Apolipoprotein A-I and B levels, dyslipidemia and metabolic syndrome in south-west Chinese women with PCOS

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STUDY QUESTION: What are the relationships between apolipoprotein (apo) A-I and apoB concentrations, the apoB/apoA-I ratio and the prevalences of dyslipidemia and metabolic syndrome (MS) in south-west Chinese women with polycystic ovary syndrome (PCOS).

SUMMARY ANSWER: There is a relatively high incidence of dyslipidemia and MS in south-west Chinese women with PCOS, especially in patients without hyperandrogenism. Patients with dyslipidemia are more obese, and have a more adverse glucose and lipid metabolic profile and higher apoB levels and apoB/apoA-I ratio. The increased apoB levels and apoB/A1 ratio and the MS are strongly associated with PCOS, suggesting that there is an increased risk of cardiovascular diseases in these patients.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS: Dyslipidemia and MS have been widely studied in women with PCOS, but to date no data from south-west Chinese subjects have been available. The apoB/apoA-I ratio has been reported to be strongly associated with MS and insulin resistance (IR) and to be a reliable parameter that reflects lipid disturbances and the potential to develop atherosclerosis, but its relationship with PCOS is unclear.

DESIGN: This case–control study included 406 patients with PCOS and 342 control women between 17 and 40 years of age from a population in south-west China during 2006–2011.

PARTICIPANTS AND SETTING: The diagnosis of PCOS was based on the revised 2003 Rotterdam criteria. The control group, consisting of women with infertility due to a Fallopian obstruction or the husband’s infertility, women undergoing a pre-pregnancy check and healthy volunteers, was recruited from the same hospital during the same period. All women were not taking any medication known to affect carbohydrate or lipid or hormone metabolism for at least 3 months prior to the study, and were studied during the follicular phase of their menstrual cycle. MS was assessed by the National Cholesterol Education Program-Adult treatment Panel (NCEP-ATP) III criteria modified for Asian populations. Dyslipidemia was defined by one or more of the following conditions: fasting total cholesterol ≥ 5.7 mmol/l, fasting triglycerides (TG) ≥ 1.7 mmol/l, fasting high-density lipoprotein cholesterol (HDL-C) < 1.29 mmol/l or fasting low-density lipoprotein cholesterol (LDL-C) ≥ 3.6 mmol/l.

MAIN RESULTS AND THE ROLE OF CHANCE: The prevalence of dyslipidemia in patients with PCOS was 52.96%, about two times than that in the controls, 28.95%. The most common components of dyslipidemia in patients with PCOS were decreased HDL-C (41.13%) and increased TG (24.14%). PCOS patients with dyslipidemia had significantly higher TG/HDL-C ratios, and lower HDL-C and apoA-I levels when compared with the controls or patients without dyslipidemia, and had significantly higher BMIs, fasting insulin concentrations, 2-h insulin and glucose levels, homeostatic model assessment IR, TG levels, LDL-C levels, atherogenic indexes, apoB concentrations and apoB/apoA-I ratios when compared with all of the control women, with or without dyslipidemia and patients without dyslipidemia. The frequency of MS in patients with PCOS was 25.62%, more than five times than that in the controls. The main two risk factors were increased waist circumference and low HDL-C levels. In the four PCOS phenotypes based on the Rotterdam criteria, the oligo- and/or anovulation + PCO presented
the highest prevalence of dyslipidemia (66.14%) and MS (34.65%). Binary logistic regression analysis showed that increased apoB levels, an increased apoB/apoA-I ratio and MS was strongly associated with PCOS (odds ratio = 17.41, 27.16 and 7.66, 95% confidence interval: 6.93–43.74, 9.46–77.93 and 4.32–13.57, respectively) after adjustment for age.

**BIAS, CONFOUNDING AND OTHER REASONS FOR CAUTION:** The relatively minor limitations of this study are discussed within the paper.

**GENERALISABILITY TO OTHER POPULATIONS:** The metabolic patterns found in south-west Chinese with PCOS are compared with that of other populations.

**STUDY FUNDING/COMPETING INTEREST(S):** This work was supported by Chinese National Natural Science Foundation (81070463), Program for Changjiang Scholars and Innovative Research Team in University (IRT0935), and Research Seed Fund from West China Second Hospital of Sichuan University (to H.B.). There are no any competing interests.

**TRIAL REGISTRATION NUMBER:** N/A.

**Key words:** apolipoprotein A-I / apolipoprotein B / dyslipidemia / metabolic syndrome / polycystic ovary syndrome

**Introduction**

Polycystic ovary syndrome (PCOS) is a common endocrine disease of uncertain etiology affecting 4–12% of women of reproductive age (Aziz et al., 2004; Norman et al., 2007; Franks, 2008; March et al., 2010). It is associated with not only reproductive and obstetric problems including hyperandrogenism (HA), menstrual dysfunction, infertility and pregnancy complications (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004; Boomsma et al., 2006), but also metabolic and long-term health risks such as dyslipidemia, insulin resistance (IR), elevated risk of impaired glucose tolerance, type 2 diabetes and metabolic syndrome (MS; Shroff et al., 2007; Cheung et al., 2008; Valkenburg et al., 2008; Moran and Teede, 2009), increased oxidative stress, systemic low-grade chronic inflammation (Diamanti-Kandarakis et al., 2006; Fan et al., 2009, 2010, 2012) and potential increased risk of cardiovascular disease (Dokras, 2008; Shaw et al., 2008). Women with PCOS also have psychological features with increased depression, poor self-image and reduced quality of life (Moran and Teede, 2009; Teede et al., 2010). PCOS thus is a complex condition that impacts on health across the lifespan and represents a major health and economic burden (Aziz et al., 2005; Moran and Teede, 2009; Teede et al., 2010). The etiology of PCOS is not clear, but studies have suggested that PCOS appears to have a complex, multi-factorial etiology (Goodarzi, 2008).

