Original Article

Pattern of urinary albumin excretion in normotensive young and adolescent Indian women with polycystic ovary syndrome

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ABSTRACT

Objective: Polycystic ovarian syndrome (PCOS) is a clinically heterogeneous endocrine disorder affecting up to 4–8% of women of reproductive age. The aim of this study was to evaluate the presence of microalbuminuria in women with PCOS and study its correlation with the various metabolic, clinical, and hormonal parameters. **Materials and Methods:** A cross-sectional study involving 69 PCOS women was carried out in a tertiary care center hospital. The diagnosis of PCOS was made according to the Rotterdam criteria. Blood samples were collected in the follicular phase of the menstrual cycle and analyzed for fasting luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), 17-hydroxyprogesterone (17-OHP), total testosterone (T), glucose, insulin, and lipid profile. Urinary albumin was measured in the first void spot urine sample. **Results:** The mean age of the subjects was 22.0 ± 4.1 years and 21.8 ± 4.7 years in normoalbuminuric and microalbuminuric groups, respectively. Urinary albumin excretion (UAE) varied from 5 mg/l to 100 mg/ml, with a median of 5 mg/l. Microalbuminuria was observed in 17/69 (24.6%) of subjects. The mean UAE was 3.65 ± 4.44 mg/l in the normoalbuminuria group versus 45.29 ± 22.74 mg/l in the microalbuminuria group. Upon univariate analysis, hip circumference, diastolic blood pressure, and fasting blood glucose showed significant correlations with urinary albumin concentration (r = 0.264, 0.264, and 0.551, respectively; *P* = 0.028, 0.029, and 0.000, respectively). No association between UAE and the usual cardiovascular risk factors could be found upon regression analysis. **Conclusion:** About 24.6% of women with PCOS showed presence of microalbuminuria in the first void spot urine sample. Screening for the presence of microalbuminuria can help in early identification of a subset of PCOS women with a high risk for future CVD, who can be subjected to preventive strategies at the earliest. However, further studies are needed before recommending routine use of UAE in PCOS cases for the detection of CVD risk.

Key words: Endothelial dysfunction, microalbuminuria, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder in women worldwide, with an estimated prevalence between 4 and 8%, and is one of the most common causes of ovulatory infertility.[1] PCOS is characterized by features of androgen excess in the form of hirsutism, alopecia, acne, elevated plasma androgens, or a combination of these. Insulin resistance (IR) is an important aspect of PCOS and may contribute to an increased risk of developing type 2 diabetes and coronary heart disease.[2,3] In view of the clustering of adverse cardiovascular risk factors like dyslipidemia, insulin resistance, and endothelial dysfunction, these patients are at an increased cardiovascular risk compared

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with the age-matched controls.[4,5] A recent meta-analysis has shown that women with PCOS have increased risk for cardiovascular events independent of body mass index (BMI).[6]

PCOS is associated with an increase in subclinical atherosclerotic disease and endothelial dysfunction.[7,8] The endothelial dysfunction is due to the altered insulin regulation of endothelial nitric oxide synthesis, leading to impaired nitric oxide dependent vasodilatation.[8,9] Urinary albumin excretion (UAE), a marker of an atherogenic milieu, directly reflects the state of endothelial function and early endothelial damage. The leakage of albumin into urine reflects widespread vascular damage as suggested by Deckert's Steno hypothesis.[10] Epidemiologic and clinical evidence shows that microalbuminuria is associated with an increased risk for all-cause and cardiovascular mortality and adverse clinical outcomes are observed at levels below the current microalbuminuria threshold.[11,12]

There is a paucity of data regarding the relationship between microalbuminuria and PCOS.[13-15] In view of the above facts, this study was conducted to evaluate the presence of microalbuminuria in women with PCOS and study its correlation with the various metabolic, clinical, and hormonal parameters.

Materials and Methods

Subjects

This study was conducted in the Department of Endocrinology, Nephrology and Clinical Biochemistry of the Sher-i-Kashmir Institute of Medical Sciences. All young women and adolescent girls who attended our clinic between Dec 2006 and Dec 2008, for symptoms of menstrual disturbances, hirsutism, or any other feature of androgen excess were subjected to detailed clinical and endocrine assessment. All the patients gave a written informed consent and the study was cleared by the Ethics Committee of the Institute. The Rotterdam 2003 consensus conference criteria were used for the diagnosis of PCOS.[16]

Methods

All patients were interviewed for a detailed menstrual history including age of menarche, regularity, duration, and number of cycles per year. Oligomenorrhea was defined as an intermenstrual interval of >35 days or a total of <8 menses per year. A detailed history of duration and extent of abnormal hair growth, weight gain, and development of acne or alopecia, along with family history of hirsutism, menstrual disorders, and diabetes mellitus (DM) or glucose intolerance was recorded. Women who had used any hormonal preparation or drugs known or suspected to affect metabolic function and glucose tolerance were excluded from the study; similarly those with DM, thyroid, renal, hepatic, or cardiac dysfunction, hyperprolactinemia, adrenal dysfunction, pregnancy, urinary tract infection, and those on lipid-lowering, antihypertensive agents, etc. were not included in the study.

