

## Does Carotid Intima-media Thickness have Relationship with Polycystic Ovary Syndrome?

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### ABSTRACT

**Background:** Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder associated with cardiovascular disease (CVD) risk factors and metabolic disturbances and a genetically heterogeneous disease. Intima-media thickness (IMT) is an indicator of atherosclerosis. This study aimed to determine the relation between IMT and PCOS in women.

**Methods:** This cross-sectional study was performed on 44 PCOS patients and 44 healthy women. Data collection included lipid profiles, blood pressure, waist circumference, body mass index (BMI), and common and internal IMT of carotid artery which were measured in studied subjects. IMT was measured by a radiologist using a linear 12 MHz ultrasound probe (LOGIC S6, GE) in carotid setting.

**Results:** IMT of common carotid artery ( $56.8 \pm 7.6$  in cases versus  $49.8 \pm 7.3$  in controls), internal carotid artery ( $56.9 \pm 6.03$  in cases versus  $49.6 \pm 6.9$  in controls), and both common and internal carotid artery ( $56.6 \pm 6.7$  in cases versus  $49.7 \pm 6.9$  in controls) were significantly higher in PCOS patients than healthy women ( $P < 0.001$ ).

**Conclusions:** In summary, results demonstrated that carotid artery thickness as a risk for premature atherosclerosis in patients with PCOS is higher than healthy subjects. And hence care and monitoring of PCOS women with these risk factors sounds to be important and necessary.

**Keywords:** Carotid intima-media thickness, carotid artery thickness, intima-media thickness, oligomenorrhea, polycystic ovarian syndrome

### INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy disorder that occurs in 5-7 percent of women of reproductive age.<sup>[1,2]</sup> The prevalence of PCOS in Iran is estimated 7% according to the National Institutes of Health (NIH) criteria and 15.2% according to Rotterdam criteria.<sup>[3]</sup> This syndrome is a common and genetically heterogeneous complex disease that increases

the risk of diabetes mellitus (DM) type II about seven times. The familial risk factors are indicated and some cultural and genetic factors have been known to be effective in the occurrence of this syndrome.<sup>[4,5]</sup>

Clinical manifestations of PCOS that can be mentioned as typical appearance of polycystic ovary are oligomenorrhea, hirsutism, obesity, and biological changes (disruption of follicle stimulating hormone/luteinizing hormone (FSH/LH) proportion, an increase in testosterone levels, hyperandrogenism, and elevated insulin levels resulting in insulin resistance and morphologic symptoms).<sup>[6]</sup>

Hormonal changes in PCOS such as metabolic abnormalities (hyperinsulinemia and dyslipidemia) have high prevalence.<sup>[6]</sup> The potential increase in PCOS patients has been demonstrated for type II diabetes, hypertension (HTN), and cardiovascular diseases (CVD);<sup>[7]</sup> but there is limited evidence regarding the relation of hyperandrogenism in PCOS and CVD consequences. Studies show that the prevalence of CVD in women with PCOS is higher than in normal population.<sup>[8-14]</sup> Epidemiological studies about the relationship between PCOS and CVD is also limited. Furthermore, although PCOS increases the risk of cardiovascular side effects, clinical studies support a poor appearance of clinical symptoms.<sup>[15]</sup> A change in intima-media thickness (IMT) level over the threshold (900  $\mu\text{m}$ ) is always clearly associated with the pathology of atherosclerosis.<sup>[8]</sup> Since the carotid vessels are elastic and their muscle layers are thin, the increased thickness of the intima-media layer depends on the intima layer and consequently the risk of CVD in PCOS patients increases.<sup>[8]</sup>

In a study on 398 women with PCOS, 35% had total cholesterol higher than 200, 31% low density lipoprotein (LDL) of above 130, 15% with less than 35 high density lipoprotein (HDL), and 16% had triglyceride (TG) above 200.<sup>[1]</sup> The disrupted lipid profile suggests that the risk of cardiovascular complications is increased in these patients.<sup>[14]</sup> It is important to note that both PCOS and CVD are common in women, and CVD is a major cause of death in women, which is considered to be one of the important risk factors in the development of atherosclerosis.<sup>[2]</sup> On the other hand, atherosclerosis is a multifactorial disease that appears differently in various populations with different

lifestyle. The diagnosis of the atherosclerosis risk factors on the basis of IMT in PCOS women can be helpful in the diagnosis, prevention, and control of CVD; but few studies have been performed on the relationship between PCOS and atherosclerosis. Therefore, the present study was aimed to determine the thickness of intima-media carotid in PCOS women in compare to healthy women.