Metabolic abnormalities, including dyslipidemia and MS, have widely been studied in women with PCOS (Shroff et al., 2007; Cheung et al., 2008; Moran and Teede, 2009; Ni et al., 2009). It is reported that the classic PCOS phenotypes according to the National Institute of Health criteria have a more adverse metabolic profile, and the two newer phenotypes according to the revised 2003 ESHRE/ASRM criteria present a milder reproductive and metabolic profile (Moran and Teede, 2009), especially the non-androgenic anovulation patients with polycystic ovaries (PCOs). However, compared with Caucasians, the Shandong Chinese women with PCOS have a low risk of MS and its presence does not vary across the specific PCOS phenotypes (Guo et al., 2010). Emerging evidence has suggested that the prevalence of metabolic abnormalities in PCOS women shows a marked variation between ethnic groups and countries, even between different regions of a country, probably due to difference in diet, lifestyle and genetic factors (Shroff et al., 2007; Cheung et al., 2008; Moran and Teede, 2009; Ni et al., 2009; Guo et al., 2010), but to date there are no data available from south-west Chinese subjects.

Dyslipidemia is the most common metabolic abnormality in PCOS. A more atherogenic serum lipoprotein profile, especially decreased levels of high-density lipoprotein (HDL) and elevated levels of triglycerides (TGs), smaller low-density lipoprotein (LDL) and oxidized LDL, has been reported to be present in women with PCOS (Dejager et al., 2001; Macut et al., 2008; Valkenburg et al., 2008; Wild et al., 2010, 2011). Apolipoprotein (apo)A-I, the major structural protein component of HDL particles, has pleiotropic biological functions such as promoting macrophage cholesterol efflux and stimulating reverse lipid transport, inhibiting LDL oxidation and scavenging toxic phospholipids, as well as anti-inflammatory properties (Navab et al., 2011; Shah, 2011). ApoB represents the total amount of potentially atherogenic circulating lipoproteins, including LDL, intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL) and lipoprotein (a) (Sierra-Johnson et al., 2009; Kappelle et al., 2011; Lee et al., 2011). Therefore, the apoB/apoA-I ratio has been proposed to be a reliable parameter that reflects lipid disturbances and the potential to develop atherosclerosis (Sierra-Johnson et al., 2009; Kappelle et al., 2011; Lee et al., 2011). Moreover, the apoB/apoA-I ratio has been reported to be strongly associated with MS (Sierra-Johnson et al., 2006) and IR (Sniderman, 2007; Sierra-Johnson et al., 2007), and predicts cardiovascular risk better than any cholesterol index (Sierra-Johnson et al., 2009). However, few studies have suggested an association between apoA-I, apoB, apoB/apoA-I ratio and PCOS.

Therefore, the aim of the present study was to investigate the relationships between apoA-I and apoB concentrations, the apoB/apoA-I ratio, dyslipidemia and the prevalence of MS in south-west Chinese women with PCOS.

**Materials and Methods**

**Subjects**

South-west Chinese women with or without PCOS between 17 and 40 years of age (n = 1369) were randomly recruited from the Outpatient...
Department of Reproductive Endocrinology of West China Second University Hospital at Sichuan University in Chengdu during 2006–2011. Of these subjects, 610 women met the revised 2003 Rotterdam diagnostic criteria for PCOS and 503 women met the control women’s inclusion criteria. After excluding subjects during the luteal phase by progesterone measurement (>3 ng/ml) or because of taking medication known to affect carbohydrates or lipids or hormones in 3 months before the study (PCOS, n = 204; control, n = 161), 406 patients with PCOS and 342 control women were finally included in the present study. All study participants gave their informed consent and the study was approved by our institutional review board.

Each patient with PCOS met diagnostic criteria for PCOS based on the revised 2003 Rotterdam ESHRE/ASRM consensus criteria and exclusion of related disorders (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004), i.e. the presence of at least two of the following characteristics: oligo- and/or anovulation (OA) which was assessed as oligomenorrhea (less than eight cycles per year); clinical and/or biochemical signs of HA which was assessed by the total testosterone (TT) levels above the 95th percentile of the levels detected in a group of normal menstruating women with normal cycles, and/or by the clinical presence of obvious acne which was defined as the number of comedones (>10) and inflammatory papules/pustules as well as nodules/cysts (>10) spread on the face, back and chest (Poche et al., 1991; Falsetti et al., 2001) and/or hirsutism with the modified Ferriman–Gallwey (F-G) score of more than 6 (Guo et al., 2010; Fan et al., 2010, 2012); PCOS which was confirmed if there were 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 ml) by ultrasonic examination; as well as the exclusion of other etiologies such as congenital adrenal hyperplasias, androgen-secreting carcinomas and Cushing’s syndrome.

The control subjects consisted of women with infertility (63.5%, 217 of 342) due to Fallopian obstruction (26.3%, 90 of 342) or the husband’s infertility, women undergoing a pre-pregnancy check (31.6%, 108 of 342) and healthy volunteers (doctors and nurses, 5.0%, 17 of 342). All were clinically healthy women who had regular menstrual cycles (between 21 and 35 days), exhibited normal circulating androgen levels and had no obvious acne or hirsutism on physical examination, and showed normal ovarian morphology as determined by ultrasound.

