Atherogenic changes in low-density lipoprotein particle profiles were not observed in non-obese women with polycystic ovary syndrome

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STUDY QUESTION: Is a preponderance of small dense low-density lipoprotein-cholesterol (LDL-C) observed in non-obese women with polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Non-obese Korean women with PCOS have no quantitative or qualitative changes in LDL-C profiles.

WHAT IS KNOWN ALREADY: Small dense LDL particles (sd-LDL) are more atherogenic than large buoyant ones and are strongly associated with coronary artery disease independent of other risk factors. Many investigators have found an increased proportion of atherogenic sd-LDL or a decreased mean LDL particle size in women with PCOS, but all of these studies have been based primarily on obese or overweight women with PCOS.

STUDY DESIGN, SIZE, DURATION: This was a case–control study evaluating complete lipid and lipoprotein profiles in 64 PCOS patients and 64 age- and BMI-matched controls. All women with PCOS in our study population were not obese. To determine the differences in the LDL particle profiles between PCOS phenotypes, the patients with PCOS were divided into two subgroups according to the presence of clinical or biochemical hyperandrogenism.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Using the Rotterdam criteria, we recruited 64 women (18–40 years) with PCOS who were attending a tertiary university hospital. A total of 64 premenopausal control women were matched with patients based on exact age and BMI (±1.0 kg/m²). All the participants fell within the non-obese range of the BMI (<25 kg/m²) according to the definition of obesity for Asians. The LDL subfraction was analyzed by 3% polyacrylamide gel tube electrophoresis. Seven LDL subclasses were quantified and LDL subclasses 3–7 were small LDL subfractions. LDL subfraction scores were calculated based on the following weighted scoring system developed by the manufacturer; scores of <5.5 were categorized as phenotype A (large, buoyant LDLs), and those >5.5 were categorized as non-A phenotype (sd-LDLs). The system also determined the mean LDL particle size diameter.

MAIN RESULTS AND THE ROLE OF CHANCE: There were no differences in the absolute level of LDL-C, mean LDL diameter or percentage of atherogenic sd-LDLs between PCOS patients and controls or between hyperandrogenic and non-hyperandrogenic PCOS subgroups. Also, none of the subjects showed a non-A LDL phenotype. The most notable finding of our study was the difference in the lipoprotein (a) levels and prevalence of its elevation in PCOS patients versus controls (P = 0.002 and P = 0.004, respectively), and between PCOS subgroups (P = 0.030 and P = 0.047, respectively).

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Introduction

Dyslipidemia is a very common metabolic abnormality in women with polycystic ovary syndrome (PCOS), with a prevalence of up to 70% (Legro et al., 2001). Insulin resistance is a core pathophysiology of PCOS, and lipid alterations in women with PCOS may, therefore, be consistent with those found in the insulin-resistant state: decreased levels of high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein (apo) A-I and increased levels of triglycerides (TG), apoB and very low-density lipoprotein (VLDL) (Sniderman et al., 2001; Barter et al., 2003; Brunzell and Ayyobi, 2003; Taskinen, 2003).

Many studies have reported that low-density lipoprotein-cholesterol (LDL-C) is increased in women with PCOS (Legro et al., 2001; Valkenburg et al., 2008). Recently, alterations in LDL quality have also been reported in women with PCOS (Legro et al., 1999; Dejager et al., 2001; Pirwany et al., 2001; Berneis et al., 2007; Doi et al., 2008; Rizzo et al., 2009; Phelan et al., 2010; Sidhwani et al., 2011). LDLs comprise different subclasses according to size, density and atherogenicity. Small dense LDL particles (sd-LDL) are more atherogenic than large buoyant ones and are strongly associated with coronary artery disease independent of other risk factors (NCEP/ATP III, 2002). Many investigators have found an increased proportion of atherogenic sd-LDL or decreased mean LDL particle size in women with PCOS (Legro et al., 1999; Dejager et al., 2001; Pirwany et al., 2001; Berneis et al., 2007; Doi et al., 2008; Rizzo et al., 2009; Phelan et al., 2010; Sidhwani et al., 2011), but all of these studies have been based primarily on obese or overweight PCOS women. Obesity is associated with a preponderance of sd-LDL particles (Howard et al., 2003; Sidhwani et al., 2011), and about 50–70% of American women with PCOS are obese (Carmina et al., 2003; Azizz et al., 2004). However, in other populations, the prevalence of obesity in women with PCOS is much lower than in Americans: 10% in a Spanish study; 20.92% in a Chinese study; and 28.4% in a Korean study (Asuncion et al., 2000; Lee et al., 2009; Chen et al., 2010). Thus, most women with PCOS are not obese. In this study, we examined whether altered LDL particle profiles are also observed in non-obese women with PCOS. Furthermore, not all PCOS phenotypes have a similar metabolic risk (Shroff et al., 2007; Chae et al., 2008; Fauser et al., 2012), and we also assessed the relative differences in the LDL particle profiles according to the PCOS Rotterdam subgroups.

