Original Article

Study of early atherosclerotic markers in women with polycystic ovary syndrome

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ABSTRACT

Objective: Women with polycystic ovary syndrome (PCOS) may represent a large underappreciated segment of female population who is at increased cardiovascular risk because of the presence of cluster of metabolic abnormalities. The aim of our study was to assess atherosclerotic risk factors in women with PCOS. **Materials and Methods:** In a cross-sectional study, 50 women with PCOS and 50 age and weight-matched healthy controls were enrolled. Endothelial dysfunction by flow-mediated dilatation (FMD) of brachial artery, highly sensitive C-reactive protein (hs CRP), and carotid intima media thickness (CIMT) were measured in both cases and control groups. **Results:** The mean age of women with PCOS was 26.82 ± 3.26 years and Body-mass index (BMI) of 26.2 ± 4.8 kg/m². Thirty-six (72%) patients were overweight or obese, 54% had central obesity and 12% had impaired glucose tolerance. Among the markers of atherosclerosis, hsCRP levels were nonsignificantly higher in patients with PCOS than in controls. The FMD was 12.18 ± 2.3% vs 8.3 ± 2.23% in patients with PCOS and controls respectively (*P*=0.01). CIMT was significantly different in two study groups (0.68 ± 0.11 in PCOS vs 0.52 ± 0.02 in normal subjects, (*P*=0.01). FMD had significant negative correlation with homeostasis model assessment (HOMA) index (r = −0.32, *P*=0.02) and hs CRP (r = −0.37, *P*=0.04) while hs CRP was correlated with BMI (r = 0.54, *P*=0.005), HOMA (r = 0.38, *P*=0.02) and FMD (r = -0.33, *P*=0.01). CIMT was significantly different in women with PCOS and control subjects, and it had significant correlation with age (r = 0.42, *P*=0.03), BMI (r = 0.36, *P*=0.01), waist circumference (r = 0.52, *P*=0.001) and HOMA (r = 0.31, *P*=0.04). **Conclusion:** Women with PCOS definitely have increased risk for future cardiovascular events. Clinicians should consider early cardiovascular screening and interventions to control all modifiable cardiovascular risk factors.

Key words: Atherosclerosis, cardiovascular risk, metabolic syndrome, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of child-bearing age with estimated prevalence of nearly 10%.[1,2] It is characterized by chronic anovulation, hyperandrogenism and/or polycystic ovaries. Its association with metabolic syndrome has placed it as ovarian manifestation of metabolic syndrome. Insulin resistance and its compensatory hyperinsulinemia is the central feature of PCOS, which it shares with metabolic syndrome. PCOS may represent a large underappreciated segment of female population who is at increased cardiovascular risk because of the presence of cluster of metabolic abnormalities such as glucose intolerance, hypertension, obesity and dyslipidemia. All of them have been associated with atherosclerosis. Glueck *et al.,* have reported that 46% of women with PCOS have the metabolic syndrome.[3]

Although the only long-term study on women with PCOS has not shown an increase in mortality[4] due to coronary artery disease, there is growing evidence that risk is substantial.[5-7] However, the question remains whether PCOS increases the risk independently of the presence of obesity. The studies have demonstrated conflicting results on atherosclerotic markers in women with PCOS. In recent times, certain surrogate markers of atherosclerosis have been devised, which can help assess the cardiovascular risk noninvasively.

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Endothelial dysfunction has been regarded as an early feature of atherosclerosis. Assessment of endothelial dysfunction by measuring flow-mediated dilatation (FMD) of the brachial artery is considered a potential tool for predicting coronary atherosclerosis.[8] Highly sensitive C-reactive protein (hsCRP)[9] and carotid intima media thickness (CIMT)[10] are other surrogate markers and good predictors of subclinical atherosclerosis and vascular events. We are facing the problem of metabolic syndrome and type 2 diabetes in epidemic proportions and not many studies have addressed this issue in our context. Therefore, this study was designed to evaluate early atherosclerotic markers in young women with PCOS and the age- and weight-matched control group.