None of the subjects had clinically evident chronic or acute diseases such as infection, tumors, thyroid dysfunction, cardiovascular diseases, endometriosis, hyperprolactinemia, hypogonadotropic hypogonadism or premature ovarian failure.

Clinical and anthropometrical variables were measured in all subjects. Waist circumference (WC) was obtained as the smallest circumference (between 21 and 35 days), exhibited normal circulating androgen levels and had no obvious acne or hirsutism on physical examination, and showed normal ovarian morphology as determined by ultrasound.

None of the subjects had clinically evident chronic or acute diseases such as infection, tumors, thyroid dysfunction, cardiovascular diseases, endometriosis, hyperprolactinemia, hypogonadotropic hypogonadism or premature ovarian failure.

Clinical and anthropometrical variables were measured in all subjects. Waist circumference (WC) was obtained as the smallest circumference at the level of the umbilicus. Hip circumference was obtained as the widest circumference at the level of the buttocks and waist-to-hip ratio (WHR) was calculated to assess the body fat distribution. Body weight and height were measured and BMI (kg/m²) was determined to assess obesity. Sitting blood pressure was measured on the right arm after a 10-min rest. The degree of hirsutism and acne were also assessed.

Ultrasound ovarian volume determination was performed using the formula for the volume of an ellipsoid (Robert et al., 1995): 0.523 × length × width × thickness.

Blood samples were obtained in the morning after overnight fasting on the 3–10th days of the menstrual cycle from regularly menstruating women or at random from oligo-amenorrheic women, placed in ice immediately and centrifuged at 1500g for 15 min at 4°C within 2 h. Sera for the measurement of apoA-I and apoB concentrations were stored at −80°C.

Analysis of hormonal, metabolic profiles and serum apoA-I and apoB concentrations

The levels of serum FSH, LH, TT, estradiol (E2), progesterone, prolactin, cortisol, thyroid-stimulating hormone and the concentrations of plasma insulin were measured by chemiluminescence assays (Diagnostic Products Corporation, Los Angeles, CA, USA). Plasma glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). The concentrations of plasma TC, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and total TGs were measured by enzymatic assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA), and serum apoA-I and B levels were determined by the polyclonal glycol-enhanced immunoturbidimetric assay (Siemens Healthcare Diagnostics Inc.) using a Hitachi 7600-010 automatic analyzer. The intra- and inter-assay coefficients of variation for all measurements were <5 and 10%, respectively.

Homeostatic model assessment (HOMA) IR was determined as fasting Glu (mmol/l) × fasting Ins (µU/ml)/22.5 (Matthews et al., 1985).

The atherogenic index (AI) was calculated using the following equation: AI = [TC – (HDL-C)/(HDL-C)] (Demirel et al., 2007).

Definition of MS and dyslipidemia

Metabolic syndrome was assessed by the National Cholesterol Education Program-Adult treatment Panel (NCEP-ATP) III criteria modified for Asian populations (Grundy et al., 2005). Diagnosis was made when there were three or more of the following risk factors: central obesity with WC ≥80 cm in women; elevated fasting TG ≥1.7 mmol/l; reduced fasting HDL-C < 1.29 mmol/l; elevated systolic and/or diastolic blood pressure ≥130/85 mmHg; or impaired fasting glucose ≥5.6 mmol/l.

Dyslipidemia was defined by one or more of the following conditions: fasting TC ≥5.7 mmol/l; fasting TG ≥1.7 mmol/l; fasting LDL-C <1.29 mmol/l or fasting LDL-C ≥3.6 mmol/l, based on the NCEP-ATP III criteria (Grundy et al., 2005) and the recommendations for the prevention and treatment of dyslipidemia in China (The expert panel on recommendations for prevention and treatment of dyslipidemia, 1997).

Statistical analysis

Data were presented as mean ± SD. Differences in variables were evaluated by the independent sample t-test between PCOS and control subjects. Variables with asymmetric distribution were evaluated by non-parametric tests (Mann–Whitney U-test). Differences in percentages were evaluated by χ² tests between PCOS and control subjects or between the four PCOS phenotypes. Differences in age, BMI, WC and WHR between the four PCOS phenotypes and control women were analyzed by analysis of variance (LSD and Dunnett’s T3). Analysis of covariance was used to estimate the differences in glucose and lipid metabolic parameters between the four PCOS phenotypes and the control women after correction for age and BMI. Multinomial logistic regression method was used to assess the association between the prevalence of MS in all four PCOS phenotypes and PCOS when the controls were defined as the reference category. Binary logistic regression method (dependent: PCOS = 1, control = 0) was used to assess the effect of each metabolic parameter including fasting and 2-h insulin and glucose, HOMA-IR, TC, TG, HDL-C, LDL-C, AI, TG/HDL-C, apoA-I, apoB, apoB/apoA-I, dyslipidemia and MS on PCOS after correcting the differences in age and BMI. Results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A P-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 13.0 for Windows (SPSS Inc., Chicago, IL, USA).
Results

Clinical and hormonal levels of subjects
As shown in Table I, BMI, WC, WHR, systolic BP, diastolic BP, F-G score, average ovarian volume, TT and LH levels and the LH-to-FSH ratio were all significantly higher, and age and FSH were significantly lower, in the PCOS group when compared with the control group. There were no differences between the two groups with regard to E2 and FSH levels after correcting for the difference in age and BMI.

