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Dyslipidemia in women with polycystic ovary syndrome

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Dyslipidemia is a very common metabolic abnormality in women with polycystic ovary syndrome (PCOS). Insulin resistance is a key pathophysiology of PCOS, thus dyslipidemia in women with PCOS may be consistent with those found in an insulin resistant state. In recent meta-analysis, triglycerides and low-density lipoprotein (LDL) cholesterol levels were 26 mg/dL and 12 mg/dL higher, and high-density lipoprotein cholesterol concentration was 6 mg/dL lower in women with PCOS than those of controls. Alterations in LDL quality also have been reported in women with PCOS: women with PCOS have an increased proportion of atherogenic small dense LDL or decreased mean LDL particle size. However, in a recent Korean study, non-obese Korean women with PCOS had no significant quantitative or qualitative changes in LDL cholesterol profile. Lipoprotein (a) has been identified as an independent risk factor for coronary heart disease, and its elevation in PCOS patients has been consistently reported in diverse studies including non-obese Korean population. Some studies have investigated apolipoprotein (Apo) A-I and ApoC-I levels in women with PCOS and levels of ApoA-I, which has cardio-protective effects, were significantly lower in women with PCOS than those of controls. ApoC-I is known to increase the postprandial serum lipid level that is common in coronary artery disease patients, and one study reported that such an elevation may be the earliest variation of lipid abnormality in women with PCOS. In conclusion, women with PCOS should receive a complete lipid test, and lifestyle modification, including diet and exercise, is the first line therapy for all women with PCOS and is particularly important for those with dyslipidemia.

Keywords: Dyslipidemia; Insulin resistance; Metabolic syndrome; Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of endocrine dysfunction in women of reproductive age with a prevalence that ranges from 4% to 7% [1,2]. Metabolic disturbances are well-recognized clinical features of this syndrome. Especially, dyslipidemia is a very common metabolic abnormality in women with PCOS, with a prevalence of up to 70% [3]. Insulin resistance is a key pathophysiology of PCOS, and dyslipidemia in women with PCOS may therefore be consistent with that 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 [4-7].

The aim of the present review was to address the detailed profile of dyslipidemia in PCOS. In addition, obesity can alter lipoprotein lipid profiles, but most of the Korean women with PCOS are not obese [8]. Thus, we also reviewed the unique characteristics in dyslipidemia profile in Korean women with PCOS.

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Serum TG, HDL cholesterol, and LDL cholesterol

Decrease in HDL-C and increase in TG levels are well known lipid profile characteristics in women with PCOS [3,9-16]. Recently, Wild et al. [17] reported meta-analysis of lipid levels in world-wide cross-sectional studies in women with PCOS (mainly performed in European and American women). In this analysis, TG levels were 26 mg/dL (95% confidence interval [CI], 17 to 35) higher and HDL-C concentrations were 6 mg/dL (95% CI, 4 to 9) lower in women with PCOS than those of controls. Also, low-density lipoprotein cholesterol (LDL-C) and non HDL-C concentrations were 12 mg/dL (95% CI, 10 to 16) and 19 mg/dL (95% CI, 16 to 22) higher, respectively. With body mass index (BMI) matching, LDL-C and non HDL-C were still higher in PCOS subjects: by 9 mg/dL (95% CI, 6 to 12) and 16 mg/dL (95% CI, 14 to 19), respectively [17].

HDL encompasses several different classes of lipoproteins (HDL_2 and HDL_3) according to its density, metabolism and properties [18]. HDL subclasses are known to differ in their capacity to confer cardio-protection, and HDL_2 has been reported as the most anti-atherogenic HDL subtype. Thus decreased levels of HDL_2 have been strongly associated with coronary heart disease, and HDL subclass profile has been investigated in women with PCOS. Talbott et al. [19] recruited a total of 206 women with PCOS and 206 age-matched controls, and total HDL and HDL_2 levels were significantly lower in women with PCOS than controls even after controlling for both age and BMI. Conway et al. [20] also found that even lean women with PCOS had reduced serum HDL and HDL_2 concentrations compared to controls. These findings suggest that women with PCOS not only have low serum HLD-C levels, but also show alterations in HDL quality.