MATERIALS AND METHODS

We conducted a cross-sectional hospital-based study in a medical college hospital that enrolled 50 patients aged 20–35 years from outpatient departments of medicine/endocrinology and gynecology who were diagnosed as PCOS according to Rotterdam criteria.[11] Two of three criteria were sufficient for confirmation of the diagnosis. We included 50 age- and weight-matched normal healthy women as controls with normal menstrual cycles, with no evidence of hyperandrogenism, and with normal ovarian morphology on pelvic ultrasonography. All study participants gave written informed consent, and the study protocol was approved by Institutional Ethics committee. All patients who had secondary causes of hyperandrogenism such as hyperprolactinemia, late-onset congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's disease, hypothyroidism, end-stage liver or kidney disease, pregnancy, hypertension and diabetes mellitus were excluded.

A detailed history and clinical examination for features of virilization and hirsutism according to Ferriman-Gallwey score was done. A thorough physical examination was performed, including measurement of weight, height and waist and hip circumferences. Weight was measured with the subject wearing light clothing without shoes, and height was measured using a stadiometer. Body-mass index (BMI) was calculated by using the formula: weight (in kg)/height (in meters)^2. Waist circumference (WC) was measured with the patient standing, at a point midway between the lower costal margin and the iliac crest in the mid-axillary line. Blood pressure was measured manually with a sphygmomanometer. Overweight (BMI >23 kg/m^2) and central obesity (WC >80 cm) were defined by Asian criteria.[12] The biochemical profile included lipids, glucose, insulin and liver and renal function tests. The serum levels of prolactin, thyroxin, total testosterone, Dehydroepiandrosterone sulfate, follicle-stimulating hormone, luteinizing hormone

(LH) and 17-hydroxy progesterone were measured in all cases and controls. Homeostasis model assessment (HOMA) method for insulin resistance was calculated by the formula: Fasting serum insulin (micro units/mL) × fasting serum glucose (mill moles/L)/22.5.

Flow-mediated dilatation measurement
Endothelial function was measured noninvasively by ultrasonographic assessment of right brachial artery dimensions.[13] The diameter of the right brachial was measured twice, first at rest, then after inducing reactive hyperemia with the help of pneumatic cuff. It was carried out by a blinded sonologist, after an overnight fast in a cool, quiet room, with B mode ultrasound scanner (Seimens, Munich, Germany) using 10 MHz linear transducer. The diameter of right brachial artery was measured 2–8 cm above the antecubital space in the end-diastolic phase from one media–adventitia interface to the other at the clearest part three times and an average was taken. After the detection of the right transducer position, skin was marked and arm kept in same position. The blood pressure cuff was tied on the upper arm and inflated to supra-systolic levels and kept inflated for 4 minutes. Sixty seconds after the cuff was released, brachial artery dimensions were again measured. The maximum diameter measurement was defined as the average of three consecutive diameters measurements. The hsCRP concentration was determined using an immunoturbidimetric method (Randox, Mauguio, France) in mg/dL. CIMT was measured by B mode ultrasound using linear probe at frequency of 10 MHz. The common carotid arteries were scanned at the level of bifurcation on either side and mean value was used for analysis. The intima media thickness was measured in the far wall of the arteries at sites identified as diffuse and continuous projections with the greatest distance between the luminal–intimal interface and media–adventitial interface but without atherosclerotic plaques. Localized lesions >2 mm thickness were considered to be atherosclerotic plaques. CIMT was assessed by single observer who was blinded for the diagnosis.

Statistical analysis
The Statistical Package for the Social Sciences (SPSS) version 15.0 was used for statistical analysis. Results were expressed as mean ± SD. The characteristics of distribution were tested with Kolmogorov-Smirnof test. Highly skewed variables were analyzed after logarithmic transformation. Spearman rank correlations were used for these variables. When variables showed persistent skewed deviation, Mann-Whitney 'U' test was used. Differences between means were analyzed by Student's unpaired 't' test. P value <0.05 was considered statistically significant. Analysis of correlations between parameters was performed by using Pearson's

correlation coefficient and regression analysis was done to predict FMD and CIMT.

RESULTS

The anthropometric data of women with PCOS and controls are listed in Table 1. The mean age of women with PCOS was 26.82 ± 3.26 years and BMI of 26.2 ± 4.8 kg/m². Thirty-six (72%) patients were overweight or obese, 54% had central obesity and 12% had impaired glucose tolerance (plasma glucose 2 h post 75 g glucose 140–199 mg/dL). There were no statistically significant differences in BMI, WC, hip circumference, waist/hip ratio, and mean systolic and diastolic blood pressure between cases and controls subjects. Table 2 summarizes the metabolic and hormonal profile of PCOS patients and control subjects that showed significant differences in levels of total testosterone, LH, insulin and HOMA index, while no difference could be demonstrated in other hormone levels between PCOS patients and control subjects.