Metabolic profiles in patients with PCOS and control women
There were higher fasting and 2-h insulin concentrations, fasting and 2-h glucose levels, HOMA-IR, TG, TC and LDL-C levels, Al, TG/HDL-C ratios, apoB concentrations and apoB/apoA-I ratios and lower HDL-C and apoA-I levels, in patients with PCOS when compared with the control women. However, there were no significant differences in fasting glucose concentration, HDL-C and apoA-I levels, and TG/HDL-C ratios between two groups after correcting for difference in age and BMI (Table I).

We further analyzed the age- and BMI-adjusted metabolic profiles in control women and in patients with different key clinical phenotypes of PCOS: (i) HA + OA + PCO, (ii) HA + OA, (iii) HA + PCO and (iv) OA + PCO (Table II). Compared with the control subjects, each of the four PCOS subgroups had higher 2-h Ins and Glu levels, Al, and apoB/apoA-I ratio; the three PCOS subgroups with PCO had higher fasting Ins concentrations, HOMA-IR scores, LDL-C and apoB levels; the three PCOS subgroups with OA had lower HDL-C levels; the patients with either HA + OA or OA + PCO had higher fasting TG levels and TG/HDL-C ratios; and the patients with either HA + OA or OA + PCO had significantly lower apoA-I levels. In addition, the 2-h Ins and Glu levels in patients with HA + OA or OA + PCO were significantly higher than those with HA + PCO or OA + PCO, but HOMA-IR scores in the four PCOS subgroups were not significantly different. Patients with OA + PCO also had lower HDL-C levels when compared with the other three PCOS subgroups, and higher Al and apoB levels and apoB/apoA-I ratios when compared with HA + OA subgroup.

We also analyzed apoA-I and apoB levels, and glucose and lipid metabolic parameters in the patients and controls stratified by normolipidemic and dyslipidemic levels. The percentage of each component of dyslipidemia in patients with PCOS and the controls was analyzed, and the results showed that more of the patients had decreased HDL-C, and increased TG, LDL-C and TC, compared with control women: 41.13 versus 23.98%, 24.14 versus 5.85%, 9.85 versus 2.92% and 7.14% versus 2.92%, respectively. (all P < 0.05). The prevalence of dyslipidemia for the four PCOS phenotype subgroups, in decreasing order, was 66.14% in OA + PCO, 48.78% in HA + OA + PCO, 45.56% in HA + OA and 40.00% in HA + PCO. The OA + PCO subgroup had higher prevalence of dyslipidemia when compared with each of the other three subgroups (P < 0.05). The total prevalence of dyslipidemia in patients with PCOS was 52.96% (215 of 406), about two times of that in the controls 24.14% (99 of 342). As shown in Table III, patients with dyslipidemia had higher BMI scores, fasting Ins concentrations, and 2-h Ins and Glu concentrations, HOMA-IR scores, Al, TG, LDL-C and apoB levels and apoB/apoA-I ratios when compared with the control women with or without dyslipidemia or patients with normolipidemia. Patients with dyslipidemia also had higher TC levels when compared with the control women with or without dyslipidemia, and had lower HDL-C and apoA-I levels and higher TG/HDL-C ratios when compared with controls or patients with normolipidemia. Patients with normolipidemia had higher 2-h Ins and Glu levels when compared with the control women with normolipidemia. The control women with dyslipidemia had higher BMI scores, TG and LDL-C levels, Al, TG/HDL-C ratios, apoB levels and apoB/apoA-I ratios, and lower HDL-C and apoA-I levels than those of the normolipidemic control women.

Prevalence of MS in patients with PCOS and control women
Table IV shows the prevalence of MS and each of the abnormalities of MS in all four PCOS phenotypes and control subjects. The frequency of MS was higher in each of the four PCOS phenotypes when compared with the controls, and higher in patients with OA + PCO when compared with patients with HA + OA + PCO or HA + OA. The multinomial logistic regression showed that the age-adjusted prevalence of MS was 23.17% for patients with HA + OA + PCO (OR = 6.61, 95% CI: 3.48–12.57, P < 0.001), 18.89% for patients with HA + OA (OR = 5.26, 95% CI: 2.47–11.18, P < 0.001), 20% for patients with HA + PCO (OR = 5.35, 95% CI: 1.75–16.11, P = 0.003) and 34.65% for patients with OA + PCO (OR = 11.23, 95% CI: 5.95–21.20, P < 0.001). The total prevalence of MS in patients with PCOS was 25.62%, more than five times of that in the controls, 4.68%. For the prevalence of each of the abnormalities of metabolism syndrome, central obesity (as measured by WC) was the most common abnormality in most of the phenotypes (35.56–40.00%) except in the OA + PCO subgroup (51.97%), where low HDL-C levels was more common (55.91%) than central obesity. Impaired fasting glucose in the OA + PCO subgroup (37.01%) or in HA + OA + PCO subgroup (26.83%) was the third most common abnormalities. Elevated blood pressure, in most phenotypes (8–18.29%) except HA + OA subgroup (17.78%), was the least common abnormality. The frequency of each abnormality in all patients with PCOS, in decreasing order, was central obesity 41.87%, reduced HDL-C 41.13%, impaired fasting glucose 29.31%, increased TG 24.14% and elevated blood pressure 16.48%.

Effects of age, BMI and metabolic variables on PCOS
Binary logistic regression analysis showed that age was a protective factor of PCOS (OR = 0.82, 95% CI: 0.79–0.86, P < 0.001) and increased BMI was a risk factor of PCOS (OR = 1.20, 95% CI: 1.14–1.25, P < 0.001).