Materials and Methods

Subjects

We recruited 64 women (18–40 years) with PCOS using the Rotterdam criteria (The Rotterdam Group, 2003). All the patients had a non-obese BMI (<25 kg/m2) according to the definition of obesity for Asians (World Health Organization, 2000). Hirsutism was assessed using the modified Ferriman and Galwey score (mF-G score) system. Nine body areas (upper lip, chin, chest, upper and lower abdomen, upper arms, thighs and upper and lower back) were graded from 0 to 4, and the scores were summed. Although intra- and inter observer variations were not evaluated, clinical hyperandrogeonism (HA) was defined as an mF-G score of ≥6 (Kim et al., 2011). 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 (Chae et al., 2008). To determine the relative differences in the lipid profiles across PCOS phenotypes, the patients with PCOS were divided into two subgroups according to the presence of clinical or biochemical HA. All the women with PCOS were screened to exclude hyperprolactinemia and thyroid dysfunction. Serum 17-hydroxypregesterone (OHP) was also measured and if the serum 17-OHP level was over 2 ng/ml, a repeat test was performed in the early morning during the follicular phase. The patients who showed continuous elevation of 17-OHP were excluded from the study group. A total of 64 premenopausal women were matched with patients based on exact age and BMI (±1.0 kg/m2). The women in this control group visited Seoul National University Hospital as part of a group checkup for work and lacked specific health problems. All the controls had regular menstrual cycles and an mF-G score of <6, and all received a transvaginal or transrectal ultrasound examination to evaluate ovarian morphology and were excluded if polycystic ovary (PCO) morphology was identified.

No PCOS patients or controls had taken prescription pills, including 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-1007-060-323), and written informed consent was obtained from each woman.

Clinical and biochemical measurements

Clinical variables, such as body weight, height, waist circumference (WC) and blood pressure were assessed in all the 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 the PCOS patients and in a subset of controls (n = 17)
Insulin resistance (HOMA-IR) was calculated as glucose (mg/dl) using 1 ng/ml insulin (BioSource Europe S.A., Belgium), and the homeostatic model assessment for insulin (HOMA-IR) was calculated as glucose (mg/dl) using 1 ng/ml insulin (BioSource Europe S.A., Belgium). The intra- and inter-assay coefficients of variation (CVs) were 4.0–11.0 and 5.9–12.0% for total testosterone and 4.0–17 and 8.0–18.3% for free testosterone, respectively.

In all the subjects, after a 12-h overnight fast, fasting plasma glucose, total cholesterol, TG, HDL-C and LDL-C were measured (Wako Pure Chemical Industries, Ltd. Osaka, Japan). Lipoprotein (a), apo A1 and apoB were measured using an immunoturbidimetric assay (Behring Nephelometer 100, Behring Diagnostics, Beringwerke, Germany). Intra- and inter-assay CVs were <5% for all the above parameters except for apoB inter-assay variation (3.6–6.8%). Circulating highly sensitive C-reactive protein was measured using a latex turbidimetric immunoassay with a sensitivity of 0.01 mg/dl (Wako Pure Chemical Industries, Ltd. Osaka, Japan). Fasting insulin levels were measured using RIA (BioSource Europe S.A., Belgium), and the homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as glucose (mg/dl) × insulin (μU/ml)/405.

To compare proportions of serum lipids or lipoproteins between women with PCOS and matched controls, the following cutoffs were considered (NCEP/ATP III, 2002): high total cholesterol ≥ 200 mg/dl, TG ≥ 150 mg/dl, LDL-C ≥ 130 mg/dl and low HDL-C < 40 mg/dl. Elevated lipoprotein (a) concentration was defined as ≥ 30 mg/dl (Davidson et al., 2011).

