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Research Article

Study of serum lipoprotein (a) and lipid profile in polycystic ovarian syndrome

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ABSTRACT

Objective: To study of serum lipoprotein (a) and lipid profile in polycystic ovarian syndrome
Methods and collection of Data: This case/control study was conducted at Department of Obstetrics and Gynecology Mayo Hospital Lahore from June 2017 December 2017. Total 30 cases of PCOS and 30 controls were selected. Lipid profile and Lp(a) was compared between cases and controls and findings noted in on pre-designed proforma.
Result: Serum TC, TG, LDL, VLDL, TC/HDL, LDL/HDL values were elevated in the cases. The number of cases with Lp(a) levels >30mg/dl were significantly higher in cases than in controls.
Conclusion: Dyslipidemia and elevated Lp(a) may be factors contributing to an increased risk of coronary artery disease in patients with PCOS.

Keywords: Polycystic ovary syndrome, lipid profile, Lp(a).

INTRODUCTION

Polycystic ovary syndrome 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 polycystic ovary syndrome (PCOS) is one of the most common female endocrinopathies affecting 6-7% of women in reproductive age. The association of amenorrhoea with bilateral polycystic ovaries was first described in 1935 by Stein and Levinthal and was known for decades as the Stein-Leventhal syndrome. In the past the clinical diagnosis rested on the triad of hirsutism, amenorrhoea and obesity. Subsequently it has been recognized that PCOS has an extremely heterogenous clinical picture and is multifactorial in etiology.[1]

PCOS may represent the largest under-appreciated segment of the female population at risk of cardiovascular disease .The pathophysiology is complex involving the hypothalamus-pituitary-ovarian axis, ovarian theca cell hyperplasia, hyperinsulinemia and a multitude of other cytokine and adipocyte-driven factors.[2]

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.[3-5] Changes in plasma lipid and lipoprotein (a) composition places the patient at an increased risk for cardiovascular diseases. Women with PCOS share many features in common with the metabolic syndrome in particular.

PCOS is associated with long-term health risks including type II diabetes mellitus and coronary artery disease. [1,2] Insulin resistance, hyperandrogenism and dyslipidemia are likely to

be the major risk factors for CVD in women with PCOS. [6,7]

The reason for the increase in the risk is not yet clear; hyperandrogenism has not yet been recognized as a risk factor for cardiovascular disease and studies on pre- and post-menopausal women do not show a clear association between hyperandrogenism and the risk of future cardiovascular events. Insulin resistance and dyslipidemia seem to have an important role on the risk of cardiovascular pathology in women with PCOS. It is still not known to what degree dyslipidemia contributes to this risk. [4]

Generally, dyslipidemia of PCOS is characterized by increased triglycerides and low HDL-cholesterol, but some studies found although low HDL-cholesterol is common, hypertriglyceridemia to be relatively uncommon.[5] To the contrary, the most classic lipid alteration determining CV risk, increase of LDL- cholesterol, is not common in all populations with PCOS. Beyond total LDL-cholesterol concentrations, the quality of LDL may exert a direct influence on the CV risk.[5]

Several reasons have been suggested for the atherogenicity of small dense LDL. In relation to larger, more buoyant LDL, small dense LDL are taken up more easily by arterial tissue, have decreased sialic acid content and receptor-mediated uptake, as well as increased oxidative susceptibility and reduced antioxidant concentrations.[3] The predominance of small, dense LDL has been associated with an approximately 3-fold increased risk for coronary artery disease, and it has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III. In particular, the association of increased small LDL with hypertriglyceridemia and low HDL-cholesterol, the so-called ALP (atherogenic lipid profile), seems to determine a particularly elevated CV risk.[5] Hyperinsulinemia and hyperandrogenemia cause 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 very low-density lipoprotein (VLDL), which ultimately leads to hypertriglyceridemia. A fundamental element surrounding PCOS is insulin resistance. Insulin resistance leads to hepatic overproduction of apoB and VLDL and ultimately to hypertriglyceridemia. In the last few years several studies have suggested that, as well as plasma lipids, different alterations of Lp and apoB significantly increase the cardiovascular risk. [3]