We further analyzed the effect of each age-adjusted or age- and BMI-adjusted metabolic variable including fasting and 2-h insulin and glucose, HOMA-IR, TC, TG, HDL-C, LDL-C, Al, TG/HDL-C, apoA-I, apoB, apoB/apoA-I, dyslipidemia and MS on PCOS by binary logistic regression analysis. The presence of PCOS was associated with all metabolic variables after adjustment for age, however, fasting Glu, HDL-C, apoA-I and the TG/HDL-C ratio were not significant in age- and BMI-adjusted analyses. As collinearity exists among
some of the variables, we choose the most informative variables and show their associations with PCOS in Table V.

Among all metabolic variables, the highest age-adjusted OR point estimates were found for apoB level, the apoB/apoA-I ratio and MS (OR = 17.41, 27.16 and 7.66, 95% CIs: 6.93–43.74, 9.46–77.93 and 4.32–13.57, all P < 0.001, respectively). These ORs were decreased after adjustment for BMI in addition to age.

Discussion

There are three important findings in this paper: (i) we show that apoB levels and the apoB/apoA-I ratio are strongly associated with PCOS, possibly explaining the increased risk of cardiovascular diseases presented in PCOS patients; (ii) we for the first time provide the basic information about the prevalence of dyslipidemia and MS in south-west Chinese women with PCOS using relatively large sample sizes (406 cases and 342 controls).

Dyslipidemia is one of the most common metabolic abnormalities in PCOS, and plays a crucial role in the incidence of MS, and is associated with increased risk of cardiovascular disease. In this study, the frequency of dyslipidemia is 52.96% in patients with PCOS, about two times that in the controls, and is similar to that in Hong Kong Chinese women with PCOS (53.1%) (Cheung et al., 2008), but is lower when compared with PCOS women in the USA (up to 70%) (Wild et al., 2010). The frequency of decreased HDL-C is 41.13%, the most common component of dyslipidemia, in patients with
Table II Metabolic profiles in different PCOS phenotypes and control women.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PCOS</th>
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<tr>
<td></td>
<td>n</td>
<td>342</td>
<td>164</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>27.92 ± 4.06</td>
<td>24.51 ± 3.90*</td>
<td>23.90 ± 4.11*</td>
<td>25.28 ± 4.87*</td>
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<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>20.78 ± 2.60</td>
<td>22.52 ± 3.69*</td>
<td>22.60 ± 4.52*</td>
<td>22.81 ± 5.07</td>
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<tr>
<td>WC (cm)</td>
<td></td>
<td>73.29 ± 7.59</td>
<td>77.41 ± 10.61*</td>
<td>77.63 ± 10.32*</td>
<td>78.80 ± 13.72</td>
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<tr>
<td>WHR</td>
<td></td>
<td>0.82 ± 0.07</td>
<td>0.84 ± 0.07*</td>
<td>0.84 ± 0.07*</td>
<td>0.84 ± 0.08</td>
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<tr>
<td>Fasting Ins (µU/ml)</td>
<td></td>
<td>9.27 ± 5.26</td>
<td>14.37 ± 8.65*</td>
<td>13.38 ± 8.54</td>
<td>16.17 ± 16.19</td>
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<tr>
<td>2-h Ins (µU/ml)*</td>
<td></td>
<td>51.27 ± 42.00</td>
<td>114.83 ± 92.99a</td>
<td>94.49 ± 72.52ab</td>
<td>86.94 ± 73.80</td>
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<td>Fasting Glu (mmol/l)</td>
<td></td>
<td>5.31 ± 0.49</td>
<td>5.39 ± 0.53</td>
<td>5.26 ± 0.45b</td>
<td>5.44 ± 0.55</td>
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<tr>
<td>2-h Glu (mmol/l)*</td>
<td></td>
<td>6.04 ± 1.32</td>
<td>7.37 ± 2.29a</td>
<td>6.65 ± 1.80b</td>
<td>6.84 ± 1.18a</td>
</tr>
<tr>
<td>HOMA-IR</td>
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<td>2.23 ± 1.42</td>
<td>3.54 ± 2.47</td>
<td>3.19 ± 2.16</td>
<td>4.03 ± 4.32a</td>
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<tr>
<td>TC (mmol/l)</td>
<td></td>
<td>4.23 ± 0.72</td>
<td>4.43 ± 0.80</td>
<td>4.31 ± 0.89</td>
<td>4.55 ± 0.75</td>
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<tr>
<td>TG (mmol/l)</td>
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<td>1.04 ± 1.01</td>
<td>1.36 ± 1.08b</td>
<td>1.26 ± 1.31</td>
<td>1.16 ± 0.66</td>
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<tr>
<td>HDL-C (mmol/l)</td>
<td></td>
<td>1.51 ± 0.32</td>
<td>1.41 ± 0.33a</td>
<td>1.45 ± 0.33a</td>
<td>1.50 ± 0.40</td>
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<tr>
<td>LDL-C (mmol/l)</td>
<td></td>
<td>2.35 ± 0.63</td>
<td>2.58 ± 0.75a</td>
<td>2.41 ± 0.73b</td>
<td>2.63 ± 0.74a</td>
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<tr>
<td>Al</td>
<td></td>
<td>1.89 ± 0.70</td>
<td>2.30 ± 0.99a</td>
<td>2.07 ± 0.75b</td>
<td>2.21 ± 0.89a</td>
</tr>
<tr>
<td>TG/HDL-C</td>
<td></td>
<td>0.79 ± 1.54</td>
<td>1.13 ± 1.53c</td>
<td>0.97 ± 1.35</td>
<td>0.89 ± 0.68</td>
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<tr>
<td>ApoA-I (g/l)</td>
<td></td>
<td>1.39 ± 0.19</td>
<td>1.38 ± 0.19</td>
<td>1.36 ± 0.19a</td>
<td>1.36 ± 0.24</td>
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<tr>
<td>ApoB (g/l)</td>
<td></td>
<td>0.76 ± 0.17</td>
<td>0.83 ± 0.20b</td>
<td>0.79 ± 0.20b</td>
<td>0.84 ± 0.21a</td>
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<tr>
<td>ApoB/apoA-I</td>
<td></td>
<td>0.56 ± 0.15</td>
<td>0.61 ± 0.17a</td>
<td>0.59 ± 0.16*</td>
<td>0.63 ± 0.18a</td>
</tr>
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</table>