All subjects underwent a detailed anthropometric assessment (measurement of height, weight, waist, and hip circumference), measurement of blood pressure (BP), and detailed systemic examination. BMI was calculated by the formula: weight in kg/height in m^2. Hirsutism was assessed using modified Ferriman–Gallwey (FG) score, counting nine specified body areas by a single observer. A score of >8 out of 36 was taken as significant.[17] Transabdominal ultrasonography (USG) was done by a single observer to demonstrate the presence of multiple peripheral ovarian follicles, each <10 mm, hyperechogenic theca, and increased ovarian volume, suggestive of PCOS.[18] In addition, USG assisted in ruling out any suspicious androgen secreting lesion in the ovary or adrenals.

Investigations

The oral glucose tolerance test (OGTT) was performed between 0800 and 0900 hours after an overnight fast (10–12 hours), with 75 g of anhydrous oral glucose load dissolved in 250–300 ml of water administered over 3–5 min. Blood samples for glucose were collected at 0, 60, and 120 min during the test. Baseline serum samples were taken in all women in a fasting state for glucose, lipids, liver and kidney function, in addition to hormonal profile including T3, T4, thyroid stimulating hormone (TSH), cortisol (morning), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), 17-hydroxyprogesterone (17-OHP), and total testosterone (T). The samples for LH, FSH, T, and 17-OHP were collected on days 3–7 (early follicular phase) of spontaneous cycle or medroxyprogester one-induced menstrual cycle in amenorrheic patients. Overnight dexamethasone suppression test, if needed, was done after taking basal samples and performing OGTT. Urinary tract infection was excluded by WBC count and negative urine culture if the WBC count was >6 cells/high power field (HPF).

Assays

Hormonal assays were done by Radioimmunoassay (RIA) (T3, T4, cortisol, 17-OHP, and T) and immunoradiometric assay (IRMA) (TSH, LH, FSH, and PRL) using commercial kits in duplicate and according to supplier protocol (Shin Jin Medics Inc. ,Gyeonggi-do, Korea, for TSH; Immunotech, Marseille Cedex 9, France, for T, 17-OHP, cortisol, PRL, LH, and FSH), and Diasorin, Stillwater,USA, for FT3 and FT4. Plasma glucose (mg/dl) was measured by glucose

oxidase peroxidase method on Hitachi 912, Japan. Intra- and inter-assay variations were within the limits permitted by the manufacturer. Urinary albumin was measured by spectrophotometery (Hitachi 912, Japan) in the first void spot urine sample.

Statistical analysis

SPSS 11.5 package (Chicago, IL, USA) was used for the analysis of data. Group I consisted of women with normal albumin excretion (n=52) and Group II had women with UAE ≥17 mg/l (n=17). The Student's t-test was used to compare the continuous variables between the two groups. Chi-square was used for comparison of non-categorical variables. Multiple logistic regression analysis and bivariate correlation was used to analyze the associations between study variables. A P value of <0.05 was taken as significant and results were expressed as Mean ± SD.

Results

The mean age of the subjects was 22.0 ± 4.1 years and 21.8 ± 4.7 years in normoalbuminuric and microalbuminuric groups, respectively, and was comparable (P=NS). UAE varied widely in PCOS subjects from 5 mg/l to 100 mg/ml, with a median of 5 mg/l. Microalbuminuria was observed in 17/69 (24.6%) subjects while using a cutoff of 17 mg/l as proposed by Gross *et al*.[19] The mean UAE was 3.65 ± 4.44 mg/l in group I versus 45.29 ± 22.74 mg/l in group II. The clinical characteristics of the study population (normoalbuminuric vs. microalbuminuric group) are summarized in Table 1.

