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Clinical and biochemical characteristics of polycystic ovary syndrome in Korean women

Soo Jin Chae[1], Jin Ju Kim[1], Young Min Choi[1,2,3], Kyu Ri Hwang[1], Byung Chul Jee[1,2], Seung Yup Ku[1,2], Chang Suk Suh[1,2], Seok Hyun Kim[1,2], Jung Gu Kim[1] and Shin Yong Moon[1,2]

[1]Department of Obstetrics and Gynecology, Medical Research Center, Seoul National University College of Medicine, 28 Yungun-dong, Chongno-ku, Seoul 110–744, South Korea; [2]Institute of Reproductive Medicine and Population, Medical Research Center, Seoul National University College of Medicine, Seoul, South Korea

[3]Correspondence address. Fax: +82-2-762-3599; E-mail: ymchoi@snu.ac.kr

BACKGROUND: We investigated the differences in anthropometrical, hormonal and insulin resistance parameters according to the subtype of polycystic ovary syndrome (PCOS) in Korean women. METHODS: We recruited 166 women with PCOS and retrospectively recruited 277 controls. PCOS was diagnosed by irregular menstruation (IM), polycystic ovary (PCO) and hyperandrogenism (HA). Subjects were divided into four subgroups: the IM/HA/PCO group ($n = 87$, 52.4%), the IM/PCO group ($n = 52$, 31.3%), the IM/HA group ($n = 23$, 13.9%) and the HA/PCO group ($n = 4$, 2.4%). Clinical and biochemical variables were compared among the PCOS subgroups. RESULTS: The IM/HA/PCO and IM/HA groups showed higher body mass index ($P < 0.001$) and waist-to-hip ratio ($P < 0.001$) than the IM/PCO group. The IM/HA group had higher triglyceride levels than the other groups ($P < 0.001$). Higher fasting insulin ($P < 0.001$) and postprandial 2 h insulin ($P < 0.01$) were noted in the IM/HA/PCO group and the IM/HA group, compared with the IM/PCO group. Women with PCOS showed lower sex hormone-binding globulin ($P < 0.001$) and higher systolic blood pressure (BP) ($P = 0.004$), diastolic BP ($P = 0.001$), fasting insulin ($P < 0.001$), postprandial 2 h insulin ($P < 0.001$), homeostatic model for insulin resistance ($P < 0.001$) and clinical and biochemical parameters of metabolic syndrome ($P < 0.05$) compared with subjects without PCOS. CONCLUSIONS: Women with PCOS without HA are common in Korea and are less likely to have metabolic dysfunction, insulin resistance and elevated BP. PCOS without HA may be a mild phenotype of PCOS. Therefore, women with PCOS in Korea could have a reduced likelihood of having metabolic syndrome compared with women of other ethnicities.

Keywords: polycystic ovary syndrome; PCOS subgroups; metabolic syndrome; insulin resistance; hyperandrogenism

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of endocrine dysfunction in women of reproductive age, affecting 5–10% of the general population (Azziz *et al*., 2004; Ehrmann, 2005). The pathogenesis of PCOS is complex and still not clear, and PCOS is considered to be a heterogeneous disorder. After the first description by Stein and Leventhal (1935), the diagnostic criteria of PCOS have developed over the years. The 1990 National Institutes of Heath (NIH) conference proposed the diagnostic criteria of oligo- or anovulation and biochemical and clinical signs of hyperandrogenism (HA). Recently, the 2003 Rotterdam consensus workshop of the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) broadened the definition by including polycystic ovary (PCO) morphology (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The newly added PCOS phenotypes were PCO with irregular menstruation (IM) without HA and PCO with HA without oligo-anovulation. Therefore, PCOS can be divided into four subtypes: (i) IM/PCO/HA, (ii) IM/PCO, (iii) IM/HA and (iv) HA/PCO. In 2006, the Androgen Excess Society (AES) Task Force on the Phenotypes of PCOS emphasized HA as the cornerstone of PCOS and excluded the IM/PCO subgroup, which was not thought to be associated with metabolic dysfunction (Azziz *et al*., 2006).

A few studies regarding clinical and metabolic differences between the different subtypes of PCOS have been performed. One study using NIH criteria, with no regard to PCO morphology, reported that oligo-anovulatory patients with a hirsutism phenotype had the lowest degrees of hyperandrogenemia and hyperinsulinemia and that those with biochemical HA demonstrated intermediate degrees of hyperandrogenemia and metabolic dysfunction (Chang *et al*., 2005). Using the

Rotterdam criteria, Welt *et al*. (2006) reported that patients with oligo-anovulatory PCO with HA had the most severe phenotype on the basis of androgen levels. Dewailly *et al*. (2006) regarded patients with oligo-anovulatory PCO without HA as having mild endocrine and metabolic features of PCOS. In Asia, there have been few studies of the various subtypes of PCOS. Hsu *et al*. (2007) described only the prevalence and basal hormone levels, including luteinizing hormone (LH), follicle stimulating hormone (FSH) and total testosterone in Taiwanese Chinese women. Shi *et al*. (2007) divided PCOS patients into two groups according to PCO. They discriminated PCOS patients with PCO from those without and found that PCOS patients without PCO showed higher cholesterol and low-density lipoprotein. To our knowledge, however, no study in Asian women has addressed the different clinical, biochemical and metabolic characteristics between the subtypes of PCOS according to the 2003 ASRM/ESHERE consensus.