Values are as means ± SD.
OA, oligo-or anovulation; HA, clinical and/or biochemical hyperandrogenism; PCO, polycystic ovaries on ultrasound; WC, waist circumference; WHR, waist-to-hip ratio; AI, atherosclerosis index; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B.
*Control group (n = 229), PCOS group: HA + OA + PCO (n = 150), HA + OA (n = 74), HA + PCO (n = 22), OA + PCO (n = 119).
P < 0.05 compared with controls.
P < 0.05 compared with HA + OA + PCO subgroup.
P < 0.05 compared with HA + OA subgroup.
P < 0.05 compared with HA + PCO subgroup.

PCOS in this study, and is similar to that in white women with PCOS (46.5%) (Shroff et al., 2007), but is significantly higher when compared with the northern Chinese women with PCOS (6.3%) (Guo et al., 2010) and Hong Kong Chinese women with PCOS (28.6%) (Cheung et al., 2008). In addition, we found that patients with dyslipidemia were more obese, and had a more adverse glucose and lipid metabolic profile and higher apoB levels and apoB/apoA-I ratio when compared with the control women with or without dyslipidemia or patients with normolipidemia, while patients with normolipidemia only presented a relatively mild abnormal glucose metabolism when compared with the control women with normolipidemia, supporting the notion that intrinsic PCOS-related abnormalities in IR, and/or a predisposition to weight gain might be greater in patients with dyslipidemia, contributing to their more severe metabolic abnormalities which might further increase risks of type 2 diabetes and cardiovascular diseases (Moran and Teede, 2009).

Moreover, patients with PCOS in this study had relatively high TG levels when compared with other Chinese PCOS patients (Cheung et al., 2008; Ni et al., 2009; Guo et al., 2010; Liang et al., 2011) and relatively low TC and LDL levels when compared with most Caucasian and Chinese PCOS patients (Guo et al., 2010; Kauffman et al., 2011; Liang et al., 2011; Rocha et al., 2011; Wild et al., 2011). This suggests that the so-called atherogenic lipoprotein phenotype that is characterized by hypertriglyceridemia, increased small dense LDL levels and decreased HDL levels, may relatively common in south-west Chinese patients with PCOS. MS, which is characterized by a cluster of cardiometabolic risk factors associated with IR, significantly increases the risks of type 2 diabetes and cardiovascular diseases (Cheung et al., 2008). The reported prevalence of MS in women with PCOS varies between 30 and 47% from Western countries (Dokras et al., 2005; Ehrmann et al., 2006; Shroff et al., 2007), and between 6.5 and 31.9% from other Asian areas (Cheung et al., 2008; Ni et al., 2009; Guo et al., 2010; Hu et al., 2010), depending on the criteria used for defining both PCOS and MS, as well as the different racial/ethnic or area populations. In this study, we also evaluated the prevalence of MS and its individual components in south-west Chinese women with PCOS. Our result shows that the prevalence of MS based on the NCEP-ATP III criteria modified for Asian population (Grundy et al., 2005) is 25.62% in patients with PCOS, which is more than five times of that in the controls, and similar to 24.9% in Hong Kong Chinese PCOS women (Cheung et al., 2008) and 31.9% in Beijing PCOS women (Hu et al., 2010), but is higher than 6.5% in Shandong Chinese women with PCOS (Guo et al., 2010) and 16.8% in Guangdong women with...
PCOS (Ni et al., 2009). Our results also show that central obesity and low HDL-C levels were the two most common abnormalities of MS.

It has been suggested that Asian populations have increased their risk of metabolic abnormalities and MS due to their adoption of a Western lifestyle and the introduction of fast food diets (Welt et al., 2006; Cheung et al., 2008). Moreover, in south-west China, especially in Sichuan province, dietary habits, characterized by the diets relatively rich in oil and/or re-used cooking fat which could contribute to increased oxidative stress and destructive effects on anti-oxidative capacity (Reaven et al., 1993; Komatsu et al., 2008), may also, to some extent, be associated with an increased risk of metabolic abnormalities and MS.

In this study, we found that patients with OA + PCO had the highest prevalence of dyslipidemia and MS, and relatively increased oxidative stress and destructive effects on anti-oxidative capacity (Reaven et al., 1993; Komatsu et al., 2008), may also, to some extent, be associated with an increased risk of metabolic abnormalities and MS.

