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Carotid intima-media thickness in mainly non-obese women with polycystic ovary syndrome and age-matched controls

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Objective
Metabolic disturbances are well-recognized clinical features of polycystic ovary syndrome (PCOS). Carotid intima-media thickness (CIMT) has been widely used as a surrogate marker of atherosclerosis and cardiovascular disease (CVD). CIMT in women with PCOS has been investigated in many studies, but there has been only one report in the Korean population. The aim of the present study was to compare the presence of subclinical atherosclerosis in young untreated Korean women with PCOS and age-matched controls, specifically by measuring their CIMT.

Methods
CIMT was measured by one radiologist in 56 PCOS patients and 56 controls. To compare the CIMT according to PCOS phenotypes, women with PCOS were divided into two subgroups according to the presence of hyperandrogenism.

Results
Although PCOS patients were more obese and had higher blood pressure and insulin resistance index than the age-matched controls, the CIMT was not different between the two groups (0.49 ± 0.09 mm in PCOS patients vs. 0.50 ± 0.11 mm in controls, respectively, $p = 0.562$). When the CIMT in the control group was compared with hyperandrogenic and non-hyperandrogenic PCOS groups, also no significant differences were found.

Conclusion
Despite the significant differences in some vascular risk factors between women with PCOS and controls, PCOS patients did not have a significantly higher CIMT (even in the hyperandrogenic subgroups). Although our study did not show the increased risk of subclinical atherosclerosis in PCOS patients, the role of CIMT continues to be investigated considering the importance of screening and monitoring CVD risk factors in women with PCOS.

Keywords: Atherosclerosis; Carotid intima-media thickness; Insulin resistance; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of endocrine dysfunction in women of reproductive age with a prevalence that ranges from 4% to 7% [1,2]. Metabolic disturbances such as visceral obesity, hypertension, dyslipidemia, insulin resistance, and glucose intolerance are well-recognized clinical features of this syndrome. These factors, which are cluster in patients with PCOS, are also closely related to atherosclerosis.

Carotid intima-media thickness (CIMT) has been widely

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used as a surrogate marker of atherosclerosis and cardiovascular disease (CVD) events [3-8]. The association between PCOS and CIMT has been investigated in many studies [9-13], but there has been only one report in the Korean population: in 24 women with PCOS and 16 matched controls, mean CIMT was significantly higher in PCOS group than controls (0.57±0.12 mm vs. 0.49±0.11 mm, respectively, $P=0.004$) [14]. The aim of the present study was to compare the presence of premature atherosclerosis in young untreated Korean women with PCOS and age matched controls, specifically by measuring their CIMT.

Materials and methods

1. Subjects

Fifty-six women with PCOS (range, 18 to 40 years) were recruited using the Rotterdam criteria [15]. Clinical hyperandrogenism (HA) was defined as a modified Ferriman and Gallwey score (mF-G score) of 6 or greater and biochemical HA was defined as follows: total testosterone>0.68 ng/mL, free testosterone >1.72 pg/mL, and free androgen index (FAI) >5.36 [16,17]. To determine the distribution of the different PCOS phenotypes, patients with PCOS were divided into two subgroups according to the presence of HA. All women with PCOS were screened to exclude hyperprolactinemia and thyroid dysfunction. Serum 17-hydroxyprogesterone (OHP) was also measured, and if the serum 17-OHP level was over 2 ng/mL, a repeat test was performed during the early morning follicular phase. The patients who showed continuous elevation of 17-OHP were excluded from the study group.

A total of 56 age-matched (±1 year) premenopausal women served as controls, and the match ratio was 1 to 1. Control women visited Seoul National University Hospital as part of a group check-up for work and lacked specific health problems. All controls had regular (21 to 35 day) menstrual cycles, a mF-G score <6, and all received a transvaginal or transrectal pelvic ultrasound examination to evaluate ovarian morphology and were excluded if PCOS morphology was identified.

None of the patients with PCOS and controls had taken combined oral contraceptives, lipid-lowering agents or insulin sensitizer. The Institute Review Board (IRB) for human research of Seoul National University Hospital approved this project (IRB number: H-0807-031-250) and written informed consent was obtained from each woman.

