sign of metabolic problems which might help in discriminating PCOS at risk of future CVD. Further studies are needed before routine use of albuminuria in PCOS cases for the detection of CVD risk.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of reproductive age [1]. Recently, PCOS has gained attention due to crucial metabolic aspects which play important roles in both the pathogenesis and the long-term sequelae of the condition. Comorbidities associated with PCOS are hypertension, dyslipidemia, metabolic syndrome, impaired glucose tolerance and type 2 diabetes mellitus [2]. Moreover, in the majority of women with PCOS central obesity aggravates the above-mentioned cardiovascular disease (CVD) risk factors [3]. Endothelial dysfunction, a prognostic parameter for CVD, is an early event in the process of atherosclerosis. In several studies, subclinical atherosclerosis in women with PCOS has been evaluated by ultrasound examination of the carotid artery, confirming significantly higher carotid intima–media thickness (CIMT) in PCOS women compared with controls matched for age and body mass index (BMI) [4–7].

Urinary albumin excretion (UAE) is another marker assumed to reflect systemic endothelial leakiness and used for identifying cases at increased risk for CVD [8]. Usually, the application of UAE is for predicting nephropathy and CVD in diabetic patients. However, albuminuria independently indicates risk of death from CVD, regardless of diabetic or non-diabetic status [9,10]. Albuminuria occurs at the start of the atherosclerotic process and reflects general vascular dysfunction [8]. UAE as a cardiovascular risk factor in cases of PCOS is less well established [11,12]. This study was planned to screen PCOS women for albuminuria and to

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evaluate the association between UAE and the metabolic disturbances of PCOS. In addition, this is the first study for evaluating the association between UAE and CIMT in PCOS.

2. Materials and methods

Sixty-five women with PCOS were enrolled in the study, which was approved by the Ethics Committee. Written informed consent was obtained from all participants. The diagnosis of PCOS was made as proposed at the Rotterdam Consensus Meeting [13] (Table 1). Oligo-menorrhea was defined as cycle intervals more than 35 days and amenorrhea as absence of menstruation for three consecutive months. Exclusion criteria were the following: hyperprolactinemia, thyroid dysfunction, adrenal dysfunction, diabetes mellitus, hypertension (blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic), and pregnancy. None of the women had received any drugs known to interfere with hormone levels for at least 3 months before the study. All of the subjects were nonsmokers. Waist circumference was measured at the narrowest level between the costal margin and iliac crest. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Subjects with BMI values of $\geq$30 kg/m^2 were considered obese and excluded. Systolic (SBP) and diastolic blood pressure (DBP) were measured twice in the right arm in a relaxed sitting position. The average of two measurements taken 15 min apart was used. The features of metabolic syndrome were identified [14].

2.1. Serum markers

Blood samples were collected during days 3–5 after spontaneous menses, after overnight fasting for at least 12 h. In cases with oligoanovulation (luteal phase progesterone measurements less than 4 ng/mL) blood samples were taken after progesterone withdrawal bleeding. Levels of glucose, insulin, creatinine, hormone profile (follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), total and free testosterone (Total-T and Free-T, respectively), dehydroepiandrosteone sulfate (DHEAS), 17 OH-progesterone (17OH-P) and thyroid-stimulating hormone (TSH)), and serum lipids (total cholesterol (Total-C), high-density cholesterol (HDL-C), low-density cholesterol (LDL-C), and triglycerides (TG)) were determined. Plasma glucose was determined with the glucose hexokinase method (Cobas Integra 400 Plus, Roche Diagnostics, Mannheim, Germany). Fasting glucose to insulin ratio (FIGR), homeostasis model assessment (HOMA-IR) [15] (insulin $\times$ glycemia in μmol/L/22.5), and quantitative insulin sensitivity check index (QUICK) [16] (1/log insulin + log glycemia in mg/dL) were estimated. Insulin resistance (IR) was defined as HOMA index $>$ 2.1 [17].