The aim of this study was to investigate anthropometrical, hormonal and metabolic difference according to the subtype of PCOS using the ASRM/ESHERE criteria in Korean women.

Materials and Methods

Subjects

This study was approved by the Institutional Review Board of Seoul National University Hospital. Informed written consent was obtained from all subjects. This retrospective study included 166 consecutive PCOS patients who visited the Department of Obstetrics and Gynecology at Seoul National University Hospital from January, 2004, to December, 2007. PCOS subjects were diagnosed using the 2003 Rotterdam criteria (2 out of 3): (i) oligo-anovulation (menstrual cycle >35 days), (ii) HA (either clinical or biochemical) and (iii) PCO and exclusion of other etiologies. Women with PCOS were divided into four subgroups: (i) the IM/HA/PCO group, (ii) the IM/PCO group, (iii) the IM/HA group or (iv) the HA/PCO group.

Clinical HA was defined by a modified Ferriman and Gallwey score (mF–G score) of more than 8 (Hatch *et al*., 1981). Biochemical HA was defined as a elevation of serum androgen levels beyond the 95% confidence limits defined in 89 ovulatory, non-hirsute controls with regular menstruation cycles, who did not show PCO on ultrasonography [total testosterone (T) >0.68 ng/ml, free T >1.72 pg/ml, free androgen index (FAI) >5.36]. All subjects underwent a transvaginal ultrasound or transrectal ultrasound in the follicular phase to evaluate ovary morphology and any lesions in the pelvic area.

Exclusion criteria were cases of abnormal thyroid function tests, abnormal prolactin levels, diagnosed cardiovascular disease and diabetes mellitus as well as those taking medication affecting gonadotrophin status in the previous 6 months and those with 17-hydroxyprogesterone (17-OHP) levels of more than 3 ng/ml (Azziz *et al*., 1999).

There were also 277 controls enrolled in this study over the same period. They visited the health-care center in our hospital as a part of group checkup for work or an association or an individual need for annual comprehensive medical checkup with no specific health problems. Subjects ranged in age from 13 to 34 years and did not show hirsutism, acne or male-type alopecia. All of them had absolutely regular menstrual cycle periods between 21 and 35 days, and none satisfied any of the PCOS criteria of the 2003 Rotterdam consensus. All control subjects received an ultrasonographic examination by one gynecologist, specialized in reproductive endocrinology, and women who had any pathologic findings or PCO in their pelvic area were excluded in the present study. Women who had any medication that may effect on endocrinologic or metabolic changes were excluded in the control group in this study.

Clinical and biochemical measurements

Clinical variables such as waist circumference, hip circumference, body weight, height and blood pressure (BP) were assessed in all subjects during a visit in the outpatient department. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Whole blood was sampled on Day 3 of the menstrual cycle or during the period of amenorrhea in PCOS patients. Basal gonadotrophin hormone levels were measured in all PCOS subjects, including serum LH, FSH and estradiol (E2). Women with PCOS and control subjects were evaluated for serum total T, free T, 17-OHP, DHEAS and sex hormone-binding globulin (SHBG) using RIA (Simens, Los Angeles, CA, USA) and plasma insulin levels were measured using a commercial kit (BioSource Europe S.A., Belgium). FAI was calculated as total T/SHBG × 100. Fasting and postprandial 2 h glucose and insulin levels were evaluated by a 75 g glucose tolerance test using commercial kits (BioSource Europe S.A.) in order to assess insulin resistance in all patients. The homeostatic model for insulin resistance (HOMA-IR) was calculated by glucose (mg/dl) × insulin (μU/ml)/405. Serum cholesterol, triglycerides and HDL were measured using a 200FR system (Toshiba, Tokyo, Japan). Intra- and inter-assay coefficients of variation were 4.0–11.0% and 5.9–11.0% for total testosterone, 4.0–17% and 8.0–18.3% for free T, 5.0–7.1% and 5.0–11.0% for 17-OHP, 3.8–5.1% and 6.3–11.0% for DHEAS, 2.8–5.3% and 7.9–8.5% for SHBG, and 1.6%–2.2% and 6.1–6.5% for plasma insulin, respectively.

All subjects were evaluated for metabolic syndrome, which was defined based on the Modified National Education Program-Adult Treatment Panel (ATP) III criteria (Grundy *et al*., 2005), applying the abdominal obesity criteria of The International Diabetes Federation (IDF), using waist circumference >80 cm (The International Diabetes Federation, 2006).

Statistical analysis

Clinical variables such as age and BMI were compared using one-way analysis of variance (ANOVA). Laboratory and anthropometric parameters were compared by analysis of covariance (ANCOVA) to correct for age and BMI. Fisher's least significant difference (LSD) *post hoc* test was used to determine significant differences between groups. Parameters of metabolic syndrome among the subgroups of PCOS were compared using a chi-square test. All data were analyzed using Statistical Package for the Social Sciences for Windows version 12.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± SD, unless indicated. A P-value of <0.05 was considered significant.

Results

For the present study, we recruited 166 PCOS subjects who met the criteria of the IM/HA/PCO group ($n = 87$, 52.4%), the IM/PCO group ($n = 52$, 31.3%), the IM/HA group ($n = 23$, 13.9%) or the HA/PCO group ($n = 4$, 2.4%). The last group was excluded from further analysis to avoid selection bias because the sample size was too small for statistical analysis (Table I).