Lipoprotein(a) is a heterogenous class of lipoproteins made up of an apo(a) molecule linked to a apoB-100 and a lipid. Lp(a) is metabolically distinct from LDL and its levels are determined genetically, with its concentration remaining stable throughout the life of a subject. 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.[6] It has also been recently demonstrated in large scale prospective studies that the concentrations of Lp(a) are strong predictors of cardiac disease. A few mechanisms have been proposed for the role of Lp(a) in IHD. Its incorporation into atherosclerotic plaque and high affinity binding to glycosaminoglycans and fibronectin suggest a direct atherogenic action in combination with elevated cholesterol. Lp(a) has less resistance to oxidation than does the LDL particle and can be actively taken up by scavenger receptors, leading to the formation of foam cells, smooth muscle cell proliferation and plaque formation. Further, Lp(a) may impair fibrinolytic activity by competing with plasminogen for fibrin binding, by competing with tissue- type plasminogen activator for fibrin binding or by direct binding to fibrin. It is interesting to note that said association of Lp(a) and coronary disease is independent of the insulin resistance factor.[4] Furthermore, univariate and multivariate analysis revealed that free androgen index, body mass index, sex hormone binding globulin and estradiol (E2) were independent determinants of apoA-I levels in women with PCOS. Although these factors accounted for no more than 17% of the variance, this supports the hypothesis that ovarian

sex steroids are involved in the pathogenesis of dyslipidemia in women with PCOS.[3]

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 dyslipidemia in PCOS.

MATERIAL AND METHODS

The study was carried out in 30 PCOS patients and 30 non-PCOS controls who attended the outpatient department of Obstetrics and Gynecology of Mayo Hospital Lahore from June 2017 December 2017. The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants. The age of the patients ranged from 18 to 35 years, who had no history of drugs affecting glucose and lipid metabolism. 30 healthy females in the age group of 18 to 35 years (with normal menstrual cycle, no evidence of clinical hyperandrogenemia or polycystic ovary) were selected as controls.

Cases with history of diabetes mellitus, hypertension, renal and liver failure, patient taking systemic drugs especially lipid lowering agents and other endocrine disorders that alter lipid profile were excluded from the study. Patients receiving hormonal and/or non-hormonal treatment were also excluded from the study group. Informed consent was taken from patients and controls.

5 ml plain venous blood sample after overnight fasting of 12 hours was obtained by venepuncture from both cases and controls. This was followed by centrifugation and then sample was processed immediately. Estimations of fasting blood glucose, blood urea, serum creatinine, serum total cholesterol and serum triglycerides, HDL cholesterol and serum Lipoprotein (a) were performed using the serum. Serum VLDL-Cholesterol is calculated using the formula, VLDL=S.TG/5. LDL cholesterol is calculated from the values of total cholesterol, triglycerides and HDL cholesterol by applying Friedewald's equation. LDL-C was estimated by direct method where TG values were more than 400mg/dl. TC/ HDL and LDL/HDL ratio are determined.

Overnight fasting urine sample was collected in a clean dry container and was tested for sugar and albumin immediately. Findings were entered on pre-designed proforma along with demographic profile of the patients.

All the collected was analyzed by using SPSS version 20. Mean and SD was calculated for numerical data and frequencies were calculated for categorical data.

