

Comparison of Carotid Intima-Media Thickness in Patients With and Without Polycystic Ovarian Syndrome

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ABSTRACT

Introduction: Women with Polycystic Ovarian Syndrome (PCOS) have higher risk of obesity, hyperlipidemia, hyperinsulinemia and insulin resistance with progression to type 2 diabetes mellitus and hypertension which are risk factors for atherosclerosis. Carotid Intima-Media Thickness (CIMT) helps to identify the association of subclinical atherosclerosis with polycystic ovarian syndrome.

Aim: To assess the presence of subclinical atherosclerosis in young untreated women with PCOS by measuring the CIMT and comparing it with age matched controls.

Materials and Methods: A case control study was conducted in radiology department of SRM medical college and research centre on 70 women fulfilling the Rotterdam's criteria for diagnosis of PCOS in the age group of puberty to 40 years and who underwent carotid Doppler and in which CIMT was measured. Seventy age matched normal women with regular menstrual cycle were enrolled as controls and their CIMT was measured. Statistical analysis was done using SPSS (IBM SPSS Statistics for Windows, Version 22.0,

Armonk, NY: IBM Corp) was used. To compare the mean values between groups independent sample t-test was used and to compare proportions Chi-Square test/Fisher's-exact test was used. Crude Odds Ratio was calculated to find the risk for Cases. Significance level was fixed as 5% ($\alpha=0.05$).

Results: Intima media thickness in carotid arteries was increased in patients with PCOS compared to that of women without PCOS, suggesting that there is presence of subclinical atherosclerosis in young untreated women with PCOS. There was significant correlation between increased CIMT and PCOS patients (p-value <0.001). In the present study, there was also statistically significant increased body mass index in PCOS patients (p-value 0.002).

Conclusion: The higher sensitivity of CIM thickness measurements in detecting early atherosclerosis is an advantage for assessing the progression or regression of subclinical atherosclerotic disease over time and this can be successfully used in PCOS patients. Further studies are required with large sample size to substantiate the study results.

Keywords: Atherosclerosis, Body mass index, Metabolic syndrome, Ultrasound

INTRODUCTION

Polycystic ovarian syndrome is one of the commonest endocrine and metabolic disorders in women of reproductive age group [1]. Three key diagnostic features, that is ovulatory dysfunction, hyperandrogenism and PCO on ultrasonography are the different phenotypes of PCOS. Rotterdam criteria states that two out of these three features should be present for diagnosis of PCOS. Polycystic ovarian morphology is defined as 12 or more follicles measuring 2-9 mm or increased ovarian volume ($>10 \text{ cm}^3$) in at least one ovary [1-4].

The prevalence of PCOS according to meta-analysis of studies done worldwide is 10% [5] and the prevalence in india varies from 9.13% to 22.5% [6,7].

In 1935, Irving Stein and Michael Leventhal published an article named "Amenorrhoea associated with bilateral polycystic ovaries" [8].

It was evident that obese women suffered from amenorrhoea and they were mostly infertile. Stein and Leventhal surgically explored these women and found that the ovaries were enlarged almost two to three times and were full of fluid filled cysts. The authors arrived with the diagnosis of enlarged polycystic ovaries [9,10].

Women with PCOS have a higher risk of developing obesity, hyperlipidemia, hyperinsulinemia and insulin resistance with progression to type 2 diabetes and hypertension. It has been stated that women with PCOS have an eleven fold increased prevalence of the metabolic syndrome compared with age matched controls [11].

Measurements of CIMT have been related to the presence of atherosclerosis in the aorta, coronary, cerebral and peripheral arteries. Increased Carotid intima thickness is positively associated with myocardial infarction, stroke and

other cardiovascular related deaths. CIMT measurement helps to predict arterial disease non-invasively and can be used as a marker in predicting subclinical atherosclerosis. The higher sensitivity of CIMT measurements in detecting early atherosclerosis is an advantage over angiography for assessing the progression or regression of subclinical disease over time [12]. Early diagnosis of subclinical atherosclerosis in patients with PCOS is important as it has been associated with several medical risks including high blood pressure and heart disease [13-16].