The mean age of women in the control group (28.2 ± 3.7 years) was significantly higher than in the PCOS group (25.5 ± 5.8 years, $P < 0.001$), but mean age was not different among the PCOS subgroups. Mean BMI was also not different

Table I. Basal characteristics and ultrasonographic findings of the subjects in each subgroup using the Rotterdam criteria.

	IM/HA/PCO ($n = 87$)	IM/PCO ($n = 52$)	IM/HA ($n = 23$)	HA/PCO ($n = 4$)	Control ($n = 277$)	*P*-value PCOS subgroups versus control
Age (years)	25.4 ± 5.7^{a}	25.7 ± 4.9^{a}	23.4 ± 6.9^{a}	27.8 ± 6.6^{a}	28.3 ± 3.7^{b}	<0.001
Weight (kg)	59.2 ± 11.5^{a}	56.1 ± 9.1	61.8 ± 13.4^{a}	56.7 ± 12.7	53.2 ± 7.4^{b}	<0.001
BMI (kg/m^2)	22.8 ± 5.1^{a}	20.9 ± 4.4	23.1 ± 4.8^{a}	21.9 ± 4.4	20.3 ± 2.8^{b}	<0.001
Waist circumference (cm)	74.8 ± 9.3^{a} ($n = 73$)	68.1 ± 9.2^{b} ($n = 49$)	76.5 ± 9.3^{a} ($n = 19$)	70.4 ± 9.1 ($n = 3$)	73.6 ± 9.3^{a} ($n = 89$)	0.001
W/H ratio	0.79 ± 0.07^{a} ($n = 70$)	0.72 ± 0.07^{b} ($n = 49$)	0.80 ± 0.07^{a} ($n = 19$)	0.76 ± 0.07 ($n = 3$)	0.72 ± 0.07^{b} ($n = 49$)	<0.001
Maximum antral follicle count (*n*)	20.3 ± 7.2^{a}	18.0 ± 5.7^{a}	6.9 ± 4.6^{b}	18.0 ± 2.8^{a}	7.7 ± 2.3^{b}	<0.001
Maximum ovarian volume (cm^3)	11.0 ± 7.3^{a}	8.4 ± 4.8^{b}	4.2 ± 2.3^{c}	6.3 ± 2.5^{c}	5.6 ± 2.0^{c}	<0.001
PCO morphology, *n* (%)	87 (100%)	52 (100%)	0 (0%)	4 (100%)	0 (0%)	

Data are shown as mean ± SD.
BMI, body mass index; W/H ratio, waist-to-hip ratio; IM, irregular menstruation; HA, hyperandrogenism; PCO, polycystic ovary.
P-values were evaluated by one-way ANOVA with Fisher's LSD *post hoc* correction and by ANCOVA, controlling for age and BMI for waist circumference and W/H ratio among each PCOS subgroup and controls.
[a–c]Values bearing different superscripts are significantly different between any two groups ($P < 0.05$).

among the PCOS subgroups, but women with IM/PCO showed lower waist circumference and waist-to-hip ratio compared with women in the IM/HA/PCO or IM/HA groups ($P < 0.001$).

Subgroup analysis using the Rotterdam criteria

The IM/HA/PCO and IM/PCO groups had higher maximum antral follicle count than the IM/HA or control groups ($P < 0.001$). Maximum ovarian volume in the IM/HA/PCO group was greater than other PCOS subgroups ($P < 0.001$), and the IM/PCO group also had a significantly greater ovarian volume than the control group ($P < 0.001$) (Table I).

mF–G score was significantly higher in women in the IM/HA/PCO and IM/HA groups than those in the IM/PCO and control groups by definition of HA ($P < 0.001$) (Table II). Subjects in the IM/HA group showed more severe hirsutism than women in the IM/HA/PCO group ($P < 0.05$). Total T was significantly lower among women in the IM/PCO group

Table II. Comparison of clinical features, hormonal and metabolic parameters between PCOS subgroups using the Rotterdam criteria.

