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Association of Coronary Heart Disease Risk and Lipid Profile in Indian Women With Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome (PCOS) has been one of the major public health problems in India. Women with PCOS are often assumed, *a priori*, to be at increased risk for cardiovascular disease, given the high prevalence of the metabolic syndrome X among them. Lipoprotein (a) (Lp(a)) is an risk factor for development of atherosclerosis and along with dyslipidemia may add to cardiovascular risk. The aim of the study was to know the lipid profile variation in Indian women with PCOS.

Methods: This cross-sectional study was conducted in West Bengal state, India. The subjects enrolled for the study included 180 women with PCOS who were compared with 95 healthy women of the control group; all of them were age and weight matched. Samples were taken after overnight fasting, and then serum lipid levels were analyzed.

Results: The mean age of subjects was 28.71 ± 4.12 years in the PCOS group and 30.14 ± 3.29 years in the control group. The lipid profile parameters were comparable between patients and control subjects. There was a statistically significant difference in the Lp(a) levels between patients with PCOS and normal controls ($P \leq 0.0001$). There were statistically significant increased levels of total cholesterol, very low-density lipoprotein and low-density lipoprotein cholesterol in PCOS group when compared with the control group ($P < 0.05$) and decreased level of high-density lipoprotein cholesterol.

Conclusion: The changed lipid profile levels may contribute to increased cardiovascular risk in PCOS patients.

Keywords: Lipid profile; Polycystic ovarian syndrome; Cardiovascular disease

Introduction

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age and has a strong genetic component. It is characterized by ovarian dysfunction and its clinical manifestations may include obesity, increased insulin resistance and compensatory hyperinsulinemia, oligo-/anovulation and infertility [1]. It has been recognized that PCOS has an extremely heterogeneous clinical picture and is multifactorial in etiology. PCOS may represent the largest under-appreciated segment of the female population at risk of cardiovascular disease (CVD). The pathophysiology is complex involving the hypo-thalamo-pituitary-ovarian axis, ovarian theca cell hyperplasia, hyper-insulinemia and a multitude of other cytokine and adipocyte-driven factors [2]. The diagnosis of PCOS is based on the Rotterdam criteria for the presence of any two of the following conditions: 1) chronic anovulation, 2) clinical/biochemical parameters for hyperandrogenism, and 3) polycystic ovaries on ultrasonography [3]. Insulin resistance, hyper-androgenism, and dyslipidemia are supposed to be the major risk factors for CVD in women with PCOS [4, 5]. Dyslipidemia allegedly plays a key role in the risk of cardiovascular pathology in women with PCOS. It is still not known to what degree dyslipidemia contributes to this risk [6].

Dyslipidemia is the most common abnormality in PCOS [7], with elevated levels of total cholesterol, triglycerides (TGs), very low-density lipoprotein (VLDL) and low-density lipoprotein cholesterol (LDL-C) and with low levels of high-density lipoprotein cholesterol (HDL-C) [8, 9]. Talbott et al reported increased level of LDL-C in patients with PCOS, and Conway et al reported that the most characteristic lipid alteration is decreased levels of HDL-C.

Lipoprotein (a) (Lp(a)) is a modified form of LDL in which apo A-1 is bound to apo B. It is metabolically distinct from LDL and its levels are determined genetically, with its concentration remaining stable throughout the life of a subject. Changes in plasma lipid and Lp(a) composition place the patient at an increased risk for CVD. High Lp(a) levels represent an independent risk factor for cardiovascular events, linked to an increased risk of myocardial infarction, stroke and coronary heart disease [10]. Early screening of modifiable cardiovascular risk factors may help in preventing development of CVD. There are few studies done to know the variation in serum lipid profile in PCOS patients; thus, this study was done to know the lipid profile variation in women with PCOS.

Materials and Methods

A cross-sectional study was carried out on 180 newly diagnosed PCOS patients (age range 18 - 35 years) based on Rot-

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Table 1. Comparison of Basic Characteristics and Lipid Profile Between Cases and Controls

Variables	PCOS group (n = 180)	Control group (n = 95)	P value
Age (years)	28.71 ± 4.12	30.14 ± 3.29	0.0037
Height (cm)	162.3 ± 4.92	164.1 ± 5.59	0.0053
Weight (kg)	68.3 ± 9.49	65.1 ± 7.34	0.0045
BMI (kg/m^2)	27.42 ± 3.27	23.72 ± 3.19	< 0.0001
Total cholesterol (mg/dL)	165.11 ± 39.1	139.32 ± 35.41	< 0.0001
TG (mg/dL)	117.52 ± 34.91	110.49 ± 24.1	0.08
LDL-C (mg/dL)	101.27 ± 22.19	67.13 ± 11.9	< 0.0001
VLDL-C (mg/dL)	25.13 ± 2.1	22.7 ± 1.7	< 0.0001
HDL-C (mg/dL)	41.81 ± 17.63	49.02 ± 14.13	0.0007
Lp(a) (mg/dL)	22.52 ± 2.37	15.42 ± 4.13	< 0.0001

