Original Article

Carotid intimo-medial thickness: A predictor for cardiovascular disorder in patients with polycystic ovarian syndrome in the South Indian population

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A B S T R A C T

Background: Polycystic ovary syndrome (PCOS) is a common endocrine problem, which is now recognized as not only a reproductive but also a metabolic disorder with long-term effects on women's health, it has a prevalence of 5–10% in India. Among PCOS, it has been reported to have a higher incidence of cardiovascular disorders. Epidemiological studies have demonstrated an association between an increase in the carotid intimo-medial wall thickness (CIMT) and cardiovascular dysfunction. The objective of this study was to compare the CIMT of PCOS with normal women. **Materials and Methods:** The cross-sectional case-control study was conducted in a tertiary care Hospital in South India. Fifty-four subjects with polycystic ovarian disease and 54 healthy women were enrolled into the study. PCOS was diagnosed by Rotterdam criteria, 2003. Both groups of women were investigated with CIMT and cardiovascular dysfunction. **Results:** The mean age of women with PCOS and controls were 24.4 ± 5.3 and 27.7 ± 6.0, respectively, whereas body mass index was significantly higher in PCOS than controls group. Mean carotid IMT was significantly higher in PCOS subjects (0.51 ± 0.078) than control subjects (0.44 ± 0.06). **Conclusion:** Higher CIMT values were observed in PCOS group compared to control group indicating the importance for measuring CIMT in women with PCOS to predict the risk of cardiovascular dysfunction (CVD).

Key words: Cardiovascular dysfunction, carotid intimo-medial thickness, polycystic ovary syndrome

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine problem, which is now recognized as not only a reproductive but also a metabolic disorder with long-term effects on women's health. The prevalence is 5–10% in India.[1,2] PCOS is associated with hyperinsulinemia which is associated with infertility and metabolic problems of diabetes and dyslipidemia.[3] Insulin resistance has been studied

extensively in PCOS including newer markers of ferritin.[4] However, few studies have looked at carotid intimo-medial wall thickness (CIMT) as a reflection of vascular health. Epidemiological studies have demonstrated an association between an increase in the carotid intima-medial wall thickness (CIMT) and cardiovascular dysfunction (CVD).[5,6] CIMT measurement is a simple and a reliable predictor for the progression of CVD.[2] Hence, carotid arterial ultrasound is an important tool that could be used to measure the thickness of the intima-media of the common carotid artery which would help us to further characterize the cardiovascular risk in the PCOS population.[7] There is not much evidence of study in this part of the state/

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India to demonstrate such a correlation. Careful carotid intimo-medial wall thickness measurement can help in early detection and management of cardiovascular disorders in patients with PCOS. Therefore, the objective of this study is to find an association between CIMT and patients with PCOS, in an Indian setting.

MATERIALS AND METHODS

The cross-sectional case-control study was conducted in a tertiary care Hospital in South India. The institutional review board approved the study. Fifty-four consecutive women with PCOS presenting to the endocrinology outpatient department who signed an informed consent were enrolled into the study and 54 healthy women were also enrolled into the study.[4] The normal healthy group of women consisted of attendants accompanying the patients and volunteers (most of them nursing staff). The study was carried out during the year 2014–2015. The inclusion criteria consisted of all subjects in the range of 16–35 years and with or without PCOS diagnosis as per the Rotterdam diagnostic criteria, 2003.[8] Similarly, all women with nonclassical adrenal 21-hydroxylase deficiency, Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, androgen-secreting tumors, diabetes mellitus, patients on medication like a steroid, anti-convulsant and anti-psychotic and history of smoking were excluded from the study. All the information relating the cases and control were collected in predesigned and pretested pro forma.

Carotid arterial Doppler was performed which evaluates the blood flow through the carotid arteries using the principle of Doppler effect to produce pictures of carotid arteries following which the intima and medial thickness of the same were measured in the test group.[9] In the case and control group, intimo-medial thickness (IMT) of the carotid artery were measured by a radiologist using a linear 8–10 MHz ultrasound probe (Voluson, GE) in carotid setting, who was blinded about the study groups. In longitudinal view, the distance between the two-echogenic lines parallel to the vessel wall was measured (between the two echogenic lines, a hypoechoic area could be seen, the first echogenic line was the intima and the next one was the contact level of media and adventitia). The measurement was done at two points of common carotid artery (CCA) on both the sides [Figure 1]. In addition to above, information of age in completed years and height in centimeters up to 0.5 cm and weight in kg up to 0.250 kg. Waist and hip circumference were all recorded up to 0.5 cm.

Statistical analysis
Statistical analysis was performed using SPSS software 18.0 version. Continuous measurements were expressed

regarding descriptive statistics. Student's *t*-test and Mann–Whitney U-test were used to compare the differences in the mean values for various parameters. The Mann–Whitney U-test was employed in case if the data did not follow the normal distribution. The level of significance is considered to be <0.05.

Data collected was stratified into the different groups based on mean CIMT, mean age, and mean body mass index (BMI) levels as observed for the control/cases group. Univariate odds ratios along with 95% confidence interval (CI) were computed between the PCOS and control group of subjects after segregating the data into two groups based on the above mean values. Further multivariate forward logistic regression was employed to control the effect of BMI and age for finding the odds ratios with regard to CIMT in PCOS and control group.