By the present study, we tried to compare the presence of subclinical atherosclerosis in young untreated women with PCOS and normal controls specifically by measuring their CIMT using Ultrasound.

MATERIALS AND METHODS

The study was a case control study conducted after getting approval from the institution's ethical committee and obtaining written informed consent from the patients during the period from January 2016 to August 2017 in the Department Of Radiology, SRM Medical College hospital and Research Centre, Kattankulathur, Kancheepuram District. Patients satisfying the Rotterdam diagnostic criteria for PCOS were considered as cases and age matched patients with no evidence of polycystic ovarian syndrome and other disorders mentioned in exclusion criteria were taken as controls and USG was done free of cost for all controls.

Atherosclerosis usually presents clinically as a cardiovascular event. It is chronic, progressive and in its early stages when there are no clinical manifestations it is called as subclinical atherosclerosis [17]. Several methods such as B-mode ultrasonogram, computerized tomography, MRI, intravascular ultrasonogram and coronary angiography can be used to assess subclinical atherosclerosis [17]. CIMT measurement with B-mode ultrasonogram was used to assess subclinical atherosclerosis in the present study.

INCLUSION CRITERIA

Women in the age group of puberty to 40 years satisfying the Rotterdam diagnostic criteria for polycystic ovary syndrome were included in the study [2,3].

EXCLUSION CRITERIA

Women over 40 years of age, those who are receiving treatment for PCOS and those with history of Thyroid dysfunctions, hyperprolactinemia, androgen-secreting tumour, cushing's syndrome, lipid metabolism disorder, diabetes mellitus, hypertension, hormone replacement therapy were excluded.

All ultrasound examinations were performed in GE LOGIQ F8. Initially ultrasound pelvis was done with full bladder. The uterus and both ovaries were evaluated. The presence of polycystic ovarian syndrome was assessed and Carotid intima media thickness was measured.

CIMT Measurement

The patient was made to lie in a supine position. The patient was well positioned with extension of neck by placing a pillow in the back. To measure the Carotid Intima media thickness on the right side, the patient's head is tilted to the left and to measure the CIMT on left side, the patient's head is tilted to right. Using a linear transducer (6-12 MHz), the Common Carotid Artery (CCA) was assessed.

The CCA was obtained in a longitudinal section along the posterior aspect of sternocleidomastoid muscle. The CCA was then divided into two as near and far walls. Three measurements were taken in both near and far walls and the maximum CIMT was considered. The focus, depth and gain settings are adjusted optimally to facilitate edge detection. Intima media thickness is defined as a double-line pattern visualised on both walls of the CCA in a longitudinal view.

Flow separation and low oscillating shear stress is found in the internal carotid artery and in the carotid bulb and the development of atherosclerosis in common carotid artery typically occurs at the bifurcation area with an increased intima media thickness [18]. Any atheromatous plaques at the common carotid bulb were excluded.

STATISTICAL ANALYSIS

SPSS (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. Released 2013) was used. To compare the mean values between groups independent sample t-test (Student's t-test) was applied. To compare proportions between study and control groups Chi-Square test was applied, if any expected cell frequency is less than five then Fisher's-exact test was used. Crude Odds Ratio was calculated to find the risk for Cases. Significance level was fixed as 5% ($\alpha=0.05$).

RESULTS

The age range of the patients enrolled in the study was from 14-40 years. The group with PCOS was considered as cases and other group without PCOS was considered as controls. The youngest patient was 13 years and oldest was 34 years in cases and the youngest was 18 years and oldest 40 years in control group. The cases had a mean age of 27.47 years and controls had a mean age of 28.4 years. This was found to be statistically insignificant (p-value <0.295). Cases had a mean height of 164.53 cm and controls had a mean height of 164.91 cm. This was found to be statistically insignificant (p-value <0.706). Cases had a mean weight of 55.4 kg and controls had a mean weight of 59.21 kg. This was found to be statistically significant (p-value <0.008). Cases had a mean BMI of 21.77 and controls had a mean BMI of 20.35. This was found to be statistically significant (p-value 0.002).