	IM/HA/PCO ($n = 87$)	IM/PCO ($n = 52$)	IM/HA ($n = 23$)	Control ($n = 277$)	*P*-value PCOS subgroups versus control
mF–G score	8.7 ± 3.1^{a} ($n = 77$)	3.1 ± 3.0^{b} ($n = 50$)	10.5 ± 3.0^{a} ($n = 20$)	1.4 ± 3.0^{c} ($n = 259$)	<0.001
Total T (ng/ml)	0.44 ± 0.19^{a} ($n = 80$)	0.35 ± 0.19^{b} ($n = 51$)	0.39 ± 0.19 ($n = 19$)	0.36 ± 0.19^{b} ($n = 91$)	0.035
Free T (pg/ml)	1.90 ± 0.69^{a} ($n = 78$)	0.87 ± 0.68^{b} ($n = 50$)	1.86 ± 0.68^{a} ($n = 18$)	0.92 ± 0.69^{b} ($n = 89$)	<0.001
17-OHP (ng/ml)	$1.4 \pm 1.1^{a,c}$ ($n = 78$)	$1.1 \pm 1.1^{a,d}$ ($n = 48$)	1.9 ± 1.1^{b} ($n = 16$)	1.9 ± 1.1^{b} ($n = 87$)	<0.001
DHEAS (ng/ml)	$2100.9 \pm 956.3^{a,c}$ ($n = 75$)	$1731.2 \pm 937.3^{a,d}$ ($n = 47$)	2109.4 ± 953.2 ($n = 17$)	2416.9 ± 985.4^{b} ($n = 89$)	0.001
SHBG (nmol/l)	38.9 ± 29.3^{a} ($n = 39$)	49.6 ± 29.8^{a} ($n = 31$)	31.5 ± 29.3^{a} ($n = 5$)	74.3 ± 29.2^{b} ($n = 89$)	<0.001
FAI	6.1 ± 4.0^{a} ($n = 39$)	3.4 ± 3.8^{b} ($n = 31$)	5.9 ± 3.9 ($n = 5$)	2.5 ± 4.0^{b} ($n = 89$)	<0.001
LH (mIU/ml)	9.8 ± 6.8 ($n = 74$)	9.0 ± 6.5 ($n = 41$)	8.8 ± 6.5 ($n = 19$)	Not checked	NS
FSH (mIU/ml)	4.7 ± 2.5 ($n = 73$)	5.3 ± 2.5 ($n = 41$)	4.9 ± 2.4 ($n = 19$)	Not checked	NS
LH/FSH	2.5 ± 1.6 ($n = 73$)	1.9 ± 1.6 ($n = 41$)	2.1 ± 1.6 ($n = 19$)	Not checked	NS
SBP (mmHg)	113.8 ± 13.1^{a} ($n = 63$)	108.9 ± 13.1 ($n = 42$)	114.9 ± 12.8^{a} ($n = 15$)	107.5 ± 13.0^{b} ($n = 240$)	0.004
DBP (mmHg)	72.5 ± 10.3^{a} ($n = 63$)	70.6 ± 10.0^{a} ($n = 42$)	73.5 ± 13.0^{a} ($n = 15$)	67.1 ± 10.2^{b} ($n = 240$)	0.001
Cholesterol (mg/dl)	175.8 ± 30.5 ($n = 33$)	173.0 ± 29.8 ($n = 19$)	174.9 ± 30.2 ($n = 10$)	168.4 ± 30.0 ($n = 219$)	0.545
Triglycerides (mg/dl)	98.4 ± 32.8^{a} ($n = 16$)	111.1 ± 31.8^{a} ($n = 10$)	155.4 ± 31.7^{b} ($n = 4$)	69.4 ± 31.7^{c} ($n = 207$)	<0.001
HDL (mg/dl)	59.0 ± 13.4 ($n = 16$)	63.9 ± 13.0 ($n = 10$)	55.7 ± 13.0 ($n = 4$)	63.7 ± 13.0 ($n = 206$)	0.369
Fasting glucose (mg/dl)	88.3 ± 12.5 ($n = 81$)	90.0 ± 12.1 ($n = 51$)	86.3 ± 12.3 ($n = 20$)	88.9 ± 12.4 ($n = 219$)	0.674
Fasting insulin (μU/ml)	13.2 ± 6.7^{a} ($n = 81$)	10.7 ± 6.6^{b} ($n = 51$)	14.9 ± 6.6^{a} ($n = 21$)	8.4 ± 6.7^{c} ($n = 109$)	<0.001
PP2 glucose (mg/dl)	112.5 ± 36.9 ($n = 78$)	101.0 ± 37.7 ($n = 50$)	105.4 ± 37.4 ($n = 18$)	Not checked	0.316*
PP2 insulin (μU/ml)	87.2 ± 75.4^{a} ($n = 73$)	41.1 ± 76.4^{b} ($n = 46$)	104.4 ± 76.3^{a} ($n = 17$)	Not checked	0.006*
HOMA-IR	2.9 ± 1.8^{a} ($n = 81$)	2.5 ± 1.7^{a} ($n = 51$)	3.3 ± 1.7^{a} ($n = 20$)	1.9 ± 1.8^{b} ($n = 109$)	<0.001

Data are shown as mean ± SD.
W/H ratio, waist-to-hip ratio; mF–G score, modified Ferriman–Gallwey score; T, testosterone; 17-OHP, 17-hydroxyprogesterone; DHEAS, dehydroepiandrostenedione; SHBG, sex hormone-binding globulin; FAI, free androgen index; PP2, postprandial 2 h; IM, irregular menstruation; HA, hyperandrogenism; PCO, polycystic ovary.
P-values are indicated for the differences in groups as analyzed by ANCOVA, controlling for age and BMI among the PCOS subgroups and controls.
[a–d]Values bearing different superscripts are significantly different between any two groups ($P < 0.05$), as demonstrated by Fisher's LSD *post hoc* correction.
**P*-values were measured among the PCOS subgroups.

than those in the IM/HA/PCO group ($P < 0.05$), and the total T of women in the IM/PCO group was not different from those in the control group. Free T concentration of women in the IM/PCO group, which was significantly lower than those in the IM/HA/PCO or IM/HA groups ($P < 0.001$), was similar to that of subjects in the control group. Serum SHBG concentration was not different among the PCOS subgroups, but it was significantly lower in PCOS subjects than in controls ($P < 0.001$). FAI in the IM/PCO group was significantly lower than in the IM/HA/PCO group ($P < 0.05$) and showed a difference of borderline significance with the HA/PCO group ($P = 0.055$). Both 17-OHP ($P < 0.001$) and DHEAS ($P = 0.001$) among women in the IM/HA/PCO and IM/PCO groups were significantly lower than in women in the control group. Women in the IM/PCO group showed the lowest level of 17-OHP and DHEAS among the three PCOS subgroups.