## METHODS

### Study design and samples

This clinical trial was performed between January, 2012 and February, 2012, on 200 pregnant. This cross-sectional study was conducted, between January, 2012 and January, 2013, on 44 PCOS patients and 44 healthy women (regular menses) who had been referred to “Shahid Beheshti” hospital in Isfahan, Iran. All cases and controls were selected in a simple random sample manner. PCOS patients aged 35-50-years-old, were eligible if they had oligomenorrhea and one of the criteria for diagnosis of PCOS which was approved by NIH including the clinical or laboratory evidence of hyperandrogenism including hirsutism, acne, male pattern hair loss, clitoromegaly, masculinization, and laboratory abnormalities including increased dehydroepiandrosterone sulfate (DHEAS), testosterone, and androstendion. No history of DM, no serious kidney diseases, and congenital heart disease were noted as other inclusion criteria, also subjects with chronic HTN in their profile, ovary and adrenal tumors, congenital adrenal hyperplasia, and known CHD were excluded from the study. Women aged 35-50 years with regular menses enrolled as control group. These women did not have hirsutism and their menstrual cycles were normal and LH/FSH ratio  $<2$ . Apparently normal nonpregnant women of same age group were recruited from female staff of Institute of Post-Graduate Medical Education and Research (IPGME and R), Kolkata. These women did not have hirsutism and their menstrual cycles were normal and LH/FSH ratio  $<2$ . Ethical review of the protocol was obtained from the institutional ethics committee at the Isfahan University of Medical Sciences, and written informed consent was obtained from studied subjects.

## Procedures

In case and control group lipid profiles, blood pressure (BP), waist circumference, body mass index (BMI), and IMT of carotid artery were measured in studied subjects. IMT of carotid artery were measured by a radiologist, who was blinded about study groups, using a linear 12 MHz ultrasound probe (LOGIC S6, GE) in carotid setting. Method of measuring was in the longitudinal view, the distance between the two echogenic lines parallel to the vessel wall was measured (between the two echogenic lines, there could be seen a hypoechoic area, that the first echogenic line is intima and the next one is the contact level of media and adventitia).<sup>[16]</sup> Measurement was done at four points of the posterior wall of common carotid artery (CCA) and 4-point internal carotid artery (ICA) on the right and left and their average was taken as two variables, one as IMT in CCA and the other as IMT in ICA and then the average of the two mentioned numbers were considered as another variable which was called combination of IMT in ICA and CCA, then these variables compared in two group.

## Statistical analysis

The sample size was calculated using the comparison of two means formula with two-sided log-rank test,  $\alpha = 0.05$ , and 90% power ( $\beta = 0.10$ ) for the absolute difference in IMT change between the groups exceeded 0.6. All statistical analyses were done using Statistical Package for Social Sciences (SPSS) 20. Variables are reported as mean  $\pm$  SD and number (percent) as appropriate. Continues variables between groups were compare using independent sample *t*-test and Chi-square test was used to compare categorical variables. The level of significance is considered to be less than 0.05.

## RESULTS

The mean of age, waist circumference, and BMI in all studied subjects were  $39.6 \pm 4.5$ ,  $89.03 \pm 11.2$ , and  $27.3 \pm 4.5$ , respectively. Results on comparison of age, waist circumference, BMI, and menstrual cycle between study groups are shown in Table 1. As shown, age and BMI were similar and there was no significant difference between study groups ( $P > 0.05$ ), but waist circumference

in cases was significantly lower than in the controls ( $P = 0.005$ ). Irregular menstrual cycle was observed in 79.5% of cases, but all controls had irregular menstrual cycle which was statistically significant between study groups ( $P < 0.0001$ ).

Results on the comparison of IMT carotid common and internal as the main variable in this study are reported in Table 2. As shown, IMT carotid common and internal in PCOS patients in comparison with control group was statistically significant ( $P < 0.0001$ ). Also, the lipid profile investigation in patients of both groups showed that mean LDL serum levels was significantly higher in PCOS patients than controls ( $P < 0.0001$ ), but levels of serum triglycerides, HDL, and total

**Table 1:** Comparison of characteristics between study groups

	Case group (n=44)	Control group (n=44)	P value
Age (year)	37.8 $\pm$ 3.8	38.3 $\pm$ 3.5	0.55*
Waist circumference (cm)	92.4 $\pm$ 11.6	85.7 $\pm$ 9.9	0.005*
Body mass index (kg/m <sup>2</sup> )	28.05 $\pm$ 5	26.6 $\pm$ 3.9	0.15*
Menstrual cycle			
Regular	9 (20.5)	44 (100)	>0.0001 <sup>†</sup>
Irregular	35 (79.5)	0	

