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Early-onset metabolic syndrome and cardiovascular risk in polycystic ovary syndrome

Dhyaneshwar M[1], Priyadarssini M[2], Latha Chaturvedula[3], Sharbari Basu[4]

[1]MSc Medical Biochemistry Student, [2]Senior Resident, [4]Professor and Head, Department of Biochemistry, [3]Professor, Department of Obstetrics and Gynaecology, JIPMER, Puducherry, India

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder which along with insulin resistance leads to infertility and metabolic syndrome (MetS). This increases the cardiovascular risk in PCOS patients. **Aims and Objectives:** The study was undertaken with the objective to assess and compare the levels of insulin, HOMA IR, lipoprotein (a), and comprehensive lipid tetrad index (CTLI) in PCOS patients with and without MetS and, thus, to compare the cardiovascular disease risk in the two groups. **Materials and Methods:** Seventy-one freshly diagnosed cases of women with PCOS were enrolled in the study. The patients were grouped into PCOS with MetS and PCOS without MetS with 32 women in each group, matched by age. Biochemical parameters were analyzed in blood chemistry autoanalysers. Insulin, lipoprotein (a), was estimated using ELISA. HOMA IR and CTLI were calculated using standard formulae. **Results:** About 48.6% of the patients with PCOS had MetS which developed at a mean age of 25 years. Blood glucose and lipid profile parameters were significantly higher, while high-density lipoprotein levels were lower in the group with MetS. Lipoprotein (a) and CTLI were also significantly higher in PCOS patients with MetS than in those without MetS. Insulin and HOMA IR, though higher in the PCOS with MetS group than in the PCOS without MetS, there was no significant statistical difference. **Conclusion:** There is a higher risk of developing cardiovascular disease in PCOS women with MetS than in the PCOS women without MetS at a relatively younger age.

Key words: Cardiovascular disease; Comprehensive lipid tetrad index; Insulin; Metabolic syndrome; HOMA IR; Lipoprotein (a);PCOS

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex hormonal disorder characterized by hyperandrogenism, ovulation abnormalities, and ovarian cysts. The manifestation of PCOS symptoms varies from isolated menstrual irregularity to infertility and severe metabolic derangements.[1-3]

The clinical spectrum of PCOS overlaps with that of obesity in causing reproductive abnormalities. It also predisposes to development of dyslipidemia and insulin resistance leading to metabolic syndrome (MetS) and further increases the cardiovascular risk in these women.[4]

Dyslipidemia with elevated triglycerides, low-density lipoprotein (LDL), cholesterol, and decreased high-density lipoprotein (HDL) is a common observation in PCOS patients, especially in obese PCOS.[5,6] It is evident from the previous studies that PCOS augments the risk of developing MetS and the insulin resistance in turn acts synergistically with hyperandrogenemia in the development of atherogenic dyslipidemia and, hence, increases the cardiovascular disease risk (CVD) in PCOS.[7,8] However, data on lipoprotein (a) {Lp(a)} levels and comprehensive lipid tetrad index (CTLI) which predict cardiovascular risk are relatively scanty in MetS and PCOS.[5]
Nevertheless, it is not very clear whether CVD worsens with the presence of MetS in PCOS. We proposed this study to look for the proportion of women with PCOS who also had developed MetS and to compare the CVD risk markers such as hyperglycemia, dyslipidemia, hypertension,

Address for Correspondence:
Dr. Sharbari Basu, Professor and Head, Department of Biochemistry, JIPMER, Puducherry, India. **Mobile:** 91+9894119387.
E-mail: sh.basu15@gmail.com

hyperinsulinemia, insulin resistance, Lp(a), and CTLI in the two groups of patients with PCOS who had or did not have MetS. This would help to advocate early lifestyle modifications and pharmacologic interventions in patients with PCOS and reduce the progression to MetS and subsequent cardiovascular morbidity.

MATERIALS AND METHODS

The present study was approved by the Institute Ethics Committee for Human studies. It was conducted in the Department of Biochemistry JIPMER, in collaboration with the Department of Obstetrics and Gynecology. A total of 71 freshly diagnosed women with PCOS in the age group of 18–40 years were enrolled into the study after getting their written informed consent. PCOS was diagnosed based on the revised Rotterdam criteria.[9] Women who had thyroid dysfunction, hyperprolactinemia, Cushing's syndrome, diabetes mellitus, or pre-existing cardiovascular diseases were excluded from the study.