Table 1: Comparative description of clinical parameters in (group I) normoalbuminuric polycystic ovarian syndrome women versus microalbuminuric group (group II)

	Group I (n=52)	Group II (n=17)	P value
	Mean ± SD	Mean ± SD	
Age (years)	22.0 ± 4.1	21.8 ± 4.7	NS
Age of menarche	13.2 ± 1.2	12.9 ± 1.4	NS
Cycles per year	9.6 ± 4.3	11.2 ± 2.9	NS
Hirsutism duration (years)	3.8 ± 2.1	3.6 ± 2.2	NS
FG score	12.5 ± 3.7	12.8 ± 3.6	NS
Height (cm)	156.46 ± 6.71	156.18 ± 6.99	NS
Weight (kg)	56.96 ± 11.34	58.00 ± 7.85	NS
BMI (kg/m^2)	23.23 ± 4.25	23.80 ± 3.15	NS
Waist circ (cm)	77.60 ± 8.81	79.88 ± 8.35	NS
Hip circ (cm)	85.12 ± 6.90	88.00 ± 6.51	NS
SBP (mmHg)	114.2 ± 8.6	115.5 ± 11.1	NS
DBP (mmHg)	75.2 ± 6.0	78.8 ± 7.1	0.040
Urine albumin (mg/l)	3.65 ± 4.44	45.29 ± 22.74	0.00

NS: Nonsignificant (P>0.005), SD: Standard deviation, FG score: Ferriman Gallwey score, SBP: Systolic blood pressure, DBP: Diastolic blood pressure Circ-circumference

Irregular cycle, alopecia, and infertility were seen in 41.2, 17.6, and 13.3% of the patients, respectively, in microalbuminuric group, while the corresponding values for normoalbuminuric group were 61.5, 44.5, and 9.6%, respectively. Grade I, II, and III acne were seen in 5.9, 29.4, and 11.8% of subjects in the microalbuminuric group, respectively, while the same in normoalbuminuric group were 36.5, 30.8, and 5.8%, respectively. Overt DM, impaired fasting glucose, and impaired glucose tolerance were seen in 23.5, 11.7, and 5.8% of the patients, respectively, in the microalbuminuric group as compared to 13.4, 9.61, and 5.77%, respectively, in the normoalbuminuric group. Obesity was seen in 52.9% of the patients in microalbuminuric group versus 51.9% in the microalbuminuric group. Using the International Diabetes Federation(IDF) criteria, 47.5% of the patients in the microalbuminuria group had a waist circumference (WC) ≥80 cm as compared to 44.2% in the normoalbuminuria group. The results remained the same even after increasing the WC cutoff to ≥88 cm as per the Adult Treatment Panel (ATP) criteria for metabolic syndrome (MetS). The IDF criteria for MetS were used to screen the participants for the presence of MetS and 19/69 (27.5%) subjects were found to have MetS.[20] MetS as per the IDF, ATP, and modified ATP criteria was present in 26.4, 35.3, and 41.2% of the patients, respectively, in the microalbuminuria group as compared to 26.9, 23.1, and 28.8%, respectively, in the normoalbuminuria group.

No clinical parameter like menstrual abnormality, hair growth, body weight, WC, or systolic BP in the normotensive range showed any difference between the two groups. However, the diastolic BP was only different between the two groups. Table 2 shows the comparative description of biochemical and the hormonal parameters in the albuminuric versus normoalbuminuric groups. None of the hormonal parameters were significantly different between the two groups. Blood glucose at 0, 1, and 2 hours was significantly higher in microalbuminuria group when compared to the values in normoalbuminuric group (P = 0.002).

The correlation between urinary albumin concentration and other parameters was carried out after log transformation as it showed marked variability and a non-normal distribution. This relationship is depicted in Table 3. Hip circumference, diastolic BP, and fasting blood glucose showed significant correlations with urinary albumin concentration (r=0.264, 0.264, and 0.551, respectively; P=0.028, 0.029, 0.000, respectively).

Binary logistic regression analysis was carried out to determine the predictors of UAE for which systolic BP, diastolic BP, WC, triglycerides (TG), fasting blood glucose, blood glucose 1 and 2 hours after oral glucose challenge,

Table 2: Comparative description of clinical parameters in normoalbuminuric polycystic ovarian syndrome women versus microalbuminuric group