The relation between CIMT (maximum and minimum) on right side for cases and controls were statistically significant (p-value 0.001) [Table/Fig-1]. Similarly the relation between CIMT (maximum and minimum) on left side for cases and controls were statistically significant (p-value 0.003) [Table/Fig-2]. Mean CIMT on right side in cases was 0.0681 and in controls was 0.0613. Mean CIMT on left side in cases was 0.0670 and in controls was 0.0614. Mean maximum CIMT in cases of Polycystic Ovary Syndrome (PCOS) was 0.0717 and in controls was 0.0651. These were found to be statistically significant (p-value <0.001) [Table/Fig-3].

CIMT Right (in cm)	Group						p-value
	Case		Control		Total		
	n	%	n	%	n	%	
0.05	8	28.6	20	71.4	28	100.0	0.001
0.06	20	46.5	23	53.5	43	100.0	
0.07	25	50.0	25	50.0	50	100.0	
0.08	11	84.6	2	15.4	13	100.0	
0.09	6	100.0	0	0.0	6	100.0	
Total	70	50.0	70	50.0	140	100.0	

[Table/Fig-1]: CIMT (maximum and minimum) on right side for cases and controls.
CIMT: Carotid Intima-Media Thickness

CIMT Left (in cm)	Group						p-value
	Case		Control		Total		
	n	%	n	%	n	%	
0.05	5	21.7	18	78.3	23	100.0	0.003
0.06	30	51.7	28	48.3	58	100.0	
0.07	20	48.8	21	51.2	41	100.0	
0.08	11	84.6	2	15.4	13	100.0	
0.09	4	80.0	1	20.0	5	100.0	
Total	70	50.0	70	50.0	140	100.0	

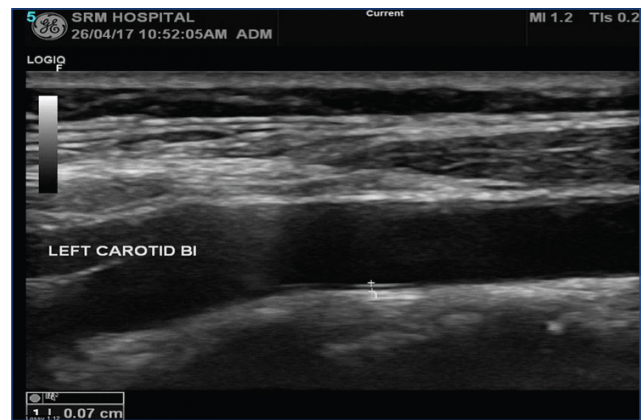
[Table/Fig-2]: CIMT (maximum and minimum) on left side for cases and controls.
CIMT: Carotid Intima-Media Thickness

CIMT	Group	n	Mean (in cm)	Std. Dev	p-value
CIMT Right	Case	70	0.0681	0.01107	<0.001
	Control	70	0.0613	0.00867	
CIMT Left	Case	70	0.0670	0.01012	0.001
	Control	70	0.0614	0.00889	
CIMT Max	Case	70	0.0717	0.01090	<0.001
	Control	70	0.0651	0.00756	

[Table/Fig-3]: Measurement of CIMT Mean (Right, Left, Maximum) between cases and controls.
CIMT: Carotid Intima-Media Thickness

The mean CIMT value obtained from control group was 0.065 cm. A total of 88 women had a CIMT of >0.065 cm, out of which 50 women (71.4% of the study population) belong to cases group [Table/Fig-4]. These were found to be statistically significant (p-value 0.036). The odds ratio was 2.11; 95%. Therefore, this suggests that there is a two fold risk of increased CIMT in women with PCOS compared to that of the normal control group. Three patients with PCOS had soft plaque in carotid bulb, two in left side and one in right side.