Many studies have reported that LDL-C is increased in women with PCOS [3,21], which is usually not noted in insulin resistant states. The reason why LDL-C in also increased in women with PCOS in not clear yet, but increased LDL-C levels in women with PCOS may be related to hyperandrogenism or genetic factor. Recabarren et al. [22] investigated the metabolic profiles in sons of women with PCOS during different stages of life. In this study, 80 sons of women with PCOS and 56 sons of control women were enrolled since early infancy, and during adulthood, sons of women with PCOS exhibited significantly higher LDL-C levels than those of controls (106.8 mg/dL [range, 52.6 to 224.3] versus 94.0 mg/dL [range, 60.4 to 142.5], respectively, $P=0.022$) [22]. Sam et al. [23] also investigated the metabolic phenotypes in 215 non-Hispanic white mothers of women with PCOS and 62 control women. In the results, mothers had higher LDL-C levels (3.58 ± 0.97 mmol/L versus 3.11 ± 0.66 mmol/L, respectively, $P=0.007$), whereas HDL-C and TG levels did not differ compared with control women. The only predictors of LDL-C level in the mothers were their daughters' LDL-C ($r^2= 0.11$, $P<0.001$) and their own unbound testosterone levels ($r^2=0.04$, $P=0.03$) [23]. Sam et al. [24] also have found that LDL-C levels are increased in sisters of women with PCOS compared to control women.

As stated above, LDL-C is increased in women with PCOS; however, recently, alterations in LDL quality also have been reported in women with PCOS [14,25-31]. LDL comprises different subclasses according to size, density and atherogenicity. Small dense LDL particles are more atherogenic than large buoyant ones, and are strongly associated with coronary artery disease [32]. Women with PCOS have an increased proportion of atherogenic small dense LDL or decreased mean LDL particle size [14,25-31], and such alterations may be associated with increased cardiovascular risk. However, all of these studies have been based primarily on obese or overweight PCOS women, but prevalence of obesity in Korean women with PCOS is low [8]. Thus, we investigated whether altered LDL particle profiles are also observed in non-obese women with PCOS. Complete lipid and lipoprotein profiles were obtained in 64 non-obese PCOS patients and 64 age- and BMI-matched controls. The results showed no differences in the absolute level of LDL-C, mean LDL diameter or percentage of atherogenic small dense LDL between PCOS patients and controls. Our findings suggest that non-obese Korean women with PCOS have no significant quantitative or qualitative changes in LDL-C profile [33].

ApoA-I, ApoB, ApoC-1, and lipoprotein (a) and lipoprotein (a)

Lipids are transported through the circulation via lipoproteins. Apolipoproteins are located on the surface of lipoproteins, and regulate lipoprotein metabolism and lipid transport. Among the 13 known apolipoproteins, ApoA-I is carried in HDL and has cardioprotective properties, and ApoB is a potential atherogenic risk factor [32]. Some studies have investi-

gated ApoA-I and ApoB measurement in women with PCOS. Valkenburg et al. [21] enrolled 557 women with PCOS and 295 controls, and found that across the entire range of BMI values, ApoA-I levels were significantly lower in women with PCOS. However, there were no differences in ApoB levels between PCOS patients and controls. They also analyzed whether hyperandrogenism and obesity were independent predictors for the presence of a more atherogenic lipid profile in women with PCOS and found that free androgen index and BMI were independent predictors for serum ApoA-I levels in women with PCOS. They concluded that ApoA-I levels were significantly lower in women with PCOS without any difference in ApoB levels, and both obesity and hyperandrogenism contribute to these changes [21].

Among human apolipoproteins, ApoC-I inhibits the uptake of TG-rich lipoproteins via hepatic receptors, and has been reported to increase postprandial serum lipid level as is common in coronary artery disease patients [34,35]. In women with PCOS, Huang et al. [36] evaluated the role of ApoC-I level and assessed relationships between ApoC-I and clinical features of PCOS. The serum levels of ApoC-I in women with PCOS were significantly higher compared with those of controls (1.23 ± 0.29 mg/mL versus 1.01 ± 0.24 mg/mL, respectively, $P < 0.05$). In PCOS patients without any abnormal serum lipid index, ApoC-I levels were still higher than in controls (1.39 ± 0.37 mg/mL versus 1.03 ± 0.22 mg/mL, respectively, $P < 0.05$), and even lean PCOS women had higher ApoC-I levels than controls. Thus, the authors concluded that ApoC-I may be the earliest variation of lipid metabolic abnormality in women with PCOS [36].