RESULTS

A total of 54 women with PCOS and 54 control subjects underwent carotid ultrasonographic scanning. Mean baseline characteristics of subjects with PCOS such as BMI and waist-hip ratio, were obtained [Table 1].

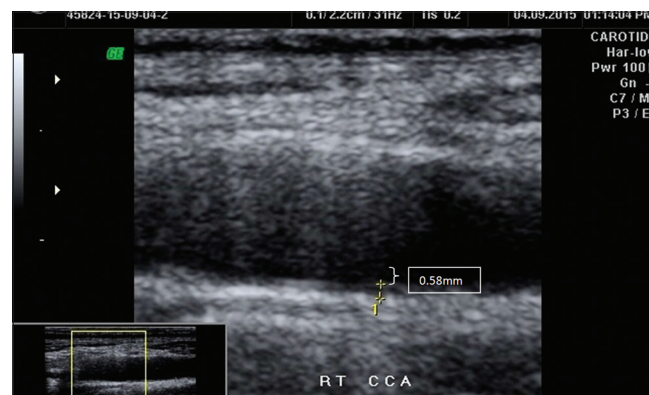The mean age of women with PCOS and controls was 24.4 ± 5.3 and 27.7 ± 6.0, respectively, which was found

Figure 1: Carotid arterial Doppler of the polycystic ovary syndrome subject showing the longitudinal section of the right common carotid artery. The distance between the two plus symbols indicates the intimo-medial thickness. Rt. CCA: Right common carotid artery

Table 1: Demographic characteristics of polycystic ovary syndrome group and control group

Parameters	Mean±SD		P
	PCOS group	**Control group**	
Weight (kg)	66.98±15.18	55.38±9.75	0.001
Height (cm)	157.42±5.74	153.89±5.43	0.001
BMI (kg/m²)	26.92±5.15	23.26±3.28	0.001
Waist-Hip ratio	0.92±0.13	0.91±0.03	0.459

The mean age of PCOS group and control group were 24.44±5.32 and 27.72±6.01. PCOS: Polycystic ovary syndrome, SD: Standard deviation, BMI: Body mass index

to be statistically significant ($P = 0.003$). However, BMI was significantly higher ($P = 0.001$) in PCOS compared to controls group (26.9 ± 5.1 vs. 23.3 ± 3.2).

Mean carotid IMT was significantly higher in PCOS subjects than control subjects (0.51 ± 0.07 vs. 0.44 ± 0.06, $P < 0.001$) [Table 2]. The CIMT range from 0.38 to 0.70 mm in women with PCOS and from 0.30 to 0.60 mm in controls group.

On the basis of mean CIMT value, data were stratified in two groups, i.e., ≤ 0.44 mm in one group and >0.44 mm in another group. It was noted that 75.9% (41) of PCOS cases had CIMT >0.44 mm as compared to only 44.4% (24) in controls group. The differences in proportion were found to be statistically significant ($P = 0.001$). The corresponding odds ratio was 3.94 (95% CI: 1.73–8.98) [Table 3].

Since the age and BMI groups of PCOS and controls were found to be statistically significant, mean CIMT values were estimated for each of the sub-groups [Table 4]. The findings indicated statistically significant CIMT values for the categories of age ≤ 24 and BMI >24 and age ≥ 25 and BMI >24.

Further odds ratio along with 95% CI were also computed for stratified data [Table 5]. Significant odds ratios were found for the categories of age ≤ 24 and BMI >24 and age ≥ 25 and BMI >24.

Through the multivariate forward logistic regression analysis attempt was made to control for the confounding effect of BMI and age with regards to CIMT values. After controlling for the effect of age and BMI, odds ratio was found to be 3.98 (95% CI: 1.612–9.811), which indicates the increased risk for cardiovascular disorders in patients with PCOS even after controlling for the effect of confounding factors age and BMI.

DISCUSSION

A woman with PCOS encompasses a collective outcome of androgen excess, insulin resistance, and dyslipidemia, which are the strong indicators of CVD. This metabolic syndrome presents early in adolescence, which leads to the development of CVD. The assessment of preclinical vascular disease by noninvasive tests in middle-aged PCOS patients with greater IMT demonstrated that tendency to atherosclerosis increased in these patients compared with healthy controls.[10,11] Previous studies suggested that women with PCOS face double risk of the metabolic syndrome comparing the nonaffected population of the women in the society.[12] In this study, we investigated CIMT

Table 2: Carotid intimo-medial wall thickness in polycystic ovary syndrome group and control group

Parameters	Mean±SD		P
	PCOS group	Control group	
Carotid intima thickness (mm)	0.51±0.07	0.44±0.06	<0.001

*Carotid intima thickness >1.0 mm as being abnormal and >1.2 mm as being high risk.[10] PCOS: Polycystic ovary syndrome, SD: Standard deviation

Table 3: Distribution of cases and controls based on mean carotid intimo-medial wall thickness values