Among the markers of atherosclerosis [Table 3], hsCRP levels were higher in patients with PCOS than in controls but the difference was not statistically significant.

The baseline brachial artery diameter was 3.78 ± 0.23 mm in women with PCOS and 3.5 ± 0.42 mm in controls. The difference was not statistically significant. On the contrary, after inducing reactive hyperemia, the mean brachial artery dimensions were 4.23 ± 0.12 and 4.08 ± 0.17 ($P = 0.02$). The FMD was 12.18 ± 2.3% vs 8.3 ± 2.23% in patients with PCOS and controls, respectively ($P = 0.01$).

CIMT was significantly different in two study groups (0.68 ± 0.11 in PCOS vs 0.52 ± 0.02 in normal subjects, $P = 0.01$). FMD had significant negative correlation with HOMA index ($r = -0.32$, $P = 0.02$) and hsCRP ($r = -0.37$, $P = 0.04$) while hsCRP was correlated with BMI ($r = 0.54$, $P = 0.005$), HOMA ($r = 0.38$, $P = 0.02$) and FMD ($r = -0.33$, $P = 0.01$). CIMT was significantly different in women with PCOS and control subjects, and it had significant correlation with age ($r = 0.42$, $P = 0.03$), BMI ($r = 0.36$, $P = 0.01$), WC ($r = 0.52$, $P = 0.001$) and HOMA ($r = 0.31$, $P = 0.04$).

Multiple regression analysis was carried out with CIMT as dependent variable. In the studied subjects ($n = 100$), PCOS status, age and BMI were the independent predictors of CIMT. Similarly for FMD, HOMA and hsCRP were the independent predictors.

Table 1: Clinical characteristics of women with polycystic ovary syndrome and control subjects

Variables	PCOS women (N = 50)	Controls (N = 50)	P value
Age (years)	26.82 ± 3.26	25.7 ± 4.6	0.78
BMI (kg/m²)	26.2 ± 4.8	25.7 ± 4.2	0.2
Waist circumference (cm)	96.2 ± 6.8	98.3 ± 6.2	0.62
Hip circumference (cm)	107.6 ± 12.4	109.2 ± 7.8	0.5
Waist/Hip ratio	0.90 ± 0.1	0.89 ± 0.08	0.12
Systolic BP (mmHg)	126 ± 20	118 ± 16	0.08
Diastolic BP (mmHg)	86.4 ± 7.2	78 ± 7.6	0.06

Table 2: Hormonal data of women with polycystic ovary syndrome and control subjects

Variables	PCOS women (N = 50)	Controls (N = 50)	P value
Fasting glucose (mg/dL)	86 ± 7.6	82.2 ± 6.0	0.08
Triglyceride (mg/dL)	132 ± 54	119 ± 32	0.01
LDL-cholesterol (mg/dL)	126 ± 39.2	123 ± 27	0.6
HDL-cholesterol (mg/dL)	46.8 ± 7.6	48 ± 9.7	0.07
FSH (miU/mL)	7.6 ± 4.5	5.62 ± .82	0.06
LH (miU/mL)	16 ± 4.6	3.7 ± 2.1	0.001
Testosterone (nmol/L)	2.8 ± 1.1	1.32 ± 0.6	0.02
DHEAS (mg/dL)	196.72 ± 82.14	179 ± 3.21	0.7
17-OH Progesterone (ng/dL)	1.72 ± 1.12	1.3 ± 0.83	0.6
Insulin (mu/mL)	10.2 ± 3.4	6.1 ± 1.8	0.05
HOMA-IR	2.5 ± 0.4	1.36 ± 0.62	0.01

Table 3: Atherosclerosis markers in women with polycystic ovary syndrome and control subjects

Variables	PCOS women (N = 50)	Controls (N = 50)	P value
HsCRP (mg/dL)	3.6 ± 2.12	3.08 ± 2.4	0.06
FMD (%)	12.18 ± 2.3	8.3 ± 2.23%	0.01
CIMT (mm)	0.68 ± 0.12	0.52 ± 0.02	0.01

DISCUSSION

Women with PCOS have a cluster of metabolic abnormalities. The proposed definition for this is female metabolic syndrome or syndrome XX[14] that starts early in adolescence and can lead to the development of premature atherosclerosis. The studies done on various atherosclerotic risk markers in women with PCOS have reported conflicting results. The variability of methodology that includes definition of PCOS, definition of metabolic syndrome, method of recruitment of PCOS group, selection of controls and the age, race or weight of the participants makes the interpretation of the results difficult in terms of prediction of the cardiovascular risk in the patients of PCOS.