**LDL particle analysis**

The LDL subfraction was analyzed by 3% polyacrylamide gel tube electrophoresis (Lipoprint TM LDL System; Quantimetrix, Redondo Beach, CA, USA). VLDL, HDL and seven LDL subclasses were quantified, and LDL subclasses 3–7 were termed the small LDL subfractions. LDL subfraction scores were calculated based on the weighted scoring system developed by the manufacturer: scores of <5.5 were categorized as phenotype A (large, buoyant LDLs) and those >5.5 were categorized as non-A phenotype (sd-LDLs). The system also determined the mean LDL particle size diameter. For the intra and inter-assay precision, CVs were <5% for LDL subfraction score and <1% for LDL particle size diameter.

**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 mean ± SD or median values with the range. If a Gaussian distribution was achieved by natural logarithmic or square root transformation, the data are shown as geometric means or square root transformed and 95% confidence intervals (95% CI). Continuous parameters were compared using Student’s t-test, and the prevalence of serum lipid and lipoprotein alterations were compared using the chi-square or Fisher’s exact test. All data analyses were performed using the Statistical Package for the Social Sciences software (version 19.0, IBM SPSS, NY, USA), and statistical significance was set at two-sided P-values <0.05.

**Results**

The clinical and biochemical characteristics of the subjects are shown in Table I. There were significant differences in the levels of fasting insulin, HOMA-IR and blood pressures between women with PCOS and matched controls. The lipid profiles of the participants are shown in Table II. Women with PCOS showed decreased plasma levels of apoA-I and higher levels of TG and lipoprotein (a) than matched controls, but they showed no differences in the levels of apoB, LDL-C, HDL-C and VLDL-C. Table III displays the prevalence of elevated serum lipids or lipoprotein. Except for lipoprotein (a), the prevalence of serum lipid and lipoprotein alterations did not differ between the patients and the controls.

In the LDL particle size analysis, mean LDL particle diameter and percentage fraction of sd-LDLs (subclasses 3–7) did not differ between the PCOS patients and controls, and none of the participants showed an atherogenic non-A LDL phenotype (Tables II and III).

PCOS is considered a disorder of androgen excess, but women with oligo- or amenorrhea and PCO but no evidence of HA (clinical or biochemical) were newly included as a form of PCOS in the Rotterdam criteria. To evaluate the metabolic risk across the Rotterdam subgroups, we determined the differences in LDL particle profile for each PCOS phenotype according to the presence of HA. The hyperandrogenic PCOS patients were more obese and had higher levels of fasting insulin and higher blood pressure than the non-hyperandrogenic patients (Table I). However, there were no differences in the LDL particle profiles between the hyperandrogenic and non-hyperandrogenic PCOS groups (Table II). The hyperandrogenic PCOS group presented markedly increased lipoprotein (a) levels compared with the non-hyperandrogenic group, but we could find no significant differences in the prevalence of other serum lipid and lipoprotein alterations between the PCOS subgroups (Tables II and III).

**Discussion**

This study focuses on complete serum lipid and lipoprotein profiles in non-obese patients with PCOS. Many studies have reported that sd-LDL is increased in women with PCOS, but none has yet provided data on the LDL particle profiles only in non-obese PCOS women. Except for American women, most PCOS patients are not obese (Asuncion et al., 2000; Lee et al., 2009; Chen et al., 2010), and thus, we sought to determine whether the ‘atherogenic non-A LDL phenotype’ is also increased in non-obese PCOS patients. Our study found no differences in the absolute level of LDL-C, mean LDL particle diameter and percentage fraction of sd-LDLs (subclasses 3–7) between non-obese PCOS women and matched controls. Additionally, none of the PCOS patients and controls presented a non-A LDL phenotype. Our findings suggest that non-obese women with PCOS have no significant quantitative or qualitative changes in LDL-C profile.

Previous studies have reported that the percentage fraction of sd-LDLs is increased or the mean LDL particle diameter is decreased in PCOS patients (Legro et al., 1999; Dejager et al., 2001; Pirwany et al., 2001; Bermeis et al., 2007; Doi et al., 2008; Rizzo et al., 2009; Phelan et al., 2010; Sidhwani et al., 2011). The prevalence of ‘non-A LDL phenotype’ in women with PCOS has also been reported in two studies. Legro et al. (1999) classified subjects as phenotype A (≥ 263 Å) and B (≤ 257 Å) based on mean LDL particle size. Although there was a high incidence (54%) of phenotype B in the Hispanic population, the study found no difference in the LDL phenotypes between 16 Hispanic women with PCOS and 21 controls. A recent study using the same scoring system as ours demonstrated that a non-A LDL phenotype was observed in 12.9% of American PCOS patients, which was significantly higher than that of the matched...
controls (2.9%) (Phelan et al., 2010). The main difference between the previous two studies and ours was the obesity of study population: mean BMI was 30.8 (± 6.2) and 31.5 (± 6.9) kg/m² in the previous two studies, while that of our study was 21.2 (95% CI, 19.9, 21.5) kg/m². However, owing to a lack of data for obese subjects, it is difficult to determine whether differences would stem from obesity alone or diverse ethnic and geographical backgrounds.