2. Clinical and biochemical measurements

Clinical variables, such as body weight, height, waist circumference, and blood pressure were assessed in all subjects. Using radioimmunoassay (RIA) (Siemens, Los Angeles, CA, USA), serum levels of total testosterone, free testosterone and sex hormone-binding globulin (SHBG) were measured in all patients with PCOS and in a subset of controls (n=14) whose blood samples were taken during the follicular phase of the menstrual cycle. FAI was calculated as total testosterone/SHBG×100, and the values for testosterone were converted from ng/mL to nmol/L using the following index proposed by the manufacturer: 1 ng/mL=3.467 nmol/L. The intra-assay and inter-assay coefficients of variation were 4.0% to 11.0% and 5.9% to 12.0% for total testosterone, and 4.0% to 17% and 8.0% to 18.3% for free testosterone, respectively.

In all subjects, after 12-hour overnight fast, fasting plasma glucose (FPG) (hexokinase method), total cholesterol (cholesterol oxidase-N-[3-sulfopropyl]-3-methoxy-5-methylaniline [HMMPS] method), triglycerides (glycerol-3-Phosphatase oxidase–HMMPS glycerol blanking), high density lipoprotein (HDL)-cholesterol (selective elimination method) and low density lipoprotein (LDL)-cholesterol (selective elimination method) were measured (Wako Pure Chemical Industries Ltd., Osaka, Japan). Circulating highly sensitive C-reactive protein (hs-CRP) was measured using a latex turbidimetric immunoassay with a sensitivity of 0.01 mg/dL (Wako Pure Chemical Industries Ltd., Japan). Fasting insulin levels were measured using RIA (BioSource Europe S.A., Nivelles, Belgium). The homeostatic model for insulin resistance was calculated by glucose (mg/dL)×insulin (μU/mL)/405, and $HOMA_{\beta cell}$ (%) was calculated as follows: (20×fasting insulin)/(fasting glucose-3.5).

Although transducer frequency is best between 8 to 12 MHz [4], CIMT measurement was conducted using a high-resolution 7.5-MHz phased-array transducer (Vivid 7 Cardiovascular Ultrasound, GE Healthcare, Milwaukee, WI, USA) by one radiologist (K.J.H.) who was blinded to the patients' clinical profiles. Depth and gain were optimized to reduce noise, and to get best image, the operator manipulated transducer for ultrasound beam is perpendicular to the intima-media structure. Both common carotid arteries were explored in B-mode and intra-assay variation was <10%. The posterior carotid wall at 1 cm of the common carotid bulb was imaged and CIMT was estimated by visual assessment of the distance between the lumen/intima and intima/adventicia interphases in longitudinal frame. Each left and right carotid artery IMT was

calculated as the average of three recordings, and the mean CIMT, which was calculated from the bilateral CIMT values, was used as the outcome variable.

3. Statistical analysis

Deviation of the data from a normal distribution was examined through visual inspection of quantile-normal plots and/or the Shapiro-Wilk test of normality. The data are shown as the mean ± standard deviation or median value with the range. If Gaussian distribution was achieved by natural logarithmic or square root transformation, the data are shown as geometric means and 95% confidence intervals (95% CI). Continuous parameters were compared using Student's *t* or Mann-Whitney *U* test. Univariate regression analyses were conducted with CIMT as a dependent variable and traditional CVD risk factors and serum androgens as independent variables. All data analyses were performed using the Statistical Package for the Social Sciences software ver. 19.0 (IBM SPSS, Somers, NY, USA), and statistical significance was set at two-sided *P*-values <0.05.

Power calculations were performed using the G-power ver. 3.1.5 software (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3). Given the specified sample size (56 PCOS patients and 56 controls), the power to detect a mean CIMT difference 0.5 mm (an α value of 0.05) was 0.75.

Results

Clinical and biochemical characteristics of the subjects are shown in Table 1. Women with PCOS and controls were same