Values are expressed as mean ± standard deviation. Lp(a): lipoprotein (a); BMI: body mass index; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

terdam criteria and 95 non-PCOS controls (showed no history of drugs affecting lipid metabolism with normal menstrual cycle and sex hormone level and no evidence of polycystic ovary) who attended the Obstetrics and Gynecology Outpatient Department of MAGS Medical & Research Center, West Bengal, Kolkata.

A written informed consent was obtained from all the participants; all of them were age and weight matched. Baseline data including age, body mass index (BMI; kg/m^2), detailed medical history, clinical examination and relevant investigations were recorded. The blood samples were obtained to determine the levels of lipids parameters. The blood samples were drawn after overnight fasting in the morning (between 8 am and 11 am). Blood samples of 5 mL from each individual of the study population were collected from both cases and controls. Enzymatic colorimetric methods were used to determine total cholesterol, TGs, HDL-C, and LDL-C levels. Estimation of serum Lp(a) was performed by immune-nephelometric method.

M-Mode, two-dimensional, and pulsed Doppler echocardiography studies were performed by one operator, who was blind with respect to the presence of metabolic abnormalities or arterial hypertension, using ultrasound systems (Apogee CX, Interspec, Inc., Ambler, PA) with a 3.5-mHz transducer during at least three consecutive cardiac cycles. All subjects were studied in the left lateral position after a 10-min resting period.

All these parameters were investigated and recorded, and then, a comparison was made between PCOS patients and control participants.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 package (SPSS, Inc., Chicago, IL). Data were expressed as the mean ± standard deviation (SD). The comparisons between patients and controls were performed using a *t*-test for unpaired data. Correlation was tested using Pearson's correlation coefficient. Significance was set at 5%.

Results

A total of 180 patients with PCOS and 95 healthy women were included in the study with a mean age of 28.71 ± 4.12 and 30.14 ± 3.29 years. Other basic characteristics of the study participants such as BMI of the PCOS patients were statistically significantly ($P \leq 0.0001$) increased when compared with control group (27.42 ± 3.27 vs. 23.72 ± 3.19). The mean ± SD of the lipid profile parameters in PCOS group of serum TG, total cholesterol, HDL, VLDL and LDL were 117.52 ± 34.91,

Table 2. Correlation Between Various Parameters in PCOS Cases

	BMI	LDL cholesterol	Total cholesterol	Lp(a)
BMI	0.9			
LDL cholesterol	0.67	1.000		
	P = 0.007			
Total cholesterol	0.509	0.951	1.000	
	P = 0.058	P = 0.001		
Lp(a)	0.476	0.5	0.565	1.000
	P = 0.021	P = 0.003	P = 0.01	

Table 3. Echocardiographic Findings in PCOS and Controls

	PCOS group (n = 180)	Control group (n = 95)	P value
Left ventricular diastolic diameter (mm)	40.9 ± 2.5	38.1 ± 1.7	< 0.0001
Left ventricular systolic diameter (mm)	28.3 ± 3.1	23.9 ± 4.7	< 0.0001
Aorta size (mm)	30.0 ± 4.9	28.1 ± 1.3	0.0003
Left ventricular posterior wall thickness (mm)	9.3 ± 2.7	6.7 ± 1.2	< 0.0001
Left atrium size (mm)	36.3 ± 5.1	25.1 ± 4.9	< 0.0001
Left ventricular mass index (g/m^2)	85.4 ± 17.9	54.9 ± 9.2	< 0.0001
Inter-ventricular septum thickness (mm)	7.3 ± 1.5	6.1 ± 0.9	< 0.0001
Early to late mitral flow velocity	1.43 ± 0.7	2.5 ± 0.3	< 0.0001
Left ventricular ejection fraction (%)	62.1 ± 5.3	68.9 ± 1.2	< 0.0001

165.11 ± 39.1, 41.81 ± 17.63, 25.13 ± 2.1 and 101.27 ± 22.19 mg/dL, respectively, while those of control group were 110.49 ± 24.1, 139.32 ± 35.41, 49.02 ± 14.13, 22.7 ± 1.7 and 67.13 ± 11.90 mg/dL, respectively (Table 1). There were statistically significantly increased levels of total cholesterol, VLDL and LDL-C in PCOS group and decreased levels of HDL-C when compared with the control group ($P < 0.05$).