Parameters	Group I (*n*=52)	Group II (*n*=17)	*P* value
	Mean ± SD	Mean ± SD	
Serum LH (IU/l)	6.05 ± 4.24	4.71 ± 1.80	NS
Serum FSH (IU/l)	6.09 ± 1.01	6.43 ± 1.01	NS
Serum total testosterone (ng/dl)	58.68 ± 31.27	51.56 ± 25.49	NS
17-OHP (ng/ml)	1.05 ±.35	1.00 ± 0.58	NS
Prolactin (ng/ml)	9.82 ± 4.89	10.40 ± 3.45	NS
T4 (mg/dl)	7.41 ± 1.13	7.27 ± 0.43	NS
TSH (mIU/ml)	2.73 ± 1.14	3.22 ± 1.32	NS
Blood glucose fasting (mg/dl)	86.31 ± 9.21	97.12 ± 32.59	0.029
Blood glucose post 1 hour (mg/dl)	123.94 ± 42.69	141.88 ± 46.35	0.029
Blood glucose post 2 hours (mg/dl)	118.82 ± 56.01	117.88 ± 32.82	0.029
Serum bilirubin (mg/dl)	0.76 ± 0.49	0.96 ± 0.48	NS
Serum SGPT (U/l)	27.63 ± 16.54	32.14 ± 13.31	NS
Serum ALP (U/l)	240.07 ± 56.16	261.00 ± 91.83	NS
Serum albumin (mg/dl)	4.61 ±.36	4.69 ± 0.33	NS
Serum creatinine (mg/dl)	0.86 ± 0.17	0.83 ± 0.19	NS
Serum total cholesterol (mg/dl)	171.55 ± 36.37	171.59 ± 26.46	NS
Serum triglycerides (mg/dl)	118.46 ± 47.87	135.59 ± 65.33	NS
Serum HDL (mg/dl)	44.95 ± 9.29	44.66 ± 4.72	NS
Serum LDL (mg/dl)	108.67 ± 28.04	104.91 ± 17.32	NS
Serum uric acid (mg/dl)	4.45 ± 1.00	4.50 ± 0.89	NS
Glycated hemoglobin [$HbA1_c$ (%)]	5.67 ± 0.37	5.53 ± 0.37	NS

NS: Nonsignificant (*P*>0.005); SD: Standard deviation, LH-Lutenizing hormone FSH: Follicle stimulating hormone, 17OHP: 17 Hydroxy progesterone, SGPT: Serum glutamic pyruvic transaminase, ALP: Alkaline phosphatase, HDL: High density lipoprotein, LDL: Low density lipoprotein

Table 3: Correlation of logarithm of urinary albumin (mg/l) with clinical, biochemical, and hormonal parameters

Variables	r	*P* value
Age in years	0.089	0.06
No of menstrual cycles per year	0.223	0.06
FG score	0.202	0.09
BMI (kg/m^2)	0.125	0.30
Waist circ (cm)	0.154	0.20
Hip circ (cm)	0.248	0.04
SBP (mmHg)	0.086	0.48
DBP (mmHg)	0.246	0.04
LH (IU/l)	–0.089	0.54
FSH (IU/l)	0.098	0.51
Total testosterone (ng/dl)	-0.044	0.77
Blood glucose fasting (mg/dl)	0.262	0.03
Blood glucose post 1 hour (mg/dl)	0.179	0.14
Blood glucose post 2 hours (mg/dl)	0.096	0.43
Serum creatinine (mg/dl)	0.091	0.45
Total cholesterol (mg/dl)	0.084	0.49
Triglycerides (mg/dl)	0.124	0.32
LDL (mg/dl)	–0.070	0.62
Calcium (mg/dl)	0.254	0.04
Uric acid (mg/dl)	0.072	0.56
$HbA1_c$ (%)	–0.037	083

r: Spearman's correlation coefficient, FG score: Ferriman Gallwey score, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Circ: Circumference, LH: Lutenizing hormone, FSH: Follicle stimulating hormone, HDL: High density lipoprotein, LDL: Low density lipoprotein

serum creatinine, cholesterol, high density lipoprotein (HDL) and MetS IDF categories were entered into the regression analysis. However,none of the parameters showed any significant predictive value for spot UAE in these subjects (*P*>0.05 in all). The R2 of the model was 0.361, meaning that 36.1% of the variation in the outcome model can be explained by this logistic model.

