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Low sex hormone-binding globulin is associated with low high-density lipoprotein cholesterol and metabolic syndrome in women with PCOS

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BACKGROUND: Decreased high-density lipoprotein cholesterol (HDL-C) and sex hormone-binding globulin (SHBG) levels, and the metabolic syndrome, are all closely associated with a higher prevalence of atherosclerotic cardiovascular disease. We investigated the association between HDL-C, SHBG and the metabolic syndrome in women with polycystic ovary syndrome (PCOS). METHODS AND RESULTS: Among 106 young Taiwanese women (mean age ± SD, 24.9 ± 4.8 years) with PCOS, 69 (65.1%) women had an HDL-C level <50 mg dl^{-1}. The level of HDL-C was highly correlated with that of serum SHBG (γ = 0.6034, P < 0.0001). The SHBG level was significantly lower in subjects with an HDL-C <50 mg dl^{-1} than that in subjects with an HDL-C ≥50 mg dl^{-1}. Using multiple linear regression models with adjustment for age, BMI and other anthropometric, metabolic, liver function and hormonal variables, we showed serum SHBG to be independently correlated with HDL-C. Based on logistic regression analysis with adjustment for age, the SHBG level was significantly lower in women with PCOS with the metabolic syndrome (odds ratio = 0.92, P = 0.003). CONCLUSIONS: Low levels of SHBG in women with PCOS were associated with low levels of HDL-C, independent of insulin resistance and obesity. The SHBG level was inversely related to the occurrence of metabolic syndrome, further strengthening the potential link between SHBG levels and cardiovascular disease in women with PCOS.

Key words: cardiovascular disease/high-density lipoprotein cholesterol/metabolic syndrome/PCOS/SHBG

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age (Carmina and Lobo, 1999). At the Rotterdam revised consensus meeting in 2003, it was proposed that oligomenorrhoea, clinical or biochemical hyperandrogenaemia and the presence of polycystic ovaries should serve as the diagnostic criteria for PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). PCOS is increasingly recognized as a variant of the metabolic syndrome in women with the characteristic features of insulin resistance, central obesity, impaired glucose metabolism, dyslipidaemia and hypertension (Hopkinson *et al*., 1998). The increased risk of cardiovascular disease in women with PCOS, however, is still controversial (Rajkhowa *et al*., 1997; Talbott *et al*., 2000; Wild, 2002). Women with PCOS have been reported to have lower serum high-density lipoprotein cholesterol (HDL-C) and higher serum triglyceride concentrations than those without PCOS (Rajkhowa *et al*., 1997). Low HDL-C has been reported to be the most important lipoprotein profile predictor for the occurrence and mortality of cardiovascular disease (Bass *et al*., 1993; Corti *et al*., 1995).

Sex hormone-binding globulin (SHBG) is a blood transport protein for testosterone and estradiol (Petra, 1991). SHBG is derived primarily from the liver (Kahn *et al*., 2002) and has been noted to be lower in women with PCOS compared with those without PCOS. A low SHBG level is inversely associated with C-reactive protein (Joffe *et al*., 2005), an inflammatory marker associated with an increased risk for cardiovascular disease, and has also been reported to be associated with a higher degree of insulin resistance, thereby serving as a biomarker for the metabolic syndrome (Cikim *et al*., 2004; Heald *et al*., 2005) and cardiovascular disease (Pugeat *et al*., 1995; Sutton-Tyrrell *et al*., 2005). Clearly, SHBG and HDL-C share many common features; both are low in women with PCOS, are secreted partially from the liver and are negatively associated with hepatic lipase activity (von Eckardstein *et al*.,

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2000; Kahn *et al*., 2002; Desmeules *et al*., 2003). Also, both SHBG and HDL-C are influenced by insulin resistance and obesity (Ducluzeau *et al*., 2003). Moreover, SHBG had been proposed in several observational studies to be a major determinant of the lipid profile, especially the levels of HDL-C and triglycerides (Bataille *et al*., 2005; Mudali *et al*., 2005; Sutton-Tyrrell *et al*., 2005). However, previous studies have focused on middle-aged men (Bataille *et al*., 2005) and peri- or postmenopausal women (Mudali *et al*., 2005; Sutton-Tyrrell *et al*., 2005), leaving the relationship between HDL-C and SHBG not being well studied in young women, especially in women with PCOS. In this study, therefore, we aimed to investigate the association between HDL-C and SHBG in young women with PCOS, who have not undergone treatment for the disorder.