Serum LH level was increased more than the serum FSH concentration in subjects with PCOS, irrespective of subgroup. Both serum LH and FSH showed no differences among the PCOS subgroups. The LH/FSH ratio showed an elevated trend among women in all of the PCOS subgroups.

Although women in the IM/HA/PCO and IM/HA groups showed higher systolic BP (SBP) than women in the IM/PCO and control groups ($P = 0.004$), diastolic BP (DBP) in all women with PCOS was higher than in controls ($P = 0.001$). Both serum cholesterol and HDL concentrations were not significantly different in women with PCOS compared with controls. Serum triglycerides, however, were elevated significantly more in PCOS patients than in controls ($P < 0.001$). Women in the IM/HA group actually showed the highest triglyceride levels among the three PCOS subgroups ($P < 0.001$).

The results of the 75 g glucose tolerance test did not show any differences in fasting glucose or postprandial 2 h glucose among the three PCOS subtypes. Fasting insulin, however, did differ in PCOS subjects compared with controls ($P < 0.001$). Women in the IM/HA/PCO and IM/HA groups especially showed significantly higher fasting insulin than women in the IM/PCO group. Postprandial 2 h insulin showed a similar trend to fasting insulin ($P < 0.001$). Although no significant differences in HOMA-IR among the PCOS subgroups were observed, it was more elevated in PCOS subjects than in controls ($P < 0.001$).

Subgroup analysis using the AES criteria

Age (25.0 ± 6.0 versus 25.7 ± 4.9 years) was similar between the IM/HA/PCO and IM/HA groups and the IM/PCO group. The IM/HA/PCO and IM/HA groups together showed higher BMI than the IM/PCO group ($P < 0.05$). Both waist circumference ($P < 0.001$) and waist-to-hip ratio ($P < 0.001$) of hyperandrogenized PCOS subjects were higher than in the non-hyperandrogenized PCOS subjects. As we expected, the IM/HA/PCO and IM/HA groups together showed higher androgen indices than the IM/PCO group, including mF–G score ($P < 0.001$), total T ($P = 0.025$), free T ($P < 0.001$), 17-OHP ($P < 0.001$), FAI ($P < 0.001$) and DHEAS ($P < 0.001$). Basal LH and FSH levels and the LH/FSH ratio were not different between the IM/HA/PCO and IM/HA groups together and the IM/PCO group. BP consisting of SBP and DBP was not significantly higher in hyperandrogenized PCOS subjects compared with non-hyperandrogenized PCOS subjects. Serum cholesterol, triglycerides and HDL in the IM/HA/PCO and IM/HA groups together and the IM/PCO group were not different, regardless of HA. In the same groups, glucose intolerance was not detected in fasting glucose or postprandial 2 h glucose. For insulin resistance, HOMA-IR between the subjects in the IM/HA/PCO and IM/HA groups together and the IM/PCO group was not different (3.0 ± 1.8 versus 2.5 ± 1.7, $P = \text{NS}$). However, fasting insulin (13.6 ± 6.8 versus 10.7 ± 6.5 μU/ml, $P < 0.001$) and postprandial 2 h insulin (90.4 ± 75.7 versus 41.2 ± 76.3 μU/ml, $P = 0.003$) were significantly higher among women in the hyperandrogenized groups compared with those in the non-hyperandrogenized group (Table III).

Metabolic syndrome in PCOS subgroups

All PCOS subgroups were more associated with metabolic syndrome than the control group ($P < 0.05$). All of the parameters that made up the metabolic syndrome, except fasting glucose, were significantly more prevalent in women with PCOS than in controls ($P < 0.05$). No differences in clinical or biochemical parameters were noted among the PCOS subgroups, but a non-significant trend towards increase prevalence of metabolic syndrome in the IM/HA group was noted (Table IV).

Discussion

To our knowledge, this is the first study to investigate the prevalence of metabolic syndrome and insulin resistance among the subgroups of PCOS according to the Rotterdam criteria in Asia. It is also the first to show a difference between the PCOS subgroups, in that PCOS subjects with HA had higher fasting and postprandial 2 h insulin levels and triglycerides compared with subjects without HA according to the Rotterdam criteria in Korea. All of the PCOS subjects had lower SHBG and higher LH, BP, fasting insulin, postprandial 2 h insulin, HOMA-IR and clinical and biochemical parameters of metabolic syndrome than controls, and PCOS subjects showed a trend towards greater prevalence of metabolic syndrome than controls.

We demonstrated that the prevalence of the IM/PCO and HA/PCO subgroup in Korean women with PCOS was different from that in other ethnicities (Belosi *et al*., 2006; Dewailly *et al*., 2006; Welt *et al*., 2006; Barber *et al*., 2007; Diamanti-Kandarakis and Panidis, 2007; Hsu *et al*., 2007; Pehlivanov and Orbetzova, 2007) (Table V). Our data show a relatively higher prevalence of oligo-anovulatory PCOS without HA (31.3%) than previous reports (6.9–18.2%) in other ethnicities. Furthermore, normo-ovulatory women with HA and PCO (2.4%) were relatively less prevalent than in other reports (5.5–24.6%). However, oligo-anovulatory women with HA and PCO (52.4%) in our study did show similar prevalence compared with the results of other studies (45.5–71.5%) (Table V). It could be postulated that the strict definition of HA might decrease the size of the subgroups with HA in this study.