The anthropometric parameters and blood pressure were recorded for all the study participants. Five milliliters of fasting blood was collected following strict aseptic precautions. Glucose, triglycerides, total cholesterol, and HDL were estimated by fully automated blood chemistry analyzer. Insulin and Lp(a) levels were estimated using ELISA. Calculation of insulin resistance by HOMA IR model and CTLI was done using standard formulae (HOMA IR =Serum insulin [mmoL/L] × Blood glucose [mmoL/L]/22.5 and Lipid tetrad index=Total cholesterol × Triglycerides × Lp[a]/HDL).[10,11] Diagnosis of MetS was done as per the NCEP ATP III criteria and the age-matched study participants were divided into two groups, as patients of PCOS with MetS and patients of PCOS without MetS.[12]

Statistical analysis

Seventy-one patients with PCOS were recruited based on the inclusion and exclusion criteria. The PCOS patients were grouped into those with and without MetS, with 32 in each group, after age matching. For comparison of means, Independent-t test and Mann–Whitney U-test were done wherever appropriate. P<0.05 was considered significant.

RESULTS

Among the 71 PCOS patients recruited for the study, 34 women (48.6%) had MetS. The remaining 37 did not have MetS. Thereafter, 32 patients in each group were chosen for data analysis after age matching. Table 1 summarizes the anthropometric parameters of the patients with and without MetS. The mean age in both the groups of women being 25 years, it was observed that MetS has presented earlier than usual. It was found that both systolic and diastolic BP were higher in the PCOS women with MetS than in those without it. There was statistically significant elevation of fasting blood glucose and lipid profile parameters and lowering of HDL levels in the PCOS patients with MetS than in the other group (Table 2). We have also found that there was a significant increase in the levels of Lp(a) and CTLI and a non-significant elevation in the levels of insulin and HOMA IR, an indirect tool for quantifying the insulin resistance in the group with MetS (Table 3).

Table 1: Anthropometric parameters of the PCOS patients

Parameter	PCOS with MetS (n=32) mean±SD	PCOS without MetS (n=32) mean±SD	P-value#
Age (years)	24.97±5.597	24.59±4.478	0.76
Waist circumference (cm)	93.725±4.014	90.416±5.043	0.05
Body mass index (kg/m^2)	26.42±5.45	25.41±4.62	0.401
SBP (mm Hg)	126.7±10.9	116.7±9.3	<0.001*
DBP (mm Hg)	84.52±7.4	78.2±9.3	0.05

#Independent t-test, *Significant

Table 2: Comparison of biochemical parameters

Parameter	PCOS with MetS (n=32) mean±SD	PCOS without MetS (n=32) mean±SD	P-value#
Glucose (mg/dL)	95.55±20.13	83.19±7.27	0.002*
Total cholesterol (mg/dL)	177.55±21.14	158.59±19.85	0.004*
HDL (mg/dL)	39.06±5.46	50.37±8.52	<0.001*
LDL (mg/dL)	123.06±20.52	103.09±19.3	0.001*
VLDL (mg/dL)	26.67±12.17	15.72±6.10	<0.001*
Triglycerides (mg/dL)	163.09±53.3	84.0±19.3	<0.001*

HDL: High-density lipoprotein, LDL: low-density lipoprotein, #Independent t-test, *Significant

Table 3: Comparison of cardiovascular risk markers

Parameter	PCOS with MetS (n=32) median (IQR)	PCOS without MetS (n=32) median (IQR)	P-value$
Insulin (μIU/L)	16.83 (8.45–23.18)	13.71 (11.59–31.09)	0.652
HOMA-IR	3.44 (2.28–7.37)	3.26 (1.93–6.36)	0.627
Lipoprotein (a) (mg/dL)	10.63 (6.93–16.82)	8.02 (5.81–10.40)	0.006*
Comprehensive lipid tetrad index	6620.71 (3665–12399)	2441.8 (1859–3059)	<0.001*

$Mann–Whitney U-test, *Significant

DISCUSSION

The myriad manifestations that comprise the clinical spectrum of PCOS are attributed to the continual muddle in the endocrine milieu, induced by ovarian dysfunction.[13] Hyperandrogenism triggers the proinflammatory state and metabolic derangements associated with PCOS and leads to numerous complications such as glucose intolerance, insulin resistance, dyslipidemia, endothelial dysfunction, oxidative stress, atherogenicity, and thus increased incidence of cardiovascular diseases.[14] In our study, we observed that 48.6% of women with PCOS had MetS. This is in accordance with the study that stated that PCOS patients are prone to develop MetS.[8,13,14] In a study on 496 women, 11.7% had PCOS like status and after a follow-up of 7 years, the incidence of MetS was 42.6%, whereas, in our study, almost half of the freshly diagnosed cases of PCOS were found to have MetS.[15]

It is generally observed that PCOS women develop MetS around 50 years of age toward the end of their reproductive phase.[15,16] However, in our study, we observed that women with PCOS have developed MetS at a relatively young age, the mean age being 25 years. This finding is of significance as these women will have a tendency toward increased CVD risk at a much younger age. Peng et al., in their study, concluded that women with PCOS developed MetS at an earlier age compared to women without PCOS.[15]