RESULTS

The present study is undertaken to evaluate the significance of serum lipid and lipoprotein(a) levels in polycystic ovary syndrome.30 PCOS cases were considered for the study. 30 age matched healthy individuals were chosen as controls. The mean age between the cases and controls is not statistically significant ($P>0.05$) (Table 1) Mean glucose between cases and controls is not statistically significant ($P>0.05$) (Table 2) Mean urea between cases and controls is not statistically significant ($P>0.05$) (Table 3) Mean creatinine between cases and controls is not statistically significant ($P>0.05$) (Table 4) Mean total cholesterol is higher in cases than in controls and the mean difference is not statistically significant ($P>0.05$) (Table 5) Mean triglyceride is higher in cases than in controls and the mean difference is not statistically significant ($P>0.05$) (Table 6) Mean LDL is higher in cases than in controls and the mean difference is not statistically significant ($P>0.05$) **(Table 7)** Mean HDL is lower in cases than in controls and the mean difference is not statistically significant ($P>0.05$) (Table 8) Mean Lp(a) is higher in cases than in controls and the mean difference is not statistically significant ($P>0.05$). Lp(a) levels > 30 mg/dl is found to be more in cases than in controls. This association is statistically significant with $P < 0.05$. (Table 9)

Table 1 Comparison of mean Age between the two groups:

Group	Mean	Std dev	P-Value
Controls	26.43	4.57	
			0.92
Cases	24.53	4.12	

Table 2 Comparison of mean Glucose between the two groups:

Group	Mean	Std dev	P-Value
Controls	91.33	11.22	
			0.559
Cases	92.5	11.66	

Table 3: Comparison of mean Urea between the two groups:

Group	Mean	Std dev
Controls	18.23	2.60
Cases	18.77	1.74

Table 4: Comparison of mean Creatinine between the two groups

Group	Mean	Std dev	P-Value
Controls	0.91	0.14	
			0.964
Cases	0.88	0.16	

Table 5: Comparison of mean Cholesterol between the two groups:

Group	Mean	Std dev	SE of Mean	Mean difference	t	P-Value
Controls	155.20	30.99	5.66			
				-8.897	-1.111	0.271
Cases	164.10	31.04	5.67			

Table 6: Comparison of mean TG between the two groups:

Group	Mean	Std dev	P-Value
Controls	120.20	36.49	
			0.336
Cases	146.03	75.07	

Table 7: Comparison of mean LDL between the two groups:

Group	Mean	Std dev	P- Value
Controls	91.13	26.50	
			0.218
Cases	98.63	19.70	

Table 8: Comparison of mean HDL between the two groups:

Group	Mean	Std dev	P- Value
Controls	39.92	10.70	
			0.383
Cases	37.62	9.58	

Table 9: Association between Lp(a) and the groups: (Chi-sq test)

Lp(a)	Controls		Cases		Total	P- Value
	n	%	n	%		
≤30 mg/dl	27	90%	20	67%	47	0.028*
>30 mg/dl	3	10%	10	33%	13	
Total	30	100%	30	100%	60	

DISCUSSION

Our study was done in 30 PCOS cases and 30 healthy controls to determine the serum lipid disturbances in polycystic ovary syndrome and to assess the significance of lipoprotein (a) levels in polycystic ovary syndrome. It was found that polycystic ovary syndrome is associated with alterations in the lipid profile.

The study was conducted at Kempegowda Institute of Medical Sciences & Hospital. The age of the patients in our study ranged from 18-35 years. The mean age between cases and controls in our study is not found to be statistically significant (P>0.05). This is in agreement to studies by Shou-Kui Xiang et al[8] and Ahmed M Mohamadin [6] who found no difference in age between PCOS and control groups. Higher mean levels of TC, TG and LDL were found in PCOS cases than in controls in our study. This is in agreement with a study by Olivier et al., which show that there is an elevation of triglycerides, cholesterol and LDL-C in combination with decreased HDL-C and apoA-I.[3]

A study conducted by Berneis et al. showed low HDL-C is commonly found in PCOS cases but hypertriglyceridemia was relatively uncommon. To the contrary, they also found that the most classic lipid alteration determining cardiovascular risk, increase of LDL-C, is not common in all populations with PCOS. Beyond total LDL-C concentrations, the quality of LDL may exert a direct influence on the CV risk. The National Cholesterol Education Program Adult Treatment Panel III accepts that small, dense LDL has an approximately 3-fold increased risk for coronary artery disease and is stated as an emerging CV risk factor.[5]

