Original Article:

Serum lipoprotein(a) and lipid profile in polycystic ovarian syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome **(**PCOS) is associated with dyslipidaemia and may render the affected women "at risk" of developing cardiovascular disease. Lipoprotein(a) [Lp(a)] is an independent risk factor for development of atherosclerosis and along with dyslipidaemia may add to cardiovascular risk. In this background the levels of Lp(a) and lipid profile are assessed in PCOS patients.

Material and Methods: The study was carried out on 30 newly diagnosed PCOS subjects aged 18-35 years and 30 age-matched healthy women. Blood samples were collected in a fasting state and serum Lp(a), lipid parameters were estimated.

Results: The lipid profile parameters were comparable between patients and control subjects. There was no statistically significant difference in the median [interquartile range (IQR)] Lp(a) levels between patients with PCOS and normal controls. However, the proportion of subjects with elevated (> 30 mg/dL) Lp(a) levels were significantly higher in patients with PCOS compared to control subjects.

Conclusion: Elevated Lp(a) levels may contribute for development of atherosclerosis and increased cardiovascular risk in PCOS patients.

Key words: *Lp(a), Lipid profile, Polycystic ovarian syndrome*

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a multifactorial and polygenic condition. It is a syndrome of ovarian dysfunction that is characterized by anovulation, hyperandrogenism and/or the presence of polycystic ovary (PCO) morphology.

The PCOS is one of the most common female endocrinopathies affecting 6%-7% of women in reproductive age. In the past the clinical diagnosis rested on the triad of hirsutism, amenorrhoea and obesity. The diagnosis of PCOS is based on the Rotterdam criteria: presence of any two of (i) chronic anovulation; (ii) clinical/ biochemical parameters for hyperandrogenism; and (iii) polycystic ovaries on ultrasonography.[1]

Subsequently it has been recognized that PCOS has an extremely heterogeneous clinical picture and is multifactorial in aetiology. PCOS may represent the largest under-appreciated segment of the female population at risk of cardiovascular disease. The pathophysiology is complex involving the hypothalamo-pituitary-ovarian axis, ovarian theca cell hyperplasia, hyperinsulinaemia and a multitude of other cytokine and adipocyte-driven factors.[2]

Insulin resistance, hyperandrogenism and dyslipidaemia are likely to be the major risk factors for cardiovascular diseases (CVD) in

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women with PCOS.[3,4] Insulin resistance and dyslipidaemia seem to have an important role on the risk of cardiovascular pathology in women with PCOS. It is still not known to what degree dyslipidaemia contributes to this risk.[5] Generally, dyslipidaemia of PCOS is characterized by increased triglycerides and low high density lipoprotein (HDL) cholesterol, but it has also been found that although low HDL-cholesterol is common, hypertriglyceridaemia is relatively uncommon.[6] On the contrary, the most classic lipid alteration determining cardiovascular risk, increase of low density lipoprotein (LDL) cholesterol, is not common in all populations with PCOS. Beyond LDL-cholesterol concentrations, the quality of LDL may exert a direct influence on the cardiovascular risk.

Although for many years it has been known that PCOS is associated with reproductive morbidity and increased risk for diabetes mellitus, ovarian and endometrial cancer, more recently a large number of studies have shown that women with PCOS also bear an increased cardiovascular risk.[6] 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 places 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.[7]

Early screening of modifiable cardiovascular risk factors may help in preventing development of cardiovascular disease. So, our study is done to find out if there is an elevated Lp(a) level and dyslipidaemia in PCOS. The objective of the study was to assess Lp(a) and lipid profile levels in women with PCOS.

MATERIAL AND METHODS

The study was carried out on 30 newly diagnosed PCOS patients (age range 18-35 years) based on Rotterdam criteria[1] and 30 non-PCOS controls who attended the Obstetrics and Gynaecology outpatient department of Kempegowda Institute of Medical Sciences, Bengaluru, during the period 2011-12. The Institutional Ethical Committee approved the study protocol. Informed consent was obtained from all the participants. Patients with PCOS had no history of diabetes, hypertension, renal and liver failure, other endocrine disorders and drugs affecting glucose and lipid metabolism. Thirty healthy females in the age group of 18 to 35 years with normal menstrual cycle, no evidence of clinical hyperandrogenaemia or PCOS were selected as control subjects.