Table III. Comparison of clinical features, hormonal and metabolic parameters in PCOS subjects using AES criteria.

	IM/HA/PCO+IM/HA ($n = 110$)	IM/PCO ($n = 52$)	Control ($n = 277$)	*P*-value PCOS subgroups versus control
BMI (kg/m^2)	22.8 ± 5.0[a]	20.9 ± 4.4[b]	20.3 ± 2.8[b]	0.177
Waist circumference (cm)	70.9 ± 6.1[a]	68.6 ± 5.9[b]	73.6 ± 9.3[c]	0.026
W/H ratio	0.78 ± 0.06[a]	0.75 ± 0.05[b]	0.72 ± 0.07[b]	0.108
mF–G score	9.1 ± 3.1[a] ($n = 97$)	3.0 ± 3.0[b] ($n = 50$)	1.4 ± 3.0[c] ($n = 259$)	<0.001
Total T (ng/ml)	0.44 ± 0.19[a] ($n = 99$)	0.35 ± 0.19[b] ($n = 51$)	0.36 ± 0.19[b] ($n = 91$)	0.025
Free T (pg/ml)	1.89 ± 0.70[a] ($n = 96$)	0.87 ± 0.67[b] ($n = 50$)	0.92 ± 0.68[c] ($n = 89$)	<0.001
17-OHP (ng/ml)	1.4 ± 1.1[a] ($n = 94$)	1.1 ± 1.1[a] ($n = 48$)	2.0 ± 1.1[b] ($n = 87$)	<0.001
DHEAS (ng/ml)	2098.7 ± 964.3[a] ($n = 92$)	1732.5 ± 936.5[b] ($n = 48$)	2434.3 ± 955.4[c] ($n = 89$)	<0.001
SHBG (nmol/l)	37.9 ± 29.5[a] ($n = 44$)	49.4 ± 28.7[a] ($n = 31$)	74.6 ± 28.9[b] ($n = 89$)	<0.001
FAI	6.2 ± 4.0[a] ($n = 45$)	3.4 ± 3.9[b] ($n = 31$)	2.4 ± 4.0[b] ($n = 89$)	<0.001
LH (mIU/ml)	9.5 ± 6.5 ($n = 93$)	8.9 ± 6.5 ($n = 41$)	Not checked	NS
FSH (mIU/ml)	4.8 ± 2.5 ($n = 92$)	5.3 ± 2.5 ($n = 41$)	Not checked	NS
LH/FSH	2.4 ± 1.6 ($n = 92$)	1.9 ± 1.6 ($n = 41$)	Not checked	NS
SBP (mmHg)	114.0 ± 13.3[a] ($n = 78$)	108.9 ± 12.7[a] ($n = 42$)	107.5 ± 13.0[b] ($n = 240$)	0.001
DBP (mmHg)	72.7 ± 10.4[a] ($n = 78$)	70.6 ± 10.0[a] ($n = 42$)	67.1 ± 10.1[b] ($n = 240$)	<0.001
Cholesterol (mg/dl)	175.5 ± 30.8 ($n = 43$)	173.0 ± 29.6 ($n = 19$)	168.5 ± 29.9 ($n = 219$)	0.370
Triglycerides (mg/dl)	109.3 ± 35.4[a] ($n = 20$)	110.3 ± 34.4[a] ($n = 10$)	70.5 ± 34.4[b] ($n = 207$)	<0.001
HDL (mg/dl)	58.4 ± 13.4 ($n = 20$)	64.0 ± 13.0 ($n = 10$)	63.6 ± 13.0 ($n = 206$)	0.253
Fasting glucose (mg/dl)	87.9 ± 12.7 ($n = 101$)	90.1 ± 12.0 ($n = 51$)	88.9 ± 12.4 ($n = 219$)	0.586
Fasting insulin (μU/ml)	13.6 ± 6.8[a] ($n = 102$)	10.7 ± 6.5[b] ($n = 51$)	8.4 ± 6.7[c] ($n = 109$)	<0.001
PP2 glucose (mg/dl)	111.2 ± 37.0 ($n = 96$)	100.9 ± 37.3 ($n = 50$)	Not checked	NS
PP2 insulin (μU/ml)	90.4 ± 75.7[a] ($n = 90$)	41.2 ± 76.3[b] ($n = 46$)	Not checked	NS
HOMA-IR	3.0 ± 1.8[a] ($n = 101$)	2.5 ± 1.7[a] ($n = 51$)	1.9 ± 1.8[b] ($n = 109$)	<0.001

Data are shown as mean ± SD.
W/H ratio, waist-to-hip ratio; mF–G score, modified Ferriman–Gallwey score; T, testosterone; 17-OHP, 17-hydroxyprogesterone; DHEAS, dehydroepiandrostenedione; SHBG, sex hormone-binding globulin; FAI, free androgen index; PP2, postprandial 2 h; IM, irregular menstruation; HA, hyperandrogenism; PCO, polycystic ovary.
P-values are indicated for the differences in groups as analyzed by ANCOVA, controlling for age and BMI among the PCOS subgroups and controls.
[a–c]Values bearing different superscripts are significantly different between any two groups ($P < 0.05$), as demonstrated by Fisher's LSD *post hoc* correction.