In 1980, Burghen et al. described the correlation between hyperandrogenism and hyperinsulinemia in women with PCOS and in 1983, Chang et al. described insulin resistance also in non-obese women with PCOS. Legro et al. reported a sevenfold increased risk of type II diabetes mellitus among young women with PCOS compared to control women of comparable age and weight. Ehrmann et al. showed an annual conversion rate from impaired glucose tolerance to type II diabetes of 6% in women with PCOS. The increased risk for glucose intolerance is the result of profound peripheral insulin resistance and pancreatic β-cell dysfunction in women with PCOS.[9] Hyperinsulinemia is a predictor of coronary artery disease.

Our study found that HDL-C is lower in PCOS group than in control group whereas higher mean VLDL was seen in PCOS compared to controls. This is consistent with the study done by Wild et al. who showed that women with PCOS had higher triglycerides and VLDL-C with lower HDL2-C and apolipoprotein A1:A2 ratios.

A study conducted by Koval et al compared levels of HDL-C between races in overweight and obese PCOS women and found that African-American women had a higher level of HDL-C by 5.1 mg/dl when compared to Caucasians. They suggested that there may be racial differences in HDL-C that could effect cardiovascular risk classification. [11]

Our study found a higher mean TC/HDL and LDL-C/HDL-C in PCOS group compared to controls. This is in consistency with the study conducted by Shou-Kui Xiang et al.[8] These lipid abnormalities were closely related to insulin resistance independent of obesity. Their research showed that serum lipoprotein ratios had significant positive correlation with insulin resistance in PCOS patients, which could be used as a simple, reliable and economic indicator to evaluate insulin resistance. Thus, this could be of important clinical significance for diagnosis and treatment options of PCOS.

Our study shows a significantly higher number of cases with Lp(a) >30mg/dl when compared to the controls($P<0.05$). Although the mean Lp(a) is higher in cases than in controls, the difference is not statistically significant.($P>0.05$). Our results are in agreement with those reported by Ahmed M Mohamadin et al. [6] who documented higher circulating ADMA, total homocysteine, hsCRP, Lp(a) and fibrinogen in PCOS than in healthy controls.

Several studies have reported unfavourable lipoprotein pattern, more carotid plaques and higher carotid intima-media thickness and a predicted increased risk for developing CVD in women with PCOS. A long-term follow up study in the UK, however failed to find an increase in cardiovascular events. This observation has raised the questions whether women with PCOS, besides having risk factors for CVD, also have protective factors. However, the UK cohort had a mean age of 58 years, and the prevalence of cardiovascular events does not begin to increase in women until the seventh and eight decades. [8-10]

In recent years, increasing attention has been paid to the non-reproductive aspects of PCOS. The long-term impact of the metabolic disturbances associated with the disorder on women's health has focused considerable interest on follow-up studies and intervention studies.

CONCLUSION :

The present study was done to see the effect of polycystic ovary syndrome on Lipid profile especially the Lipoprotein(a) which is one of the most atherogenic lipid parameter. The various parameters like TC, TG, LDL, VLDL, TC/HDL ratio, LDL/HDL ratio and TG/HDL ratio were elevated in the study group and also there was a reduction in the HDL levels in the study group. Lp(a) levels were found to be >30mg/dl in higher number of cases than in controls. All the above derangements confirm that polycystic ovary syndrome contributes to the development of an atherogenic lipid profile and places the patient at a higher risk of metabolic syndrome. Further studies are however required with higher number of cases to confirm the contribution of polycystic ovary syndrome to the alterations in the lipoprotein(a) levels and a more detailed exploration of issues such as education, parity, physical activity, social class and family history has to be considered.

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