There is increasing evidence that suggests atherosclerosis is a chronic inflammatory process. Several large-scale prospective studies have shown that inflammatory markers

like hsCRP provide an adjunctive method for assessment of cardiovascular risk. Many studies have also shown high hsCRP levels in women with PCOS[15-17] in contrast to others that say it is related only to obesity.[18] In our study, hsCRP level was not significantly higher in women with PCOS than the controls and it had correlation with BMI, FMD and decreased insulin sensitivity. Kim *et al.*[19] have reported higher hsCRP levels even in lean PCOS women. A meta-analysis of cardiovascular risk markers that included hsCRP by Toulis *et al.,*[20] concluded that women with PCOS have increased incidence of inflammatory markers compared with controls.

One of the earliest processes in the pathogenesis of atherosclerosis is impaired endothelial dysfunction that can be quantified by noninvasive methods. In FMD of brachial artery, dilatation is measured ultrasonographically after inducing brachial artery ischemia, which leads to release of endothelial nitric oxide and relaxation of vascular smooth muscle. FMD is a marker of sub-clinical atherosclerosis since it is well correlated with impaired endothelial function in the coronary arteries.[21] A link has been established between insulin resistance and endothelial dysfunction. Paradisi *et al.,*[22] first reported that PCOS is characterized by endothelial dysfunction. Although exact mechanism how insulin resistance leads to endothelial dysfunction is not clear, it has been proposed that overproduction of free fatty acids and inflammatory cytokines such as tumor necrosis factor alpha and leptin cause endothelial dysfunction, which is contributed by oxidative stress.[23,24] In our study, FMD was significantly different in cases and control subjects. It also had correlation with HOMA index.

CIMT is an easy and reliable marker of early atherosclerotic changes and is widely used to predict cardiovascular events. Multiple investigators have found that patients with PCOS have a greater prevalence of abnormal CIMT than the general population. The significant difference was demonstrated in CIMT between women with PCOS and controls in our study, similar to reports by Lakhani and Talbott *et al.*[25,26] In multiple regression analysis, PCOS status, age and BMI were the independent predictors of CIMT, while HOMA and hsCRP were the independent predictors of FMD.

Orio *et al.,*[27] also found an early impairment of endothelial structure and function and greater CIMT in normal-weight women with PCOS. In addition, Talbott and colleagues[17] also found a relationship between the degree of CIMT thickening in PCOS patients and levels of CRP. The insulin resistance is the key component of PCOS, which is present in both obese and lean women with PCOS[28] and is linked with the increased cardiovascular risk markers. The

diagnosis of PCOS implies cardiovascular risk. Although a recent study published by Schmidt *et al.,*[29] after 21 years follow-up in PCOS women of postmenopausal age does not entail an evident increase in cardiovascular events, Meyer *et al.,*[30] in a systematic review and meta-analysis concluded that women with PCOS are at greater risk of premature atherosclerosis.

Indian women are reported to have a high prevalence of PCOS[31] and Indian patients have higher fasting insulin levels and greater insulin resistance compared with white women with PCOS.[32,33] A high prevalence of impaired glucose tolerance and diabetes mellitus has been reported.[34,35] Sundararaman *et al.,*[36] reported south Indian women with reproductive abnormalities had greater insulin resistance and CIMT compared with controls. The difference persisted when non-obese women with PCOS were compared with controls. Not many studies in India have addressed this issue and none of them have used the same surrogate markers of early atherosclerosis[37,38] as have been studied by us. The limitations of our study were small sample size and that we did not analyze obese and lean PCOS with obese and lean controls separately.

CONCLUSION

Women with PCOS definitely have increased markers of atherosclerosis independent of obesity, so they are at risk for future cardiovascular events because of the presence of metabolic derangements, although larger studies with well-defined PCOS population may be required to draw a more robust conclusion.

Clinicians should consider early cardiovascular screening and interventions to control all modifiable cardiovascular risk factors in women who are diagnosed to have PCOS.

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