For same mean BMI with increasing mean age cases had statistically significant increased mean max CIMT than controls. Independent of BMI value, the CIMT was more in PCOS group and with increase in age the CIMT value also increased [Table/Fig-5].



[Table/Fig-4]: Young PCOS patient with increased CIMT: A 15-year-old PCOS patient showing increased CIMT in left CCA of 0.07 cm proximal to the bifurcation.
CIMT: Carotid Intima-Media Thickness; PCOS: Polycystic Ovary Syndrome; CCA: Common Carotid Artery



[Table/Fig-5]: PCOS patient with raised BMI values showing increased CIMT. 29-year-old PCOS patient with BMI of 26.95 kg/m² showing increased CIMT just proximal to carotid bulb.
CIMT: Carotid Intima-Media Thickness; PCOS: Polycystic Ovary Syndrome; BMI: Body Mass Index

DISCUSSION

Atherosclerosis is the major cause of cardiovascular and cerebrovascular diseases [19]. Measurement of CIMT by

B-mode ultrasonogram is a widely used method to quantify subclinical atherosclerosis [20]. Atherosclerosis has several risk factors of which insulin resistance is one which has a well established association with PCOS [21]. The assessment of subclinical atherosclerosis by measuring CIMT in PCOS patients show that there is increased risk of atherosclerosis in these patients compared with controls [22,23].

Most of the studies state there is a correlation between increased CIMT and PCOS as mentioned in [Table/Fig-6] [24,25-28].

The mean age of women with PCOS and control women in the present study were similar to the study conducted by Manonmani D et al., [24]. A 22.5% women with PCOS in their study and 35.7% women with PCOS in the present study had a CIMT >0.7mm. There was statistically significant association between increased CIMT and PCOS in their study like present study, however the percentage of PCOS cases with increased CIMT were more in our study compared to their study. In the study conducted by Garg N et al., the mean CIMT for cases and controls was statistically significant with a p-value <0.001, similar to this study showing statistically significant association between increased CIMT and PCOS [25].

In the study conducted by Karoli R et al., the mean CIMT measured for the PCOS cases and controls was statistically significant with a p-value 0.01, similar to the present study (p<0.001). The present study also showed statistically significant association between increased CIMT and PCOS and increased BMI in PCOS cases [29].

The mean CIMT for the PCOS cases and control women was shown to be statistically significant with a p-value <0.01 in the study done by Carmina E et al., correlating with our study (p-value <0.001) [26].

Saha S et al., studied the impact of abnormal lipid profile on atherosclerosis in PCOS women by measuring the CIMT in 30 PCOS women and in age matched 30 healthy controls. The mean CIMT for the PCOS cases and control women was shown to be statistically significant with a p-value <0.001, similar to our study stating statistically significant association between increased CIMT and PCOS [27].

Mohammadi A et al., evaluated the early atherosclerotic changes in PCOS women by measuring the CIMT and Flow-Mediated Dilatation (FMD) in both cases and age matched controls. The mean CIMT for cases and controls was statistically significant with a p-value of 0.001. In the present study, the mean CIMT for cases and controls, was statistically significant with a p-value <0.001. Similar to the study conducted by Mohammadi A et al., the present study also showed statistically significant association between increased CIMT and PCOS and increased BMI in PCOS Patients [28].

There are also few studies which state that there is no correlation between increased CIMT and PCOS [Table/Fig-7] [30,31].

Pamuk BO et al., evaluated the plasma Asymmetric Dimethyl Arginine (ADMA) levels and CIMT in patients with PCOS [30]. There were no significant differences in CIMT between the two groups with statistically insignificant p-value of 0.51.

About 45 women with PCOS were taken as cases and about 32 age matched normal women were taken as controls in the study conducted by Ilie IR et al., [31]. In their study, the mean CIMT for cases and controls was statistically insignificant with a p-value of 0.89.