In our study, fasting blood glucose, triglycerides, total cholesterol, LDL, and VLDL were significantly higher in PCOS with MetS than in the other group without MetS, while HDL levels were low. This is in concordance with another study that found an impaired glucose tolerance and altered lipid profile in PCOS patients with different phenotypes.[17]

BMI was comparable between the two groups, but waist circumference and blood pressure were higher in the group with MetS. Waist circumference was notably higher than 85 cm in both groups which could be justified by the fact that obesity and insulin resistance are common features of both PCOS and MetS.[18]

Insulin levels and insulin resistance were found to be on the higher side in the PCOS group with MetS than in the non-MetS group, although not significant statistically. The median value of insulin resistance, calculated by HOMA IR, was found to be 3.44 in the group with MetS and 3.26 in the group without MetS, which are anyway higher than 2.5, the cutoff value for insulin resistance in the diagnosis of MetS according to the NCEP ATP III and International Diabetes Foundation criteria.[19] Insulin resistance is an early step in the pathogenesis of PCOS and it predicts the subsequent development of MetS in these women.[7,8] Hence, intervention in this group of women with underlying insulin resistance but without metabolic abnormalities may prevent development of MetS. However, this should be substantiated by further research. The hyperinsulinemia and insulin resistance suggests a probable defect in the intraovarian insulin androgen signaling pathway in PCOS, which could be probably explained by the role of insulin in increasing the androgen synthesis and attenuation of SHBG levels, thereby increasing the bioavailability of free testosterone leading to hyperandrogenism in PCOS.[14]

Lp(a), plasminogen homologue, is by itself atherogenic, independent of dyslipidemia, and insulin resistance and is known to increase cardiovascular risk.[20,21] In our study, the median levels of Lp(a) were significantly higher in the group having MetS in comparison with the group not having MetS. This is in line with the findings of a Turkish study, which had demonstrated higher Lp(a) levels in obese PCOS subjects compared to the non-obese PCOS subjects.[22] Another study conducted in adolescent girls with PCOS also had similar observations.[23] This could be related to the regulation of Lp(a) by sex hormones. A previous study has stated that higher Lp(a) was not associated with PCOS patients.[19] Hence, the exact role of Lp(a) in increasing the risk of CVD associated with PCOS is yet to be explored.

A study on CTLI has stated that it predicts coronary artery disease, compared to other lipid profile parameters.[11] We also observed statistically significantly higher CTLI levels in the group having MetS in comparison with the group not having MetS. The studies on Lp(a) and CTLI in PCOS patients are scarce and there are no conclusive data on levels of Lp(a) in PCOS patients and need further elaboration.

This study shows that MetS develops not just early but also in a significant number of women with PCOS. They have deranged levels of blood glucose and lipid profile parameters besides obesity, hypertension, insulin resistance, and higher levels of Lp(a) and CTLI. Hence, timely early intervention with lifestyle modifications will definitely help to improve the insulin resistance and prevent risk of cardiovascular disease.

Limitations of the study

1. A larger sample size could have brought about a significant difference in levels of serum Insulin and HOMA IR amongst the two groups.
2. Including a group of healthy women as control would have shown the metabolic differences between patients with PCOS and normal and further strengthened the study.

CONCLUSION

In this study, 48.6% of women with PCOS were found to have MetS at a mean age of 25 years which is relatively a young age group for developing MetS. Glucose intolerance, dyslipidemia, Lp(a), and CTLI were significantly higher in the PCOS patients with MetS than in those without MetS. In addition, insulin levels and insulin resistance were also higher in the PCOS patients with MetS than in those without MetS, but the difference was not significant. Thus, there tends to be a higher risk of developing cardiovascular disease in patients with MetS than in those without MetS. It is postulated that PCOS patients could be detected at an early stage when MetS has not set in and they can be encouraged for pharmacologic and non-pharmacologic interventions, which would help in improving the quality of life of these patients by slowing the progression to MetS and further preventing cardiovascular events.

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DM- Literature survey, implementation of study protocol, data collection, data analysis, statistical analysis and interpretation, manuscript preparation; **PM-** Data collection, data analysis, manuscript preparation, editing and manuscript revision; **LC -** Clinical protocol, data collection, manuscript preparation; **SB –** Concept, definition of intellectual content, design of study, over all supervision of the study, manuscript preparation, and submission of article.

Work attributed to:
JIPMER, Puducherry, India.

Orcid ID:
Dr. Dhyaneshwar M - https://orcid.org/0000-0002-1450-7238
Dr. Priyadarssini M - https://orcid.org/0009-0005-1593-1654
Dr. Latha Chaturvedula - https://orcid.org/0000-0002-6237-6551
Dr. Sharbari Basu - https://orcid.org/0000-0002-3296-9831

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