Perhaps the most notable finding from our study, which was unrelated to its main objective, was the difference in the lipoprotein (a) level and the prevalence of its elevation between groups. Non-obese women with PCOS presented a significantly higher level of lipoprotein (a) than matched controls [15.3 mg/dl (95% CI, 12.8–17.8) versus 9.1 mg/dl (95% CI, 7.2–11.0), P = .002], and one-third (29.7%) of the PCOS patients had elevated lipoprotein (a) levels. Lipoprotein (a) has been identified in large-scale meta-analyses as an independent risk factor for coronary heart disease (Erqou et al., 2009, 2010; Dube et al., 2012). Genetic factors are major contributors to variation in plasma lipoprotein (a) concentrations, which remains stable over an individual’s lifespan (Clarke et al., 2009; Li et al., 2011; Dube et al., 2012). Lipoprotein (a) concentration is also known to vary between ethnic groups (Lanktree et al., 2010). Further investigations are needed to determine whether the lipoprotein (a) alteration in non-obese Korean women with PCOS is also found in other ethnic groups. Recently, Rizzo et al. (2009) also reported that non-obese women with PCOS presented elevated levels of lipoprotein (a).

One outstanding issue is the role of androgens in cardiovascular risk. In this study, we found that the hyperandrogenic women with PCOS had a significantly higher BMI, WC and fasting insulin levels compared with the non-hyperandrogenic group, but no difference in LDL particle profiles. The only significant finding was a difference in serum lipoprotein (a) levels. Future studies are essential to assess whether measurement of atherogenic lipoproteins, such as lipoprotein (a), may be a useful tool to assess different cardiovascular risks in PCOS subgroups.

The present study has some limitations. Although, there have been studies reporting a similar occurrence of metabolic risk across PCOS subgroups (Guo et al., 2010; Wijeyaratne et al., 2011), subjects with oligo-amenorrhea and PCO but no evidence of HA may have a milder metabolic profile compared with the other phenotypes (Shroff et al., 2007; Zhang et al., 2009). In the current study, almost half (45.3%) of the PCOS subjects had this phenotype, and thus, no difference in LDL particle profile between PCOS patients and controls may stem from the presence of this mild phenotype. However, in our study, there were no differences in LDL particle profiles between hyperandrogenic and non-hyperandrogenic groups. There were also no differences in LDL particle profiles between each PCOS subgroup and normal controls (data not shown). These findings suggest that composition of the PCOS subgroup is not likely to influence our results. Second, the prevalence of atherogenic LDL particle pattern increases with age (Friedlander et al., 2000), and the absence of a