Biochemical HA is difficult to define because normative data in a normal female population are lacking. It was thought that free T and FAI were more sensitive markers to assess hyperandrogenemia in PCOS (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). In AES, free T was recommended as a variable to evaluate biochemical HA in PCOS (Azziz *et al*., 2006). The cut-off value for serum androgen levels in women is not clearly settled in regard to confounding factors such as age, menstruation cycle and diurnal variation (Barth *et al*., 2007). Serum androgen concentration was used only as a surrogate for the diagnosis of PCOS (Azziz *et al*., 2006). Therefore, we evaluated three kinds of androgens (total T, free T and 17-OHP) and FAI to classify PCOS patients as having HA. Our criteria of hirsutism were much stricter than other studies because Asian women were known to show less prominent hirsutism (Carmina *et al*., 1992). Because the evaluation of hirsutism was relatively subjective (Wild *et al*., 2005) and the natural cut-off value of mF–G score was not distinct (DeUgarte *et al*., 2006); however, we used the highest score in other studies as an upper normal limit (Hatch *et al*., 1981).

Table IV. Prevalence of metabolic syndrome parameters among the PCOS subgroups.

	IM/HA/PCO* ($n = 87$)	IM/PCO† ($n = 52$)	IM/HA‡ ($n = 23$)	Control ($n = 277$)	*P*-value PCOS versus control
No. of subjects with metabolic syndrome	3/16 (18.8%)	2/10 (10.0%)	2/4 (50.0%)	3/207 (1.4%)	0.040
Waist circumference >80 cm	21/73 (28.8%)	5/49 (10.2%)	7/21 (33.3%)	37/255 (14.5%)	0.050
BP ≥130/85 mmHg	15/63 (23.8%)	5/42 (11.9%)	5/15 (33.3%)	7/237 (3.0%)	<0.001
Triglycerides ≥150 mg/dl	2/16 (12.5%)	4/10 (40.0%)	2/4 (50.0%)	2/207 (1.0%)	<0.001
HDL <50 mg/dl	3/16 (18.8%)	4/10 (40.0%)	2/4 (50.0%)	27/207 (3.0%)	0.004
Fasting glucose ≥100 mg/dl	11/81 (12.5%)	4/51 (7.8%)	1/20 (5.0%)	11/231 (5.2%)	0.475
Normal	69/81 (85.2%)	50/51 (98.0%)	15/20 (75.0%)		
Impaired glucose tolerance	14/81 (17.3%)	0/51 (0.0%)	4/20 (20.0%)		
Diabetes mellitus	2/81 (2.5%)	1/51 (2.0%)	0/20 (0.0%)		

Data are shown as *n* (%).
IM, irregular menstruation; HA, hyperandrogenism; PCO, polycystic ovary.
P-values were calculated using Pearson's chi-square test.
*Six subjects were not assessed for postprandial 2 h glucose.
†One subject was not assessed for postprandial 2 h glucose.
‡Three subjects were not assessed for postprandial 2 h glucose.

Table V. Prevalence of the PCOS subgroups.

	Ethnicity	IM/HA/PCO	IM/PCO	IM/HA	HA/PCO
Diamanti-Kandarakis and Panidis (2007)	Greece	284 (45.5%)	43 (6.9%)	251 (40.2%)	46 (7.4%)
Pehlivanov and Orbetzova (2007)	Bulgaria	41 (58.6%)	7 (10.0%)	8 (11.4%)	14 (20.0%)
Shroff *et al*. (2007)	USA	150 (58.1%)	37 (14.3%)	37 (14.3%)	34 (13.2%)
Welt *et al*. (2006)	USA, Iceland	298 (71.3%)	36 (8.6%)	7 (1.7%)	77 (18.4%)
Dewailly *et al*. (2006)	France	246 (60.6%)	66 (16.3%)	27 (6.7%)	67 (16.5%)
Barber *et al*. (2007)	UK	191 (61.8%)	42 (13.6%)	0 (0.0%)	76 (24.6%)
Belosi *et al*. (2006)	Italy	254 (73.6%)	46 (13.3%)	26 (7.5%)	19 (5.5%)
Hsu *et al*. (2007)	Taiwan	88 (51.8%)	31 (18.2%)	15 (8.8%)	36 (21.2%)
Our data	Korea	87 (52.4%)	52 (31.3%)	23 (13.9%)	4 (2.4%)

Values expressed as number (%).
IM, irregular menstruation; HA, hyperandrogenism; PCO, polycystic ovary.

Using the Rotterdam criteria, the present study shows that BMI in women with PCOS in Korea was lower than in studies of Caucasian women with PCOS (Belosi *et al*., 2006; Welt *et al*., 2006; Barber *et al*., 2007) and that it was similar to other studies of Asian patients with PCOS (Chen *et al*., 2006; Park *et al*., 2007). Women in the IM/PCO group had a similar waist circumference to controls, whereas women in the IM/HA/PCO and IM/HA groups had a greater waist circumference than those in the IM/PCO and control groups. W/H ratio is known to be a measure of abdominal obesity. The present study demonstrates that W/H ratio among the PCOS subgroups differed, suggesting that those in the IM/PCO group had less central obesity and were similar to normal controls. This finding is quite relevant (Belosi *et al*., 2006; Welt *et al*., 2006) and contradicts previous studies (Hsu *et al*., 2007). mF–G score, FAI and serum levels of total T, free T, 17-OHP and DHEAS were found to be significantly increased among women in the IM/HA/PCO group compared with the IM/PCO group, as expected by definition. The same parameters representing HA, except free T, were higher among women in the IM/HA group compared with the IM/PCO group, although this was not statistically significant.