Materials and methods

Subjects

A total of 106 women with PCOS, not undergoing treatment, were enrolled in the current study. They registered for care in our reproductive endocrinology clinic with a chief complaint of irregular menstrual cycles and/or clinical hyperandrogenism. The Institutional Review Board of National Taiwan University Hospital approved the study, and all patients and/or their parents signed an informed consent before data collection commenced. The diagnosis of PCOS was made according to the criteria proposed at the Rotterdam revised consensus meeting (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), that is, the presence of oligomenorrhoea or amenorrhoea, clinical hyperandrogenism and/or hyperandrogenaemia and polycystic ovaries as visualized by pelvic ultrasonography (Balen *et al*., 2003). Oligomenorrhoea was defined as less than eight spontaneous menstrual cycles per year, with an interval between cycles greater than 45 days within the 3 years before enrollment. Hyperandrogenism was defined as an elevated serum total testosterone level (i.e. >0.8 ng ml^{-1}) with persistent acne or hirsutism (i.e. a Ferriman and Gallwey score >8) or with androgenic alopecia. Women with disorders of non-ovarian origin that are known to be aetiologic for anovulation or hyperandrogenism, such as hyperprolactinaemia, thyroid dysfunction, Cushing syndrome, congenital adrenal hyperplasia and adrenal tumours, as well as virilizing ovarian tumours, were ineligible for participation. All subjects were non-smokers with regular daily activity and were not regular consumers of alcoholic beverages. For subjects with an alanine aminotransferase (ALT) >35 U l^{-1}, abdominal sonography and test to detect hepatic viral markers were carried out to exclude organic lesions in the liver.

Additional exclusion criteria included an ongoing pregnancy, pregnancy in the past year, prescription of oral contraceptives or other medications that have an effect on the hypothalamic–pituitary–ovarian axis within the previous 6 months and a concomitant major systemic disease, such as autoimmune disease, malignancy, central nervous system disease, prior chemotherapy or immunosuppressive agents.

Data collection

For women with spontaneous menstrual cycles, blood samples were collected between the third and seventh day of a spontaneous menstrual cycle between 08.00 and 10.00 hours after an overnight fast. For women with amenorrhoea for longer than 3 months, blood samples were collected without hormone-induced withdrawal bleeding with pelvic sonography and determination of the serum progesterone level. If a dominant follicle was present by sonography, the serum estradiol level exceeded 150 pg ml^{-1}, or the serum progesterone was >2 ng ml^{-1}, the blood sample was discarded. The subjects were then asked to measure their basal body temperature, and blood samples were collected during the next cycle about 2–3 weeks following the menstruation which occurred after spontaneous ovulation. The blood was processed within 30 min of collection. Blood glucose and insulin samples were stored at 4°C and analysed on the day of sampling. The serum and plasma were aliquoted and frozen at −70°C until assay. Anthropometric measurements, pelvic sonography and the measurement of blood pressure were done on the day of venipuncture. BMI was calculated as the weight (kg) divided by the height (m^2).

The five components of the metabolic syndrome were established by the modified Asian criteria from the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III (Tan *et al*., 2004) and included a systolic blood pressure (SBP) ≥130 mmHg and/or a diastolic blood pressure (DBP) ≥85 mmHg, a fasting glucose ≥100 mg dl^{-1}, a fasting triglyceride ≥150 mg dl^{-1}, an HDL-C <50 mg dl^{-1} and abdominal obesity (waist circumference for women >80 cm).

Assay methods

The concentration of plasma glucose was measured with an autoanalyzer (Toshiba TBA-120 FR; Toshiba, Tokyo, Japan). The serum levels of total testosterone, low-density lipoprotein (LDL) cholesterol, HDL-C, triglycerides and ALT were measured with a biochemical autoanalyzer (Toshiba TBA-200FR; Toshiba). Serum insulin levels were determined by a microparticle enzyme immunoassay using an AxSYM system (Abbott Laboratories, Dainabot Co., Tokyo, Japan). The homeostasis model assessment was applied to estimate the degree of insulin resistance [HOMA-IR = (glucose × 0.05551) × insulin/22.5] and β cell function [HOMA-β-cell = 20 × insulin/(glucose × 0.05551) – 3.5], where insulin is expressed in μU ml^{-1}, and glucose is expressed in mg dl^{-1}, as previously described (Matthews *et al*., 1985). Serum FSH, LH, estradiol and progesterone were measured by indirect chemiluminescence (Vitros Eci; Ortho-Clinical Diagnostics, Rochester, NY, USA). Serum SHBG was measured by electrochemiluminescence (Elecsys 2010; Roche Diagnostics GmbH, Mannheim, Germany). Serum total testosterone and dehydroepiandrosterone sulphate (DHEA-S) were measured by radioimmunoassay (RIA; Diagnostic Systems Laboratories, Webster, TX, USA). The free androgen index (FAI) was calculated according to the equation, FAI (%) = testosterone (ng ml^{-1}) × 3.47 × 100/SHBG (nmol l^{-1}). The intra-assay and inter-assay coefficients of variation (CVs) of the aforementioned assays were all <10%.