Baseline data including age, body-mass index (BMI; kg/m^2), detailed medical history, clinical examination and relevant investigations were recorded.

Five mL peripheral venous blood sample was obtained after overnight fasting of 12 hours by venepuncture from both cases and controls and the serum was separated. Estimation of serum Lp(a) was performed by immuno-nephelometric method. Total cholesterol (TC), serum triglycerides (TG), HDL cholesterol, fasting blood glucose, blood urea, serum creatinine were estimated using commercial kits on A25 auto analyzer (Biosystems, Spain). Serum very low density lipoprotein (VLDL) cholesterol and LDL cholesterol were calculated from the values of TC, TG and HDL cholesterol by applying Friedewald's formula.[8] TC/HDL cholesterol and LDL cholesterol/HDL cholesterol ratios were determined.

Statistical analysis

Comparisons between groups were performed using the Mann-Whitney U-test. Comparison

of proportions of parameters was done using Chi-square test. Correlation was tested using Pearson's correlation coefficient. SPSS software version 13.0, SPSS Inc., Chicago, USA was used for statistical analysis. A p value < 0.05 was considered statistically significant.

RESULTS

The parameters studied are shown in Table 1. Correlations are shown in Table 2. There was no statistically significant difference in age and BMI between cases and controls. TC, TG, LDL cholesterol, HDL cholesterol, VLDL cholesterol, TC/HDL cholesterol and LDL cholesterol/HDL cholesterol also did not show significant difference between cases and controls. Median Lp(a) levels in patients with PCOS were similar compared to control subjects ($p = 0.273$). The proportion of patients with Lp (a) greater than 30 mg/dL was higher in patients with PCOS compared to control subjects (33% Vs 10%; $p = 0.028$). A positive correlation was observed between Lp(a) and BMI ($p = 0.016$), TC ($p = 0.001$) and LDL cholesterol ($p = 0.010$) (Table 2).

DISCUSSION

PCOS is the most common endocrine disorder to affect women. It is a genetically complex disorder that is characterized by hyperandrogenemia and amenorrhoea or oligomenorrhoea resulting in infertility among reproductive age women. Cardinal features of PCOS include chronic anovulation, clinical or biochemical hyperandrogenism, obesity and polycystic ovaries.

Obesity, insulin resistance and hyperinsulinaemia are commonly associated with recognized increased risk for the development of metabolic syndrome and diabetes mellitus. The metabolic syndrome is a cluster of risk factors for the development of CVD.

We did not find any significant difference in TC, TG, LDL cholesterol, HDL cholesterol, VLDL cholesterol, TC/HDL cholesterol and LDL cholesterol/HDL cholesterol in patients with PCOS and control subjects. However, higher TG, TC and LDL cholesterol, lower HDL cholesterol and apoA-I were observed in PCOS

Table 1: Comparison of basic characteristics, Lp(a) and lipid profile between controls and cases

Parameter	Controls (n = 30)	Cases (n = 30)	p-value
Age (years)*	26.4 ± 4.5	24.5 ± 4.1	0.92
BMI (kg/m^2)*	24.9 ± 2.5	25.5 ± 3.4	0.47
Total cholesterol (mg/dL)*	155.2 ± 31.0	164.1 ± 31.0	0.271
TG (mg/dL)†	113.0 (89.0-146.5)	114.4 (91.8-188.2)	0.336
LDL cholesterol (mg/dL)*	91.1 ± 26.5	98.6 ± 19.7	0.218
VLDL cholesterol (mg/dL)	22.6 (17.0-30.0)	26.0 (19.0-34.0)	0.255
HDL cholesterol (mg/dL)*	39.9 ± 10.7	37.6 ± 9.6	0.383
TC/HDL cholesterol (mg/dL)*	4.1 ± 1.0	4.6 ± 1.4	0.095
LDL/HDL cholesterol (mg/dL)*	2.4 ± 0.8	2.8 ± 0.9	0.079
Lp(a) (mg/dL)†	16.5 (10.7-24.0)	21.4 (106-40.6)	0.273