Mean Lp(a) levels in patients with PCOS were higher compared to control subjects ($P < 0.0001$) (Table 1). The proportion of patients with Lp(a) greater than 30 mg/dL was higher in patients with PCOS compared to control subjects.

In our study, the correlations between BMI and all the parameters in the study were found. A positive correlation was observed between Lp(a) and BMI ($P = 0.021$), total cholesterol ($P = 0.01$) and LDL-C ($P = 0.003$) (Table 2).

Women with PCOS had a cardiac size significantly increased compared with controls. They had also inter-ventricular septum, left ventricular (LV) posterior wall thickness and left ventricular mass index (LVMi) significantly higher than controls. Additionally, PCOS patients had significantly lower left ventricular ejection fraction (LVEF) and E/A than controls (Table 3).

Discussion

There is increasing evidence that patients with PCOS have increased cardiovascular risk compared with age matched controls. It has been estimated that myocardial infarction is seven times more likely in patients with PCOS [11]. This increased cardiovascular risk is probably the result, in part, of the metabolic disturbance associated with PCOS. Dyslipidemia, diabetes, and obesity are all potent cardiovascular risk factors that tend to cluster in women with PCOS. However, it is not known whether the increased cardiovascular risk seen in PCOS is mediated through obesity per se or is independent of BMI and the result of other metabolic factors. Cardiovascular risk factors seem to cluster in women with PCOS when compared with general population [12].

In our study, levels of total cholesterol, VLDL and LDL-C were statistically higher, and level of HDL-C was lower in PCOS patients, when compared with age matched healthy females (Table 1). Moreover, similar results found by some studies suggest that PCOS patients were hyper-lipidemic with higher total cholesterol, LDL-C, and TGs concentrations and lower HDL-C levels than control [13]. On the other hand, our results were not concurrent with the study done by Bickerton et al, who demonstrated that there were no significant differences in lipid or lipoprotein concentrations between patients with PCOS and weight matched controls.

Lp(a) is a heterogeneous class of lipoproteins, metabolically distinct from LDL and its levels are determined genetically. High Lp(a) levels represent an independent risk factor for cardiovascular events. Our study showed a statistically significantly higher Lp(a) level in PCOS patients than control ($P \leq 0.0001$). The simultaneous increase of Lp(a) and LDL-C could increase the cardiovascular risk with synergistic effect. Lp(a) greater than 30 mg/dL has been considered as elevated [14]. However, our study showed a significantly higher number of cases with Lp(a) > 30 mg/dL. Lipid abnormalities were closely related to insulin resistance independent of obesity [15]. The increase in TGs may be because of the accumulation of TGs, which may occur owing to the increased lipogenesis, decreased clearance, or reduced oxidation of fatty acids. Increased secretion of VLDL particles by the liver resulted in elevated plasma TGs concentration. This may occur because of insulin resistance, which is seen in PCOS patients. Insulin resistance also contributes more to catabolism of HDL-C particles and formation of LDL-C [16]. Hyper-androgenism also contributed to altered lipid profile. Hyper-androgenism has been associated with increased hepatic lipase activity and plays a role in the catabolism of HDL-C particles. Increased serum concentrations of TGs have also been recognized as a risk factor for CVD [17]. Left ventricular hypertrophy (LVH) is an important predictor of cardiovascular morbidity and mortality [18], but determinants of LV mass (LVM) in non-hypertensive subjects are still incompletely understood [19]. We also confirmed increased LVM and diastolic dysfunction in PCOS women. PCOS could be considered an aggravating factor causing LVH and could play a role in the early CVD in PCOS. Among the various echocardiographic parameters that were different between PCOS and controls, the increased LVMi in PCOS patients has clinical importance, because it represents the main cause of both LVH and diastolic dysfunction in PCOS women,

worsening from early to elderly age.

Conclusion

In this background, it is concluded that women with PCOS have altered Lp(a), lipid profile, with higher levels of TGs, total cholesterol, VLDL and LDL and low level of serum HDL; this difference may play a role in the pathophysiology found in women with PCOS. At the moment, it is not known to what degree these different forms of dyslipidemia may contribute to increasing this cardiovascular risk in PCOS and further studies are needed to clarify the role of lipids in these women. Moreover, elevated Lp(a) levels and lipid profile levels may contribute to development of atherosclerosis and increased cardiovascular risk in PCOS patients.

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Author Contributions

DS carried out the data collection, participated in the data analysis and drafted the manuscript. RC helps in study design, diagnosis of study groups and preparing the manuscript.

Competing Interests

The authors declare that they have no competing interests.

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