Ramoglu S et al., evaluated that if cardiovascular risk varied according to different PCOS criteria, using CIMT, which was an

Study	Study Population (n)	Mean Age±SD (Years)	Mean BMI±SD (Kg/m ²)	Mean CIMT±SD (mm)	p-value
Manonmani D et al., [24]	Cases:40 Controls:50	Cases: 24.35±4.99 Controls: 25.1±4.7	Cases: 26.46±5.17 Controls: 23.23±3.02	Cases: 0.531±0.145 Controls: 0.386±0.062	<0.001
Garg N et al., [25]	Cases:54 Controls:54	Cases: 24.4±5.3 Controls: 27.7±6.0	Cases: 26.92±5.15 Controls: 23.26±3.28	Cases: 0.51±0.078 Controls: 0.44±0.06	<0.001
Carmina E et al., [26]	Cases:50 Controls:50	Cases: 25.2±1 Controls: 28.5±0.5	Cases: 28.7±0.8 Controls: 28.5±0.5	Cases: 0.5±0.01 Controls: 0.41±0.01	<0.01
Saha S et al., [27]	Cases:30 Controls:30	Cases: 26.11±4.23 Controls: 28.7±7.06	Cases: 25.75±4.58 Controls: 21.97±2.99	Cases: 0.63±0.19 Controls: 0.44±0.05	0.001
Mohammadi A et al., [28]	Cases:46 Controls:45	Cases: 23.02±5.17 Controls: 27.96±3.97	Cases: 25.08±5.54 Controls: 21.59±3.08	Cases: 0.63±0.16 Controls: 0.33±0.06	0.001
The Present Study 2017	Cases:70 Controls:70	Cases: 27.47±5.2 Controls: 28.47±5.9	Cases: 21.77±2.9 Controls: 20.35±2.3	Cases: 0.717±0.01 Controls: 0.65±0.007	<0.001

[Table/Fig-6]: List of published articles stating the correlation between increased CIMT in PCOS patients [24,25-28].

Study	Study Population (N)	Mean Age±SD (Years)	Mean BMI±SD (Kg/M ²)	Mean CIMT±SD (Cm)	p-value
Pamuk BO et al., [30]	Cases:35 Controls:31	Cases:26 Controls:27	Cases: 29.7 Controls:28.4	Cases:0.52 Controls:0.49	0.51
Ilie IR et al., [31]	Cases:45 Controls:32	Cases: 23.11±4.14 Controls: 23.06±5.37 0.876	Cases: 28.41±5.97 Controls: 25.87±6.89 0.043	Cases: 0.55±0.11 Controls: 0.55±0.1	0.89

[Table/Fig-7]: List of published articles stating no correlation between increased CIMT and PCOS [30,31].

important marker of major cardiovascular disease [32]. Their study concluded that the CIMT levels in the PCOS group did not differ from that of the control group and hence evaluation of CIMT alone may not be sufficient to determine endothelial dysfunction in a reproductive age group.

Most of the studies published in the literature especially from Indian subcontinent show positive correlation of PCOS with increased CIMT, however few of the studies which are done outside Indian subcontinent shows no statistically significant correlation between increased CIMT and PCOS. This may be due to different set of population. Hence screening of patients with PCOS for subclinical atherosclerosis appears to be necessary and CIMT is a useful tool.

CONCLUSION

The higher sensitivity of CIM thickness measurements in detecting early atherosclerosis is an advantage for assessing the progression or regression of subclinical atherosclerotic disease over time and it can be successfully used in PCOS patients to assess subclinical atherosclerotic disease. Further studies are required with large sample size to substantiate the present study results.

LIMITATION

The limitations of the present study were less sample size, blood tests like sugar, lipid profile and biochemical hyperandrogenism analysis was not done. Abdominal circumference and blood pressure measurement was not done. These parameters could have made the study analysis much better.

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