* Values are expressed as mean ± standard deviation

† Values are expressed as median (interquartile range)

Lp(a) = lipoprotein (a); BMI = body-mass index; TG = triglycerides; LDL = low density lipoprotein; VLDL = very low-density lipoprotein; HDL = high-density lipoprotein

Table 2: Correlation between various parameters in PCOS cases

	BMI	Cholesterol	LDL cholesterol	Lp(a)
BMI	1.000	-	-	-
Cholesterol	0.488	1.000	-	-
	(p = 0.006)			
LDL cholesterol	0.405	0.805	1.000	-
	(p = 0.026)	(p= 0.001)		
Lp(a)	0.438	0.564	0.465	1.000
	(p = 0.016)	(p = 0.001)	(p = 0.01)	

BMI = body-mass index; LDL = low density lipoprotein; Lp(a) = lipoprotein(a); PCOS=polycystic ovarian syndrome

patients in another study.[9] A higher mean TC/HDL cholesterol and LDL cholesterol/HDL cholesterol were observed in PCOS compared to controls in another study.[10] Low HDL (<50 mg/dL) as a component of dyslipidaemia was observed in 86.7% of cases in our study. This is similar to the findings in south Indian population where low HDL was seen 93.3% cases with PCOS.[11] The reason for dyslipidaemia in PCOS may be attributed to hyperinsulinaemia and hyperandrogenemia. This causes adipocytes to undergo increased catecholamine-induced lipolysis and release of free fatty acids into the circulation. Increased free fatty acids in the liver stimulate secretion of VLDL which ultimately leads to hypertriglyceridaemia.[12] Through the reverse cholesterol transport pathway, hypertriglyceridaemia leads to low HDL cholesterol and increased LDL cholesterol levels. Further priming of adipocytes by androgens in early life predisposes to the dyslipidaemia associated with PCOS. Conversely, it is also possible that hyperandrogenaemia is a consequence of more metabolically active adipocytes.[13] Hyperandrogenism may also affect lipid metabolism by the induction of hepatic lipase activity which has a role in the catabolism of HDL particles.[11] Insulin resistance has been associated with decreased levels of HDL cholesterol and increased levels of LDL cholesterol and TG. This has been associated with increased risk of CAD.[14]

Lp(a) greater than 30 mg/dL has been considered as elevated.[15] Although the median Lp(a) was higher in cases than in controls, the difference was not statistically significant (p = 0.273). However, our study showed a significantly higher number of cases with Lp(a) >30 mg/dL (33% in cases Vs 10% in controls) when compared to the controls (p = 0.028). Our results are in agreement with observation from another study[3] where higher circulating asymmetric dimethylarginine (ADMA), total homocysteine, high sensitive C-reactive protein (hsCRP), Lp(a) and fibrinogen were observed in PCOS than in healthy controls.

Studies were conducted to find out other lipids promoting arteriosclerosis in women with PCOS. Apoprotein B (ApoB) is the main structural component of LDL and its evaluation represents a more accurate measurement of the relative number of LDL particles compared to the more common measurement of LDL cholesterol. One study[5] did not find a difference in apoB levels between women with PCOS and the controls. This they attributed to genetic and environmental factors that determine different lipid patterns. Lipoprotein(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. Their study showed a quarter of the

subjects to have elevated Lp(a) level (>30 mg/dL). The simultaneous increase of Lp(a) and LDL cholesterol could increase the cardiovascular risk with synergistic effect. Lp(a) also did not correlate with levels of insulin or insulin resistance suggesting that dyslipidaemia can stem from different metabolic mechanisms. At the moment, it is not known to what degree these different forms of dyslipidaemia may contribute to increasing this cardiovascular risk in PCOS and future prospective studies are needed.[5]

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