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, 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
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, an 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-sulpropyl]-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\(_{\text{IR}}\) = \((20\times\text{fasting insulin})\times(\text{glycemia}-3.5)\) 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, Milwaukie, 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 measured their CIMT.