Statistical analyses

The numeric variables are presented as the means ± SD, unless indicated otherwise. The difference between high and low HDL-C groups was calculated with two-sample Student's *t*-test. Pearson correlation coefficients were calculated to investigate the correlations between the clinical characteristics and the HDL-C or SHBG levels. Forward stepwise multiple linear regression models were performed using HDL-C as the dependent variable and anthropometric, metabolic, liver function and hormonal factors as independent variables. Logistic regression analysis was performed to assess the relationship between categorical data of HDL-C (with a threshold value at 50 mg dl^{-1}) and SHBG after adjustment for anthropometric, metabolic, liver function and hormonal factors. In multiple linear and logistic models, only BMI, HOMA-IR and total testosterone, representing waist circumference, fasting glucose and insulin and FAI, respectively, were used to avoid collinearity. Logistic regression analysis was also applied to demonstrate the association between the metabolic syndrome and the level of SHBG. The presence of the metabolic syndrome was used as a dependent variable and the level of SHBG as an independent variable after adjustment for age. The least square (LS) means of SHBG levels

were calculated after adjustment for age among the subjects with different numbers of metabolic syndrome characteristics by using ANOVA. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using the PC version of the Statistical Analysis System (SAS, edition 9.1, SAS Institute Inc., Cary, NC, USA).

Results

Among the 106 participants, 95 subjects were nulligravidas before enrollment (89.6%). The mean age of the participants was 24.9 ± 4.8 years (range, 16–37), and 78% of the women were in the third decade of life. The basic characteristics of these subjects are summarized in Tables I and II. The frequency distributions of the five parameters of the metabolic syndrome amongst the participants were as follows: 65.1% (69 had an HDL-C level <50 mg dl^{-1}), 35.9% (38 had a waist circumference >80 cm), 6.9% (7 had a fasting glucose level ≥100 mg dl^{-1}), 11.3% (12 had a SBP ≥130 mmHg or a DBP ≥85 mmHg) and 10.4% (11 had a fasting triglyceride level ≥150 mg dl^{-1}). The prevalence of the metabolic syndrome was 16.0% (17/106). There was only one subject who met the diagnostic criteria for diabetes, and no subjects met the diagnostic criteria for hypertension. Among a total of 23 subjects with an ALT level >35 U l^{-1}, three were hepatitis B virus carriers, one was a hepatitis C virus carrier and no subjects had organic lesions based on abdominal sonography.

Table I. Clinical and hormonal characteristics of the 106 women with PCOS

	n (%)	Mean (SD)
Nulliparity	97 (91.5)	
BMI <20 (kg m^{-2})	31 (29.2)	
BMI 20–24 (kg m^{-2})	36 (34)	
BMI 25–29 (kg m^{-2})	20 (18.9)	
BMI ≥30 (kg m^{-2})	19 (17.9)	
Hirsutism	53 (50.0)	
Acne	48 (45.28)	
Androgenic alopecia	23 (21.7)	
Estradiol (pg ml^{-1})		41.1 (24.6)
FSH (mIU ml^{-1})		5.4 (1.2)
LH (mIU ml^{-1})		11.6 (6.6)
DHEA-S (μg dl^{-1})		300.4 (94.2)

DHEA-S, dehydroepiandrosterone sulphate.

HDL-C levels correlated significantly with waist circumference, BMI, fasting glucose and insulin levels, HOMA-IR, HOMA-β cell, total cholesterol, triglyceride and SHBG levels, FAI and SBP, but no such correlation existed with total testosterone, LDL-cholesterol, DBP or ALT levels (Table II). On the contrary, SHBG levels correlated with waist circumference, BMI, fasting glucose and insulin levels, HOMA-IR, HOMA-β cell, total testosterone, triglyceride and HDL-C levels, FAI, SBP, DBP and ALT levels but not with estradiol, total cholesterol or LDL-cholesterol levels (Table II). Notably, HDL-C levels were significantly correlated with SHBG levels among these women with PCOS.