Our data indicate that each PCOS subgroup showed no difference in serum glucose levels according to the 75 g glucose tolerance test, which is consistent with previous reports, although those studies did not report postprandial 2 h serum glucose (Belosi *et al*., 2006; Welt *et al*., 2006; Barber *et al*., 2007; Diamanti-Kandarkis and Panidis, 2007).

The present study shows that the PCOS subjects in Korea had the similar metabolic features, including insulin resistance and lipid profile, in spite of relatively lower BMI, than the previous studies. HOMA-IR, as a good indicator of insulin resistance, did not show any differences among the PCOS subgroups, but it was significantly higher in PCOS subjects than in controls in our study. As another indicator of insulin resistance, serum SHBG in all the PCOS subgroups was revealed to be significantly lower than in the control group in our study, which was in agreement with previous studies (Dewailly *et al*., 2006; Welt *et al*., 2006; Barber *et al*., 2007; Diamanti-Kandarakis and Panidis, 2007). Each PCOS subgroup showed similar trends in fasting insulin to the Caucasian studies (Welt *et al*., 2006; Barber *et al*., 2007), which was contrary to the study of Shroff *et al*. (2007). Our data show that fasting insulin in the IM/PCO group was lower than that of the IM/HA/PCO group. The present study also shows that postprandial 2 h serum insulin levels were significantly higher in the IM/HA/PCO and IM/HA groups than in the IM/PCO group. This may suggest that postprandial hyperinsulinemia plays an important role in HA and ovarian function in Korean women with PCOS. Therefore, we analyzed our subjects with respect to HA.

In AES, HA is supposed to be the key feature of PCOS, so we reclassified the subgroups according to HA. Our data show that the IM/HA/PCO and IM/HA groups versus the IM/PCO group (PCOS subjects with and without HA, respectively) showed different clinical and biochemical characteristics. Though PCOS patients with HA had similar BP and basal gonadotrophin levels to those without, higher fasting insulin and postprandial 2 h insulin, which may be associated with insulin resistance, were shown in PCOS subjects with HA, consistent with a study by Barber *et al*. (2007). Although they did not use HOMA-IR, Belosi *et al*. (2006) found higher fasting insulin levels in PCOS subject according to NIH criteria (IM/HA/PCO+IM/HA) than in PCOS with non-NIH criteria (IM/PCO+HA/PCO). Welt *et al*. (2006) found higher insulin levels in subjects with oligo-anovulation regardless of androgenic status, which was contrary to our study.

Subgroup analysis in our study shows that 17-OHP differed within the normal range among PCOS subgroups. The control group showed higher 17-OHP levels than PCOS subjects, who were also within the normal range. This implies that 17-OHP is not associated with PCOS in Korea. Belosi *et al*. (2006) showed that 17-OHP level was not different among the NIH criteria PCOS groups (IM/HA/PCO and IM/HA) and the non-NIH PCOS groups (IM/PCO and HA/PCO). Welt *et al*. (2006) found that the PCOS subgroups according to the Rotterdam consensus showed more elevated 17-OHP levels compared with controls. The 17-OHP levels of PCOS patients were, however, within the normal range. Glucose tolerance and insulin resistance were not different between the two groups. However, our data showed lower triglycerides in the PCO-containing subgroup than in the IM/HA group. Shi *et al*. (2007) reported that the non-PCO group showed higher total T, total cholesterol, LDL and hirsutism scores than the PCO group, which may be due to different compositions of the PCO group.

Recently, metabolic syndrome has been emphasized in PCOS, although its diagnostic criteria in Asia are not the same as in Western populations (Tan *et al*., 2004). Amato *et al*. (2007) compared PCOS patients according to the Rotterdam, AES and NIH criteria, and metabolic parameters and insulin sensitivity were important for diagnosis of PCOS irrespective of the various criteria. Though we did not complete data regarding metabolic syndrome in a retrospective study, some important baseline parameters showed no significant differences among the three PCOS subgroups (Table IV). Waist circumference, lipid profile and BP in the diagnostic criteria of metabolic syndrome were significantly higher in PCOS subjects than in controls. However, fasting glucose was not different. Those same parameters were not different among the PCOS subgroups.

It is not clear why all PCOS patients do not have HA or PCO morphology. As PCOS is a heterogeneous disease, diverse mechanisms could be involved in its pathogenesis. Some studies have shown that ovulatory PCOS, which was less prevalent in our study, is associated with metabolic and cardiovascular risk (Carmina *et al*., 2005, 2006).

In conclusion, PCOS subjects without HA were more prevalent among Korean women than in other ethnicities and showed lower fasting and postprandial 2 h insulin levels than PCOS subjects with HA. PCOS without HA could simply be a milder phenotype of PCOS, similar to the normal population, and may be less associated with metabolic complications. Therefore, Korean women with PCOS could be at lower risk for metabolic syndrome than other ethnicities. Further study is needed to substantiate the present results in a larger population and in other Asian ethnicities.

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