Serum levels of FSH, LH, E2, PRL, DHEAS, Total-T, insulin and TSH were measured with electrochemiluminescence assays. (ELECYS 2010 HITACHI, Roche Diagnostic, Germany). Serum levels of 17OH-P and Free-T were measured by radioimmunoassay. The serum levels of Total-C, HDL-C, LDL-C, and TG were determined with enzymatic colorimetric assays (Roche Diagnostic, Mannheim, Germany). The intra- and interassay coefficients of variation (CV) were $<$1.9% and $<$4%, respectively, for all assays performed.

Table 1
Diagnostic criteria for PCOS according to The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.

Revised 2003 criteria (diagnosis with 2 out of 3)[a]
- Oligo- or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries determined by ultrasonography ($\geq$12 follicles of 2–9 mm diameter in each ovary and/or ovarian volume $>$ 10 mL)

[a] With the exclusion of other androgen excess or related disorders.

2.2. Common CIMT measurement

Imaging was conducted using a high resolution ultrasound machine (Logic Q7, General Electric, USA) with a 7.5 MHz mechanical sector transducer in all cases. The posterior carotid wall at 1 cm of the common carotid artery was imaged in B-mode and CIMT was estimated by visual assessment of the distance between the lumen–intima and intima–adventitia interfaces in longitudinal frames acquired during arterial diastole [18]. The mean of measurements of CIMT made at the greatest thickness on both sides was used for statistical analyses. Ultrasonographic measurements were performed by the same experienced radiologist.

2.3. Urine samples

Participants collected 24-h urine samples. Urinary albumin concentration was measured by an automated immunoturbidimetric assay (ALBT2, Tina-Quant, Albumin Gen.2, Roche). Total protein (pyrogallol red) and immunoturbidimetric urine albumin assay were performed on the Roche, Cobas Integra 400 otoanalyzer (Roche Diagnostics, Mannheim, Germany). The immunoturbidimetric assay had within-assay and between-assay CV of 0.94% and 1.4%, respectively. Urine creatinine was assayed by modified Jaffe reaction. Glomerular filtration rate (GFR) was calculated from serum creatinine with Cockcroft-Gault formula: GFR (mL/min) = (140 − Age) $\times$ weight ($\times$0.85 for women)/Plasma creatinine $\times$ 72. UAE is given as urinary albumin-to-creatinine ratio (uACR) defined as microgram of albumin per milligram of creatinine (μg/mg). The median value of uACR (6.93 μg/mg) for women in the general population was taken as the cutoff value [19]. Sex-specific uACR cutoff value for microalbuminuria in women is 25 μg/mg [20].

2.4. Statistical analysis

Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Whether the distributions of continuous variables were normal or not was determined by the Shapiro Wilk test. Data were shown as mean $\pm$ standard deviation or median (minimum–maximum), where applicable. The mean differences between groups were compared by Student's t test. Otherwise, Mann–Whitney U test was applied for the comparisons of the median values. Nominal data were analyzed by Chi-square or Fisher's exact test, where appropriate. Multiple Logistic Regression analysis was used to determine the independent predictors which mostly affected uACR. Any variable whose univariable test had a p value $<$0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratio and 95% confidence intervals for independent variables were calculated. A p value less than 0.05 was considered statistically significant.

3. Results

The baseline characteristics are given in Table 2. Amenorrhea/oligo-menorrhea was present in 43 cases (66.1%). The mean SBP and DBP were 110 $\pm$ 12 mm Hg and 64 $\pm$ 8.8 mm Hg, respectively. The mean waist circumference was 71.9 $\pm$ 7 cm. The fasting insulin and glucose levels, and insulin sensitivity indexes are in Table 2. The hormone and lipid parameters are given in Table 3. The median value of UAE was 7.0 (range from 0.3 to 154) mg/day and the median value of uACR was 5.6 (range from 0.28 to 159) μg/mg. Microalbuminuria (uACR $>$ 25 μg/mg) was present in 6.2% (n = 4) of the study