Table 1. Clinical features of the patients with PCOS and matched controls

Clinical feature	PCOS (n=56)	Control (n=56)	*P*-value[a]
Age (yr)[b]	30.9 ± 4.6	30.8 ± 4.8	0.904
BMI (kg/m^2)[b]	21.2 ± 2.8	19.8 ± 2.1	0.004
Prevalence of obesity (BMI=25 kg/m^2) (%)	12.5 (7/56)	1.8 (1/56)	0.061
WC (cm)[b]	76.2 ± 7.0	74.6 ± 6.9	0.223
Hirsutism score[c]	6 (0–20)	1 (0–5)	<0.001
Total T (ng/mL)[d]	0.30 (0.26–0.34)	0.23 (0.21–0.25) (n=14)	0.323
Free T (pg/mL)[d]	0.56 (0.45–0.67)	0.37 (0.33–0.41) (n=14)	0.119
SHBG (nmol/L)[d]	42.6 (37.9–47.3)	72.6 (77.3–67.9) (n=14)	0.013
FAI[d]	4.53 (3.53–5.53)	1.36 (1.27–1.45) (n=14)	0.205
SBP (mm Hg)[b]	108.0 ± 11.8	102.1 ± 9.0	0.005
DBP (mm Hg)[b]	67.4 ± 10.1	62.9 ± 7.9	0.012
Fasting plasma glucose (mg/dL)[b]	87.4 ± 6.3	86.6 ± 7.7	0.577
Fasting insulin (μU/mL)[d]	7.8 (7.4, 8.2)	6.4 (6.0–6.8) (n=40)	0.053
HOMA-IR[d]	1.7 (1.6, 1.8)	1.4 (1.3–1.5) (n=40)	0.048
HOMA-BC[d]	114.2 (109.4–119.0)	102.5 (97.3–107.7)	0.262
hs-CRP (mg/dL)[c]	0.01 (0.01–1.15)	0.02 (0.01–0.29)	0.286
A1C (%)[b]	5.62 ± 0.30	5.59 ± 0.31	0.639
Total C (mg/dL)[b]	183.0 ± 29.2	176.3 ± 28.0	0.221
TG (mg/dL)[b]	78.5 ± 28.3	72.4 ± 31.6	0.285
HDL-C (mg/dL)[b]	64.6 ± 15.4	64.7 ± 14.2	0.980
LDL-C (mg/dL)[b]	126.3 ± 30.5	96.7 ± 22.9	0.203
CIMT (mm)[b]	0.49 ± 0.09 (range, 0.30–0.70)	0.50 ± 0.11 (range, 0.24–0.82)	0.562

PCOS, polycystic ovary syndrome; BMI, body mass index; WC, waist circumference; T, testosterone; SHBG, sex- hormone binding globulin; FAI, free androgen index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-BC, homeostatic model assessment for beta cell capacity; hs-CRP, high-sensitivity C-reactive protein; A1C, hemoglobin A1c; C, cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CIMT, carotid intima media thickness.
[a]*P*-values were analysed by Student's *t* test or Mann-Whitney *U* test except the prevalence of obesity (Fisher's exact test); [b]Data are shown as means ± standard deviations; [c]Medians (ranges); [d]Geometric means with 95% confidence intervals.

Table 2. Comparison of CIMT between the control group and hyperandrogenic and non-hyperandrogenic PCOS patients

	No. of subjects	CIMT	*P*-value (vs. control)[a]
PCOS phenotypes			
Hyperandrogenic	33	0.49 ± 0.10	0.913
Non-hyperandrogenic	23	0.47 ± 0.08	0.360
Control	56	0.50 ± 0.11	

CIMT, carotid intima media thickness; PCOS, polycystic ovary syndrome.
[a]*P*-values were analysed by Student's *t* test or Mann-Whitney *U* test.

Table 3. Univariate linear regression analysis with CIMT as the dependent variable

Factors	All subjects (n=112)		PCOS (n=56)	
	Standardized ß-coefficient	*P*-value	Standardized ß-coefficient	*P*-value
Age	0.163	0.086	0.204	0.131
BMI	0.014	0.887	0.037	0.789
Waist circumference	-0.058	0.547	-0.085	0.537
SBP	-0.056	0.566	-0.124	0.363
DBP	-0.081	0.405	-0.058	0.670
TG	0.158	0.096	0.139	0.403
HDL-C	-0.122	0.199	0.172	0.361
LDL-C	-0.029	0.762	0.001	0.996
Fasting glucose	-0.126	0.194	-0.021	0.877
Root HOMA-IR	0.014 (n=96)	0.903	0.190	0.240
A1C	-0.028	0.769	-0.045	0.799
Root total testosterone	0.045 (n=70)	0.769	0.064	0.737
Root free testosterone	0.079 (n=70)	0.609	0.084	0.659
Root FAI	0.025 (n=70)	0.879	0.023	0.905

CIMT, carotid intima media thickness; PCOS, polycystic ovary syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; A1C, hemoglobin A1C; FAI, free androgen index.

in age (30.9 vs. 30.8, $P=0.904$). Although mean BMI of the PCOS patients was significantly higher than that of the controls (21.2 kg/m^2 vs. 19.8 kg/m^2, respectively, $P=0.004$), most (87.5%) of the women with PCOS in the present study were not obese. The PCOS group had significantly higher blood pressure, HOMA-IR as well as lower SHBG levels than the controls, but there were no significant differences in serum androgen, lipid profiles, fasting glucose and A1C levels between the two groups.