| Table I Demographic, androgenic and metabolic features of Korean patients with PCOS and matched controls. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | PCOS (n = 64) | Controls (n = 64) | P-value | Hyperandrogenic | Non-hyperandrogenic |
| | | | | PCOS (n = 35) | PCOS (n = 29) |
| Age (years) | 24.9 ± 6.0 | 24.8 ± 5.9 | 0.953 | 24.9 ± 6.6 | 24.4 ± 5.2 | 0.756 |
| BMI (kg/m²) | 21.2 (19.9, 21.5) | 20.7 (20.0, 21.4) | 0.533 | 21.9 (20.9, 29.9) | 19.8 (18.7, 20.9) | 0.017 |
| WC (cm) | 69.8 (68.7, 70.9) | 70.4 (69.3, 71.5) | 0.245 | 72.2 (71.0, 73.4) | 67.2 (66.1, 68.3) | 0.033 |
| Hirsutism score | 5 (0–24) | 1 (0–5) | <0.001 | 6 (0–24) | 2 (0–5) | <0.001 |
| Total testosterone (ng/ml) | 0.42 (0.41, 0.43) | 0.34 (0.33, 0.35)* | 0.220 | 0.49 (0.48, 0.50) | 0.33 (0.32, 0.34) | 0.003 |
| Free testosterone (pg/ml) | 1.06 (0.96, 1.16) | 0.54 (0.50, 0.58)* | 0.011 | 1.33 (1.21, 1.44) | 0.73 (0.65, 0.81) | 0.001 |
| SHBG (nmol/l) | 45.2 (43.3, 47.1) | 65.1 (63.4, 66.8)* | 0.099 | 40.0 (37.9, 42.1) | 53.4 (51.6, 55.2) | 0.079 |
| FAI | 2.93 (2.01, 3.85) | 1.62 (1.13, 2.11)* | 0.039 | 3.91 (3.01, 4.81) | 2.05 (1.60, 2.50) | 0.001 |
| Fasting plasma glucose (mg/dl) | 87.2 (86.1, 88.3) | 84.3 (83.2, 85.4) | 0.070 | 87.8 (84.9, 90.7) | 86.7 (85.0, 88.4) | 0.612 |
| Fasting insulin (µU/ml) | 9.00 (7.23, 10.77) | 6.22 (4.41, 8.03) | 0.016 | 10.3 (8.5, 12.1) | 7.7 (6.0, 9.4) | 0.037 |
| HOMA-IR | 2.13 (1.90, 2.36) | 1.40 (1.27, 1.53) | 0.010 | 2.24 (1.53, 3.24) | 1.67 (1.01, 2.33) | 0.053 |
| SBP (mmHg) | 114.1 ± 13.6 | 102.4 ± 11.7 | <0.001 | 117.2 ± 15.6 | 110.6 ± 9.1 | 0.046 |
| DBP (mmHg) | 75.3 ± 9.0 | 64.1 ± 8.6 | <0.001 | 77.8 ± 8.3 | 72.6 ± 8.5 | 0.022 |
| 2-h OGTT glucose (mg/dl) | 99.1 (97.8, 100.4) | Not checked | – | 99.2 (97.9, 100.5) | 100.3 (92.6, 108.0) | 0.877 |
| 2-h OGTT insulin (µU/ml) | 47.1 (45.2, 49.0) | Not checked | – | 52.2 (50.1, 54.3) | 40.1 (39.0, 41.2) | 0.140 |
| hs-CRP (mg/dl) | 0.02 (0.01–0.06) | 0.02 (0.01–0.28) | 0.071 | 0.01 (0.01, 0.65) | 0.02 (0.01, 0.48) | 0.198 |
| A1C (%) | 5.35 ± 0.34 | 5.37 ± 0.23 | 0.730 | 5.34 ± 0.39 | 5.37 ± 0.29 | 0.757 |

A1C, hemoglobin A1c; DBP, diastolic blood pressure; FAI, free androgen index; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; WC, waist circumference.

*PCOS patients versus controls.
*Hyperandrogenic versus non-hyperandrogenic PCOS patients and P-values are indicated for the differences between groups as analyzed by Student’s t-test.
*Data are shown as mean ± SD.
*Geometric means with 95% confidence interval (CI).
*Median (range).
*n = 17.
Table II Lipid and lipoprotein levels of Korean patients with PCOS and matched controls.