Data are mean $\pm$ standard deviation (SD) and number (%). Cases included polycystic ovary syndrome (PCOS) patients and controls included healthy women. *P*-values calculated by \*independent sample *t*-test and <sup>†</sup>Chi-square test

**Table 2:** Comparison of lipid profile, hormone levels, and intima-media thickness between study groups

	Case group (n=44)	Control group (n=44)	P value
Common carotid artery IMT (mm)	56.8 $\pm$ 7.6	49.8 $\pm$ 7.3	<0.0001
Internal carotid artery IMT (mm)	56.9 $\pm$ 6.03	49.6 $\pm$ 6.9	<0.0001
Common and internal carotid artery IMT (mm)	56.6 $\pm$ 6.7	49.7 $\pm$ 6.9	<0.0001
Triglycerides (mmol/l)	137.7 $\pm$ 45.6	129.7 $\pm$ 34.5	0.36
HDL cholesterol (mmol/l)	44.8 $\pm$ 8.5	48.3 $\pm$ 10.2	0.08
LDL cholesterol (mmol/l)	128.6 $\pm$ 35.6	102.9 $\pm$ 25.9	<0.0001
Total cholesterol (mmol/l)	169.9 $\pm$ 30	176.2 $\pm$ 56.1	0.51

Data are mean $\pm$ SD. Cases included polycystic ovary syndrome (PCOS) patients and controls included healthy women. *P*-values calculated by independent sample *t*-test. HDL=High density lipoprotein, LDL=low density lipoprotein, IMT=Intima-media thickness



cholesterol were not significantly different between the two groups ( $P > 0.05$ ).

## DISCUSSION

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.<sup>[16,17]</sup> Also, other studies have shown that increased IMT as a noninvasive marker is a powerful predictor of coronary and cerebrovascular events and has been found to correlate well with traditional cardiovascular risk factors such as increasing age, obesity, and adverse lipid profiles; as commonly observed in PCOS.<sup>[18-21]</sup> Results of the present study, to assess the relation between IMT carotid common and internal with PCOS, show that significant association was found between IMT carotid common and internal, waist circumference and LDL serum levels with PCOS. IMT carotid common and internal and LDL serum levels were higher and waist circumference was lower in PCOS patients compared with healthy controls.

Previous studies suggested that women with PCOS face double risk of the metabolic syndrome comparing nonaffected population of the women in the society.<sup>[9]</sup> Also the most common type of occurrence of metabolic syndrome is obesity, HTN, and lipid disorders.<sup>[10]</sup> The results for both groups in this study were not significantly different regarding BMI index, but some criteria for metabolic syndrome such as waist circumference in patients with PCOS was higher than normal.

Benítez *et al.*, study have shown that this disease is a common disorder of lipoprotein abnormalities including elevated levels of total cholesterol, triglycerides, and LDL and reduced levels of HDL.<sup>[11]</sup> Similar to Benítez *et al.*'s, study; our results show increase in the level of LDL and reduction in the levels of HDL in the PCOS patients compared with control group. But other lipoprotein including total cholesterol and triglycerides were similar in studied groups.

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<sup>[12]</sup> which was similar to our results

that showed IMT artery in PCOS were significantly higher compared with controls. Also, in similar to present study, Luque-Ramírez *et al.*, reported that carotid IMT in PCOS women was significantly higher than the healthy group.<sup>[13]</sup> Moreover, another study was performed by Teng *et al.*, on young Chinese-Taiwanese women including patients with PCOS and healthy women, and showing that though the prevalence of atherosclerosis risk factors in women with PCOS was higher, but there was no evidence of increased IMT in young women suffering from PCOS.<sup>[14]</sup> These findings were in difference with significant increase in IMT which was observed in PCOS women aged between 35- and 50-year-old compared with controls in present study. Despite of some differences in study's findings, as mentioned above, it appears that the thickness of the carotid artery in patients with PCOS is higher and as a consequence patients are at increased risk for premature atherosclerosis, and hence the care and monitoring of PCOS women with risk factors for CVD is important and necessary.

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, or other lipoprotein. 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. Furthermore, additional well-designed studies with good sample size that control for all variables will be necessary to determine a potential relation between for vitamin D in the prevention of preeclampsia IMT and PCOS.

## CONCLUSIONS

The results of the present study demonstrated that thickness of the carotid artery in patients with PCOS is higher than healthy women and as a consequence patients are at increased risk for premature atherosclerosis, and hence the care and monitoring of PCOS women with risk factors for CVD is important and necessary.

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