Among the human lipoproteins, lipoprotein (a) has been identified as an independent risk factor for coronary heart disease in large-scale meta-analyses [37-39]. Lipoprotein (a) concentration in women with PCOS has been reported in some studies. Recently, we compared serum lipoprotein (a) concentration in 64 lean women with PCOS and 64 age- and BMI-matched controls. In this study, non-obese women with PCOS presented a significantly higher level of lipoprotein (a) than matched controls (15.3 mg/dL [95% CI, 12.8 to 17.8] versus 9.1 mg/dL [95% CI, 7.2 to 11.0], $P = 0.002$), and one-third (29.7%) of the PCOS patients had elevated (≥30 mg/dL) lipoprotein (a) levels [33]. Berneis et al. [40] also reported that lipoprotein (a) abnormalities may be found in one-third of Mediterranean women with PCOS who have a normal lipid pattern, which was similar with our previous results. Rizzo et al. [29] investigated the prevalence of dyslipidemia in different PCOS phenotypes and also reported that levels of lipoprotein (a) were significantly increased in anovulatory women with PCOS than ovulatory women. Thus, they concluded that measurement of lipoprotein (a) in women with different PCOS phenotypes may potentially help to assess cardiovascular risk.

Prevalence of dyslipidemia in Korean women with PCOS

Chae et al. [41] reported the clinical and biochemical characteristics of PCOS in Korean women. In 166 women with PCOS and 277 controls, prevalence of elevated TG (≥150 mg/dL) was 26.7%, whereas that of controls was 1.0% ($P < 0.001$); prevalence of low HDL-C (<50 mg/dL) was 30.0%, whereas that of controls was 3.0% ($P = 0.004$) [41]. Recently, we investigated complete phenotypic and metabolic profiles in a large cohort of untreated Korean women with PCOS. From May 2010 to December 2012, consecutive women with PCOS were recruited from 13 medical centers; three were infertility clinics, and the remaining ten were tertiary university hospitals. The mean age of the patients was 24.9 (±6.0) years, the mean BMI was 22.4 (±4.1) kg/m^2, and the prevalence of dyslipidemia was 35.7% in 865 consecutive patients (unpublished). These findings also suggest that even young and non-obese Korean women with PCOS also have increased prevalence of dyslipidemia.

Implication for treatment

The Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society has recommended that women with PCOS receive a complete lipid test (total cholesterol, LDL-C, non-HDL-C, HDL-C, and TG). The primary target goal is LDL-C, with level of non-HDL-C as the secondary target. Lipid target values are categorized according to cardiovascular disease risk factors. In women with PCOS without additional cardiovascular disease risk factors, LDL-C levels should be less than 130 mg/dL and target serum non-HDL-C levels should be 30 mg/dL higher than the designated LDL-C goal. Serum TG levels should be less than 150 mg/dL. Lifestyle modification, including diet and exercise, is the first line therapy for all women with PCOS and is particularly important for those with dyslipidemia (individu-

als with serum LDL-C levels greater than 160 mg/dL and/or non-HDL-C levels of at least 190 mg/dL according to the AE-PCOS Society). Statin drugs are used when lifestyle modifications are not enough, and have emerged as a novel therapeutic approach to PCOS. In addition to improvement of lipid profiles, PCOS women receiving statins showed a significant decrease of testosterone, free androgen index, C-reactive protein, and insulin resistance [42-44]. However, the use of statins in pregnancy is contraindicated, and contraception is required.

Conclusion

Although prevalence of obesity in Korean women with PCOS is low, even young and non-obese Korean women with PCOS have substantially increased prevalence of dyslipidemia. Dyslipidemia in women with PCOS may be consistent with those found in the insulin resistant state: decreased levels of HDL-C and ApoA-I, increased levels of TG. Women with PCOS have both quantitative and qualitative changes in LDL-C profile: not only increased LDL-C level but also increased proportion of atherogenic small dense LDL. However, in a recent Korean study, non-obese Korean women with PCOS had no such abnormalities. In women with PCOS, ApoA-I, ApoC-I, and lipoprotein (a) abnormalities were also reported. Women with PCOS should receive a complete lipid test, and lifestyle modification is the first line therapy for all women with PCOS and is particularly important for those with dyslipidemia.

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