Discussion

This study describes the association between PCOS and UAE in normotensive young women with PCOS, with the aim of identifying PCOS women at high risk for cardiovascular disease (CVD). Microalbuminuria is defined as the presence of albumin in the urine above the normal range which depends on whether a random spot sample, a 24-hour collection, or a timed collection has been used.[21] The National Health and Nutrition Examination Survey (NHANES) 1999–2000 data had reported the microalbuminuria prevalence as 8.8%,[22] while the NHANES III (conducted in 1988–1994) data suggested a prevalence of 5.1% in a subpopulation with no risk factors.[23] An UAE above the upper quartile, i.e. 4.8 μg/min, has been shown to increase the risk of coronary heart disease (RR, 2.0; 95% CI, 1.4–3.0; *P*< 0.001) and death (RR, 1.9; 95% CI, 1.5–2.4; *P*<0.001) independently of age, sex, renal creatinine clearance, DM, hypertension, and plasma lipids.[24] UAE has been shown to predict cardiovascular events in non-diabetic subjects independently of traditional risk factors.[25] Adverse clinical outcomes have been observed at levels below the current microalbuminuria threshold.[12] Microalbuminuria (UAE ≥17 mg/l) was present in 17/69 (24.6%) subjects. This is similar to the report of Duleba *et al*.,[14] who found a level of 24% while using a cutoff of 20 mg/l. However, in the same study, when a different criterion in the form of >25 μg of albumin per milligram of creatinine was used, the reported prevalence of microalbuminuria decreased to 16%. Caglar *et al*. have demonstrated that UAE, expressed as urinary albumin creatinine ratio (uACR) >6.93 μg/mg, is associated with metabolic abnormalities in women with PCOS and might be helpful in identifying PCOS woman with greater risk for future CVD.[15] However, the reported rate of microalbuminuria (uACR > 25 μg/mg) in this study was 6.2%. According to NHANES III (conducted in 1988–1994) data, 28.8% of participants with diabetes and 16.0% with hypertension had microalbuminuria.

This study showed an independent correlation of diastolic BP with UAE, which is in agreement with the study conducted by Duleba *et al*.[14] Woo *et al*. showed that only systolic BP and fasting glucose in men and diastolic BP and fasting insulin in women independently contributed to urinary albumin: creatinine in a group of population in a Chinese community with a normal glucose tolerance defined by World Health Organization (WHO) criteria.[26] Albumin leakage into the urine is a reflection of widespread vascular dysfunction and increased intraglomerular pressure. This is important in normotensive PCOS women as it could predict new-onset hypertension.

The fasting blood glucose is another variable showing significant correlation with the UAE in this study. This could be a reflection of the prevalent insulin resistance in PCOS patients. Duleba *et al*. have shown that the insulin area under the curve during 2-hour GTT is an independent predictor of UAE.[14] The proposed mechanism by which hyperinsulinemia causes increased UAE is multifactorial: glomerular hyperfiltration,[27] endothelial dysfunction,[28] and increased vascular permeability.[29] The stimulation of the sympathetic nervous system by central actions of insulin also contributes to hypertension by enhancing renal sodium reabsorption and causing renal damage through increased intraglomerular pressure and protein delivery.[30]

We could not demonstrate a correlation between UAE and known risk factors for CVD like obesity (BMI), dyslipidemia (lipid profile), androgens, and uric acid. Thus, there are unknown mechanisms that need to be unraveled in order to explain the high prevalence of microalbuminuria which obviously puts them at a high risk for developing future CVD events and associated morbidity.

There are several limitations in our study. A control group comprising normal menstruating women could have better characterized the difference in UAE between the two groups and also the impact of normoandrogenemia on insulin resistance and markers of subclinical atherosclerosis [carotid intima media thickness, markers of systemic inflammation, high-sensitivity C-reactive protein (hsCRP), and cytokines]. Secondly, we did not estimate plasma insulin, and thereby parameters of insulin resistance, which could help in better understanding the predictors of UAE. Thirdly, the cohort is small and introduction of another arm consisting of patients with metabolic syndrome could have increased the values of results. However, the cut-off value of 17 mg/l in a random urine specimen has been shown to have a sensitivity of 100% and a specificity of 80% for the diagnosis of microalbuminuria when 24-hour timed urine collection was the reference standard.[31] The advantage of using a spot UAE is that it is cheaper and more convenient screening tool.

Further studies are needed before recommending routine use of UAE in PCOS cases for the detection of CVD if CVD risk markers are also estimated. The exact threshold for UAE to be considered as a significant risk for future CVD events needs to be determined as adverse clinical outcomes have been observed at levels below the current microalbuminuria threshold. Data regarding the threshold level in PCOS women are scarce and need further corroboration by studies with a large sample size and those which are prospectively designed to study future CVD events.

We conclude that this is the first study from India focusing on UAE in women with PCOS without hypertension. The prevalence of microalbuminuria (>17 mg/l) in morning spot sample was seen in 24.6% of women with PCOS. We did not find significant clinical predictors of UAE except hip circumference, diastolic BP in normotensive levels, and fasting blood glucose, which showed significant correlations with UAE. Spot urine for detection of microalbuminuria may be a convenient, economical mode of investigation in office setting for care of PCOS women, for early identification of a subset with a high risk of future CVD. A well-designed study with a controlled cohort, using cardiovascular risk markers and insulin resistance parameters is required to understand the risk in better way.

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