### Table III Metabolic profile according to serum lipid levels in patients with PCOS and control women.

<table>
<thead>
<tr>
<th></th>
<th>Controls Normal</th>
<th>Controls Abnormal</th>
<th>PCOS Normal</th>
<th>PCOS Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>243</td>
<td>99</td>
<td>192</td>
<td>214</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.98 ± 4.03</td>
<td>27.78 ± 4.16</td>
<td>23.88 ± 3.94*</td>
<td>25.43 ± 3.99*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.40 ± 2.46</td>
<td>21.73 ± 2.71*</td>
<td>21.12 ± 3.31</td>
<td>24.48 ± 4.31*</td>
</tr>
<tr>
<td>Fasting Ins (µU/ml)</td>
<td>8.75 ± 5.25</td>
<td>10.53 ± 5.09</td>
<td>11.34 ± 8.10</td>
<td>17.64 ± 11.41*</td>
</tr>
<tr>
<td>2-h Ins (µU/ml)*</td>
<td>48.05 ± 35.15</td>
<td>58.97 ± 54.61</td>
<td>75.09 ± 58.84*</td>
<td>125.56 ± 91.22*</td>
</tr>
<tr>
<td>Fasting Glu (mmol/l)</td>
<td>5.29 ± 0.49</td>
<td>5.35 ± 0.49</td>
<td>5.28 ± 0.47</td>
<td>5.52 ± 0.69</td>
</tr>
<tr>
<td>2-h Glu (mmol/l)*</td>
<td>5.95 ± 1.33</td>
<td>6.24 ± 1.28</td>
<td>6.45 ± 1.54*</td>
<td>7.68 ± 2.69*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.11 ± 1.44</td>
<td>2.54 ± 1.34</td>
<td>2.75 ± 2.55</td>
<td>4.47 ± 3.29*</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>4.25 ± 0.61</td>
<td>4.18 ± 0.93</td>
<td>4.30 ± 0.59</td>
<td>4.49 ± 1.00*</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>0.86 ± 0.30</td>
<td>1.47 ± 1.75a</td>
<td>0.88 ± 0.33</td>
<td>1.78 ± 1.33*</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.63 ± 0.25</td>
<td>1.23 ± 0.29a</td>
<td>1.60 ± 0.26</td>
<td>1.19 ± 0.32*</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>2.29 ± 0.54</td>
<td>2.52 ± 0.77a</td>
<td>2.31 ± 0.56</td>
<td>2.78 ± 0.86*</td>
</tr>
<tr>
<td>Al</td>
<td>1.65 ± 0.42</td>
<td>2.48 ± 0.87a</td>
<td>1.73 ± 0.46</td>
<td>2.90 ± 1.00*</td>
</tr>
<tr>
<td>TG/HDL-C</td>
<td>0.54 ± 0.21</td>
<td>1.41 ± 2.76a</td>
<td>0.57 ± 0.31</td>
<td>1.67 ± 1.75*</td>
</tr>
<tr>
<td>ApoA-I (g/l)</td>
<td>1.44 ± 0.17</td>
<td>1.28 ± 0.18a</td>
<td>1.42 ± 0.18</td>
<td>1.30 ± 0.18*</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>0.74 ± 0.15</td>
<td>0.82 ± 0.20a</td>
<td>0.75 ± 0.15</td>
<td>0.90 ± 0.23*</td>
</tr>
<tr>
<td>ApoB/ApoA-I</td>
<td>0.52 ± 0.12</td>
<td>0.65 ± 0.17a</td>
<td>0.54 ± 0.13</td>
<td>0.70 ± 0.19*</td>
</tr>
</tbody>
</table>

Values are as means ± SD.

Normal, normolipidemia; Abnormal, dyslipidemia; Al, atherosclerosis index; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B.

All comparisons were corrected for differences in age and BMI between the two groups expect the parameters of age and BMI.

*Controls: normal (n = 159), abnormal (n = 70); PCOS: normal (n = 166), abnormal (n = 199).

<table>
<thead>
<tr>
<th>Differences</th>
<th>Controls</th>
<th>HA + OA + PCO</th>
<th>HA + OA</th>
<th>HA + PCO</th>
<th>OA + PCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>342</td>
<td>164 (40.39%)</td>
<td>90 (22.17%)</td>
<td>25 (6.16%)</td>
<td>127 (31.28%)</td>
</tr>
<tr>
<td>WC ≥ 80 cm</td>
<td>57 (16.67%)</td>
<td>62 (37.80%)*</td>
<td>32 (35.56%)*</td>
<td>10 (40%)*</td>
<td>66 (51.97%)*</td>
</tr>
<tr>
<td>TG ≥ 1.7 mmol/l</td>
<td>20 (5.85%)</td>
<td>40 (24.39%)*</td>
<td>15 (16.67%)*</td>
<td>7 (28%)*</td>
<td>36 (28.35%)*</td>
</tr>
<tr>
<td>HDL-C &lt; 1.29 mmol/l</td>
<td>82 (23.98%)</td>
<td>60 (36.59%)*</td>
<td>29 (32.22%)</td>
<td>7 (28%)</td>
<td>71 (55.91%)*</td>
</tr>
<tr>
<td>Fasting Glu ≥ 5.6 mmol/l</td>
<td>76 (22.22%)</td>
<td>44 (26.83%)</td>
<td>19 (21.11%)</td>
<td>9 (36%)</td>
<td>47 (37.01%)*</td>
</tr>
<tr>
<td>BP ≥ 130/85 mmHg</td>
<td>40 (11.70%)</td>
<td>30 (18.29%)*</td>
<td>16 (17.78%)</td>
<td>2 (8%)</td>
<td>23 (18.11%)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>16 (4.68%)</td>
<td>38 (23.17%)*</td>
<td>17 (18.89%)*</td>
<td>5 (20%)*</td>
<td>44 (34.65%)*</td>
</tr>
</tbody>
</table>

Differences in percentages between two groups were evaluated by χ² tests.

*P < 0.05 compared with controls.

**P < 0.05 compared with HA + OA + PCO subgroup.

*P < 0.05 compared with HA + OA subgroup.