<table>
<thead>
<tr>
<th></th>
<th>PCOS (n = 64)</th>
<th>Controls (n = 64)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hyperandrogenic PCOS (n = 35)</th>
<th>Non-hyperandrogenic PCOS (n = 29)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein AI (mg/dl)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>128.4 ± 19.3</td>
<td>137.1 ± 29.0</td>
<td>0.047</td>
<td>125.3 ± 20.0</td>
<td>131.7 ± 18.3</td>
<td>0.194</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dl)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>78.2 ± 18.4</td>
<td>76.7 ± 22.8</td>
<td>0.686</td>
<td>80.3 ± 18.9</td>
<td>75.3 ± 17.8</td>
<td>0.288</td>
</tr>
<tr>
<td>Apolipoprotein B/Al&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.64 ± 0.28</td>
<td>0.60 ± 0.35</td>
<td>0.583</td>
<td>0.69 ± 0.36</td>
<td>0.57 ± 0.14</td>
<td>0.102</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15.3 (12.8, 17.8)</td>
<td>9.1 (7.2, 11.0)</td>
<td>0.002</td>
<td>23.7 (18.5, 28.9)</td>
<td>14.0 (11.7, 16.3)</td>
<td>0.030</td>
</tr>
<tr>
<td>Total C (mg/dl)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>174.4 ± 26.2</td>
<td>174.4 ± 27.1</td>
<td>0.994</td>
<td>172.9 ± 22.5</td>
<td>175.8 ± 30.9</td>
<td>0.668</td>
</tr>
<tr>
<td>TG (mg/dl)&lt;sup&lt;d&lt;/sup&gt;</td>
<td>75.4 (72.9, 76.9)</td>
<td>60.3 (58.8, 61.8)</td>
<td>0.003</td>
<td>79.9 (78.4, 81.4)</td>
<td>68.4 (66.9, 69.9)</td>
<td>0.150</td>
</tr>
<tr>
<td>HDL-C (mg/dl)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>62.6 ± 13.9</td>
<td>60.7 ± 11.6</td>
<td>0.392</td>
<td>60.2 ± 14.0</td>
<td>65.4 ± 13.7</td>
<td>0.145</td>
</tr>
<tr>
<td>LDL-C (mg/dl)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>99.3 (98.0, 100.6)</td>
<td>97.7 (96.4, 99.0)</td>
<td>0.684</td>
<td>100.3 (98.0, 99.3)</td>
<td>98.0 (96.7, 99.3)</td>
<td>0.709</td>
</tr>
<tr>
<td>VLDL-C (mg/dl)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>22.0 (20.6, 23.4)</td>
<td>22.5 (21.2, 23.8)</td>
<td>0.718</td>
<td>21.2 (19.8, 22.6)</td>
<td>23.0 (21.7, 24.3)</td>
<td>0.644</td>
</tr>
<tr>
<td>LDL 1–2 (large) (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33.4 ± 5.6</td>
<td>32.0 ± 6.4</td>
<td>0.198</td>
<td>34.4 ± 5.0</td>
<td>31.4 ± 4.7</td>
<td>0.021</td>
</tr>
<tr>
<td>LDL 3–7 (small) (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.48 ± 2.60</td>
<td>1.64 ± 1.62</td>
<td>0.686</td>
<td>1.34 ± 1.95</td>
<td>1.72 ± 3.27</td>
<td>0.573</td>
</tr>
<tr>
<td>Mean LDL size (Å)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>269.8 ± 4.2</td>
<td>269.8 ± 2.7</td>
<td>0.981</td>
<td>269.6 ± 3.1</td>
<td>269.4 ± 3.9</td>
<td>0.984</td>
</tr>
</tbody>
</table>

C, cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein-cholesterol.

<sup>a</sup>PCOS patients versus controls.

<sup>b</sup>Hyperandrogenic versus non-hyperandrogenic PCOS patients.

<sup>c</sup>Data are shown as mean ± SD.

<sup>d</sup>Geometric means with 95% CI.

<sup>*</sup>P-values are indicated for the differences between groups as analyzed by Student’s t-test.
non-A LDL phenotype might stem from the young age of the subjects. However, previous studies, which found that the prevalence of an atherogenic non-A LDL phenotype varies from 13 to 44% (Legro et al., 1999; Phelan et al., 2010), were also mainly performed in patients under 30 years of age. Third, although the purpose of our study was to investigate the lipid and lipoprotein patterns in non-obese women with PCOS, data on obese subjects could also offer complementary findings about the possible relationship between the magnitude of obesity and LDL phenotype. Fourth, the screening cutoff for the presence of metabolic syndrome in our study was to investigate the lipid and lipoprotein patterns in non-obese women with PCOS, data on obese subjects could also offer complementary findings about the possible relationship between the magnitude of obesity and LDL phenotype. Finally, while our findings were independent of several factors that affect lipid status, including age and BMI, we cannot exclude the possibility of the presence of other potential confounding factors, such as differences in diet and/or exercise patterns.

In summary, although non-obese women with PCOS had metabolic derangement compared with controls, none of the non-obese patients had an atherogenic non-A LDL phenotype. Our findings suggest that non-obese women with PCOS may have no significant quantitative or qualitative changes in LDL-C profiles. A lipoprotein profile characterized by increased lipoprotein (a) was the most notable difference between the non-obese PCOS patients and controls as well as between the PCOS subgroups. Future studies are necessary to explore the role of lipoprotein (a) in patients with PCOS in this context.

**Authors’ roles**

J.J.K.: analysis and interpretation of data and drafting the article; S.J.C.: analysis and interpretation of data and drafting the article; Y.M.C.: final approval of the version to be published; K.R.H.: reviewing the manuscript; S.H.S.: contribution to discussion and writing; S.H.Y.: contribution to discussion and writing; S.H.S.: contribution to discussion and writing; S.H.Y.: approval of the version to be published; K.R.H.: reviewing the manuscript; S.J.C.: final approval of the version to be published.

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