The CIMT ranged from 0.30 to 0.70 mm in women with PCOS and from 0.24 to 0.82 mm in controls. Despite the significant differences in some vascular risk factors between women with PCOS and controls, the mean CIMT was not different between the two groups (0.49±0.09 mm in PCOS patients vs. 0.50±0.11 mm in controls, respectively, $P=0.562$). When the CIMT in the control group was compared with hyperandrogenic and non-hyperandrogenic PCOS groups, there were also no significant differences between the groups (Table 2). The univariate linear correlations between CIMT and common atherogenic factors or androgenic parameters are presented in Table 3. CIMT was not correlated with any of the above parameters in all subjects as well as the subset of PCOS patients.

Discussion

We have presented a case-control study of the CIMT, a marker of subclinical atherosclerosis, in women with PCOS and age-matched controls. Although young Korean PCOS patients

were more obese and had higher blood pressure and insulin resistance index than the age-matched controls, carotid artery intima-media thickness measurements as a pre-indicator of CVD was not found to be different between the patients and controls.

Numerous studies have investigated whether CIMT is elevated in women with PCOS or not [9-13]. However, these studies have not shown consistent results, and it may stem from the quality of the CIMT measurement, small sample sizes and young age of the subjects. Recently, systematic review and meta-analysis has been reported [18]. Eight studies were included in the systematic review and 19 studies were included in the meta-analysis (total n = 1,123 women with PCOS, n = 923 controls). In this analysis, the mean difference in CIMT among women with PCOS compared with controls was 0.072 mm (95% CI, 0.040–0.105; $P < 0.0001$) for highest quality studies, and 0.084 mm (95% CI, 0.042–0.126; $P < 0.0001$) for good quality studies, and the authors concluded that women with PCOS demonstrated higher CIMT than controls. However, in our current study, there were no significant differences in CIMT between the PCOS group and controls. Additionally, there were also no significant associations between CIMT and serum androgen and metabolic markers.

One outstanding issue is the role of androgens in cardiovascular risk, and in the current study, PCOS cases with HA did not show higher CIMT than the controls. Although there have been studies reporting similar occurrence of metabolic risk across PCOS subgroups [19,20], patients with no evidence of HA may have milder metabolic profile compared with the other phenotypes [21,22]. In current study, mean serum androgen levels of the whole PCOS patients were not different compared to those of the controls, and almost half (41.2%) of the PCOS subjects had non-hyperandrogenic phenotype. Thus, no difference in CMIT between PCOS patients and controls may stem from the presence of this mild phenotype.

Although our study could not find any difference in CIMT between PCOS patients and controls, the present study has some limitations that need to be discussed. First, mean age of the patients was 30.9 (±4.6) years old, and mean BMI was 21.2 (±2.8) kg/m^2, suggesting that the subjects mainly consisted of young and non-obese women. The prevalence of atherogenic CIMT pattern increases with age and BMI [3,4], thus the absence of CIMT difference between PCOS patients and controls may be, in part, due to the relatively young age of our subjects. However, previous studies, which found that the PCOS patients presented with an increased CIMT, were also performed using patients under 35 years of age [11,12,23], suggesting that the premature atherosclerosis may be found even in these young PCOS patients. Second, as mentioned above, no difference in CIMT between patients and controls also might stem from non-obese state of the subjects. Although mean BMI of the PCOS patients was significantly higher than that of the controls (21.2 ± 2.8 kg/m^2 vs. 19.8 ± 2.1 kg/m^2, respectively, $P = 0.004$), women with PCOS in the present study were definitely thin. Thus, the degree of metabolic dysfunction in this study was modest such that serum insulin, lipid, hs-CRP levels of the patients were not different compared to the controls. This would be the most important reason why there were no differences in CIMT. Data on obese subjects could offer complementary findings about the possible relationship between the magnitude of obesity and CIMT. Third, given the specified sample size (56 PCOS patients and 56 controls), the power to detect a mean CIMT difference 0.5 mm (an α value of 0.05) was 0.75. Since this study has limited power for the small CIMT difference, no difference between PCOS patients and controls could be due to insufficient power. Finally, we cannot exclude the possibility of other potentially confounding factors, such as differences in diet and/or exercise patterns.

In conclusion, despite the significant differences in some vascular risk factors between women with PCOS and controls, PCOS patients did not have a significantly higher CIMT (even in the hyperandrogenic subgroups). Although our study did not show the increased risk of subclinical atherosclerosis in PCOS patients, the role of CIMT continues to be investigated considering the importance of screening and monitoring CVD risk factors in women with PCOS.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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