**P < 0.05 compared with HA + PCO subgroup.

**P < 0.05 compared with OA + PCO subgroup.
Table V Association of each important metabolic variable with PCOS by binary logistic regression analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1a</th>
<th>Model 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odd ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.47 (1.32–1.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AI</td>
<td>2.50 (1.97–3.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG/HDL</td>
<td>1.68 (1.32–2.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>ApoB</td>
<td>17.41 (6.93–43.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoB/apoA-I</td>
<td>27.16 (9.46–77.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3.27 (2.34–4.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>7.66 (4.32–13.57)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence intervals; AI, atherosclerosis index; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B.

aAge-adjusted.
bAge- and BMI-adjusted.

WC, WHR and BMI among the four PCOS phenotypes, which is different from most of other publications (Moran and Teede, 2009; Wild et al., 2010). We also showed that after correcting for differences in age and BMI, patients with OA + PCO had lower HDL-C levels than other three phenotypes, and higher apoB levels, AIs and apoB/apoA-I ratios than the HA + OA phenotype (Table II). These results suggest that patients with OA + PCO have more severe abdominal adiposity and a more adverse lipid metabolic profile. The abdominal adiposity might, at least in part, contribute to these metabolic abnormalities.

The apoB/apoA-I ratio, which reflects the status of potentially atherogenic and antiatherogenic lipoproteins, has been reported to be a better predictor of cardiovascular diseases than traditional lipid measurements (Fernandez and Webb, 2008; Sierra-Johnson et al., 2009; Sasongko et al., 2011). Recent studies have demonstrated that the apoB/apoA-I ratio is associated with the incidence of type 2 diabetes (Ley et al., 2010), MS (Sierra-Johnson et al., 2006) and IR (Sniderman, 2007; Sierra-Johnson et al., 2007), and increased free androgen index and visceral adiposity (Lee et al., 2011). These results support the hypothesis that the apoB/apoA-I ratio might serve as a new and reliable index for estimating risks of cardiovascular disease, type 2 diabetes or MS. In addition, the apoB concentration has been found to be comparable with the apoB/apoA-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality in a multi-ethnic US population (Sierra-Johnson et al., 2009). Our findings that increased apoB concentrations and an increased apoB/apoA-I ratio are more strongly associated with PCOS in the age-adjusted logistic regression analyses (OR = 17.41 and 27.16, 95% CIs: 6.93–43.74 and 9.46–77.93, respectively) than routine glucose and lipid metabolic parameters (Table V), suggest that apoB and the apoB/apoA-I ratio might also be potential biomarkers in predicting risk of cardiovascular diseases in patients with PCOS. The present study also shows that the above-mentioned predictive roles of apoB and the apoB/apoA-I ratio are significantly weakened after further adjusting for BMI (OR = 7.81 and 6.66, 95% CIs: 2.98–20.48 and 2.14–20.75, respectively) (Table V), hinting that obesity has an apparent effect on serum apoB levels and the apoB/apoA-I ratio. ApoB, apoA-I and serum lipids reflect different aspects of lipoprotein particles: apoB, the ligand of LDL receptor (apoB100), is able to exactly represent the total amount of potentially atherogenic circulating lipoproteins, since there is only one apoB moiety per particle of apoB-containing lipoproteins including VLDL, LDL, LDL, lipoprotein(a) and chylomicrons (Sierra-Johnson et al., 2009; Kappelle et al., 2011; Lee, et al., 2011); apoA-I is the major structural protein component of HDL particles and has reverse cholesterol transport, antioxidant and anti-inflammatory functions (Navab et al., 2011; Shah, 2011); while serum lipids such LDL-C and HDL-C refer to the cholesterol lipid content of LDL and HDL. The distributions of apoB and apoA-I in lipoproteins and their pleiotropic biological functions may be an important reason why apoB and the apoB/apoA-I ratio are better at predicting the risk of cardiovascular diseases than traditional lipids in patients with PCOS.

There are several limitations to the present study. First, some subjects declined oral glucose tolerance test because it is uncomfortable and time-consuming, so 2-h Ins and Glu indexes in these women were not taken, which might influence the power of these parameters. Second, we only measured TT which may be a less sensitive marker for HA than free testosterone levels. Third, in this study, the presence of tubal factor or male infertility may have biased the control population. In addition, the HA + PCO phenotype needs a larger number of subjects to properly evaluate its characteristics.

In conclusion, the present study for the first time shows that apoB levels and the apoB/apoA-I ratio, which are better parameters than routine lipid measurements in predicting risk of cardiovascular diseases, might also be potential biomarkers in predicting risk of cardiovascular diseases in patients with PCOS. There is a relatively high prevalence of dyslipidemia and MS in south-west Chinese women with PCOS, especially in the new phenotype (OA + PCO), and patients with dyslipidemia are more obese, and have a more adverse glucose and lipid metabolic profile and higher apoB levels and a higher apoB/apoA-I ratio, suggesting that a greater risk of type 2 diabetes and cardiovascular diseases might present in these patients. Therefore, therapy and future management for these patients should go beyond the target of short-term symptom control to the early screening and long-term effective prevention of type 2 diabetes and cardiovascular risks.
Acknowledgements

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Authors’ roles

P.F. designed, performed the study, analyzed the data and revised the paper. J.Z. collected the samples, analyzed the data and drafted the paper. H.L. was responsible for patient screening. Y.W. and F.Z. collected the samples and helped with the experiments. H.B. revised the paper.

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Conflict of interest

None declared.

References


Cheung LP, Ma RC, Lam PM, Lok IH, Haines CJ, So WY, Tong PC, Cockram CS, Chow CC, Goggins WB. Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. Hum Reprod 2008; 23:1431–1438.