CIMT (mm)	Cases (%)	Control (%)
>0.44	41 (75.9)	24 (44.4)
≤0.44	13 (24.1)	30 (55.6)

χ^2=11.17, P<0.001, OR is 3.94 with 95% CI (1.73-8.98). CIMT: Carotid intima-medial wall thickness, OR: Odds ratio, CI: Confidence interval

Table 4: Mean±standard deviation of carotid intimo-medial wall thickness in cases and controls stratified according to age and body mass index categories

Age (years)	BMI (kg/m²)	Cases		Controls		P
		n	Mean±SD	n	Mean±SD	
≤24	≤24	7	0.48±0.093	9	0.44±0.098	0.57
	>24	20	0.50±0.075	7	0.42±0.029	0.016
≥25	≤24	8	0.48±0.073	24	0.43±0.073	0.788
	>24	19	0.53±0.077	14	0.46±0.051	0.007

SD: Standard deviation, BMI: Body mass index

Table 5: Odds ratio with 95% confidence interval for polycystic ovary syndrome and controls stratified according to age, body mass index and carotid intimo-medial wall thickness values

Age (years)	BMI (kg/m²)	CIMT (mm)	Cases (%)	Controls (%)	OR 95% CI	P
≤24	≤24	≤0.44	3 (42.9)	4 (44.4)	1.07 (0.145-7.82)	1
		>0.44	4 (57.1)	5 (55.6)		
	>24	≤0.44	5 (25)	6 (85.7)	18 (1.72-188.02)	0.009
		>0.44	15 (75)	1 (14.3)		
≥25	≤24	≤0.44	3 (37.5)	14 (58.3)	2.33 (0.45-12.09)	0.423
		>0.44	5 (62.5)	10 (41.7)		
	>24	≤0.44	2 (10.5)	6 (42.9)	6.375 (1.05-38.86)	0.047
		>0.44	17 (89.5)	8 (57.1)		

BMI: Body mass index, CIMT: Carotid intima-medial wall thickness, OR: Odds ratio, CI: Confidence interval

thickness in PCOS women and control group. Studies of CVD events in women with PCOS are limited, but a recent meta-analysis showed that women with PCOS had twice the relative risk of coronary heart disease or stroke than controls (de Groot *et al.*, 2011). Some studies discussed the association of PCOS with the risk of CVD and its risk factors (Legro, 2003; Loverro, 2004; Cussons *et al.*, 2006; Dokras, 2008; Mak and Dokras, 2009; Wild *et al.*, 2010).[2]

The sustained exposure of women with PCOS to higher androgens was not connected with an overload of CVD or mortality even with the rise in cardiovascular risk

factors. Calderon-Margalit *et al.* studied CIMT and found a positive association between PCOS and CIMT. He also found an association with CCA.[13] Another study carried out in Taiwan did not show an association between CIMT and PCOS and the author surmised that might be it was too early to find the difference.[14] This also brings out that different Asian countries have different correlations of CIMT. Studies have also evaluated the fasting blood glucose quartiles with CIMT and found that the correlation was good.[15]

In a retrospective study conducted in 2012 by Meyer *et al.*, evaluation of the sum of 36 articles including 1,123 cases of PCOS women and 923 healthy women showed that the IMT artery in women with PCOS was significantly higher than healthy women[2] which was similar to our results that showed IMT artery in PCOS were significantly higher compared with controls.

The study parameters in the two groups-age, height and BMI were significantly equivalent. Waist-hip ratio was not significant between two groups. Reports show that the BMI was higher in the test group than the control group. The majority of the people reported with infertility and irregular menses. FG score was applied in this study to evaluate and quantify hirsutism in women. The mean FG score in the test group was reported implicating that the women with PCOS have hirsutism. Increase in total testosterone in longer period impacts in the body fat distribution with an accumulation of fat. The mean CIMT in test group showed an increase compared to the control group.

This is a novel study conducted in south Indian population. In this study, the BMI, waist-hip ratio, FG score, and Carotid intima-media thickness (CIMT) in the test group and control group showed a significant variation akin to the previous studies. This explains the link between the study parameters, which act as potential risk factors for developing the PCOS.

Conclusion

Hyperinsulinemia and cardiovascular disease have a high prevalence in our country. These disorders also occur at a much earlier age. CIMT is a noninvasive simple method to evaluate vascular health.[3] Higher CIMT values were observed in the test group compared to control group ($P < 0.001$). Thus, it is important to measure CIMT in women with PCOS to predict the risk of cardiovascular disease (CVD). This simple noninvasive test can be done to manage these women with PCOS to prevent endothelial function and preserve cardiovascular function.

Limitation of the study

The limitation of this study was a selection of a small sample size. Some limitations of the present study that should be addressed and noted in future studies are included unmeasured variables such as physical activity, diet, socioeconomic backgrounds, lifestyle habits, and association with lipid status. Therefore, we are not able to differentiate the effect of diet, increased physical exercise and weight loss on the features of PCOS and metabolic syndrome and different socioeconomic backgrounds or lifestyle habits in our study. Hence, a further study in larger populations with other associated parameters is necessary for better assessment of the results.

Conflicts of interest

There are no conflicts of interest.

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