The women with PCOS were further divided into two groups, (i) HDL-C <50 mg dl^{-1} and (ii) HDL-C ≥50 mg dl^{-1}. The metabolic profiles, including plasma glucose and insulin levels, HOMA-IR, HOMA-β-cell, triglyceride and ALT levels as well as BMI, SBP, DBP and waist circumference, were significantly higher in women with HDL-C <50 mg dl^{-1} than in those women with HDL-C ≥50 mg dl^{-1} (Table III). No difference existed in the concentrations of LDL-cholesterol, estradiol, total testosterone and DHEA-S between the two groups. In contrast, the SHBG level was significantly lower in the lower HDL-C group in comparison with the higher HDL-C group ($P < 0.0001$, Table III).

After calculation using forward stepwise multiple linear regression analyses, the HDL-C level was significantly ($P < 0.0001$) related to the SHBG level after adjustment for age, as well as for age, BMI, plus any one of the following variables:

Table II. Basic characteristics of women with PCOS and the correlation between high-density lipoprotein cholesterol (HDL-C), as well as sex hormone-binding globulin (SHBG) and anthropometric, hormonal and metabolic variables

	Mean (SD)	HDL-C (mg dl^{-1})		SHBG (nmol l^{-1})	
		γ	*P*-value	γ	*P*-value
Age (years)	24.9 (4.8)	–0.0267	NS	–0.0508	NS
Waist circumference (cm)	78.6 (13.6)	–0.3525	<0.001	–0.5601	<0.0001
BMI (kg m^{-2})	24.3 (5.9)	–0.3967	<0.0001	–0.5610	<0.0001
Glucose (mg dl^{-1})	85.0 (12.2)	–0.2338	<0.05	–0.3339	<0.001
Insulin (μU ml^{-1})	13.2 (12.3)	–0.3446	<0.001	–0.4767	<0.0001
HOMA-IR	3.0 (3.6)	–0.3194	<0.001	–0.4305	<0.0001
HOMA-β cell	212.4 (154.6)	–0.3468	<0.001	–0.4329	<0.0001
LDL-cholesterol (mg dl^{-1})	104.8 (30.7)	0.0060	NS	–0.1264	NS
HDL-C (mg dl^{-1})	46.9 (10.4)			0.6034	<0.0001
Total cholesterol (mg dl^{-1})	191.3 (36.3)	0.4579	<0.0001	0.1430	NS
Triglyceride (mg dl^{-1})	85.8 (46.7)	–0.2710	<0.01	–0.3574	<0.001
Total testosterone (ng ml^{-1})	0.98 (0.38)	–0.1383	NS	–0.3265	<0.001
SHBG (nmol l^{-1})	38.4 (22.6)	0.6034	<0.0001		
FAI (%)	13.5 (11.9)	–0.3363	<0.001	–0.6657	<0.0001
SBP (mmHg)	112.2 (15.0)	–0.3154	<0.005	–0.4006	<0.0001
DBP (mmHg)	72.3 (10.6)	–0.1642	NS	–0.2334	<0.05
ALT (U l^{-1})	26.7 (33.8)	–0.1218	NS	–0.2900	<0.005

ALT, alanine aminotransferase; DBP, diastolic blood pressure; FAI, free androgen index; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β cell, homeostasis model assessment of β cell function; LDL, low-density lipoprotein; NS, not significant by $P \geq 0.1$; SBP, systolic blood pressure; γ, Pearson correlation coefficient.

Table III. The differences between anthropometric, hormonal and metabolic variables in the two groups of subjects using 50 mg dl^{-1} as a threshold value for HDL-C

	HDL-C <50 (mg dl^{-1}) (n = 69)	HDL-C ≥50 (mg dl^{-1}) (n = 37)	P-value
Age (years)	25.4 ± 5.3	24.1 ± 3.7	NS
Waist circumference (cm)	82.6 ± 14.2	71.4 ± 8.8	<0.0001
BMI (kg m^{-2})	26.2 ± 5.9	20.7 ± 3.9	<0.0001
Glucose (mg dl^{-1})	87.4 ± 14.1	80.4 ± 5.7	<0.005
Insulin (μU ml^{-1})	16.5 ± 13.9	6.9 ± 3.8	<0.0001
HOMA-IR	3.9 ± 4.1	1.4 ± 0.8	<0.0001
HOMA-β cell	248.2 ± 175.2	144.7 ± 66.2	<0.001
Total cholesterol (mg dl^{-1})	183.8 ± 36.8	205.3 ± 25.4	<0.005
Triglyceride (mg dl^{-1})	96.5 ± 43.8	65.8 ± 28.3	<0.0001
SHBG (nmol l^{-1})	29.1 ± 14.5	55.8 ± 24.9	<0.0001
FAI (%)	16.7 ± 13.1	7.5 ± 6.1	<0.0001
SBP (mmHg)	115.6 ± 13.6	106.0 ± 15.6	<0.005
DBP (mmHg)	74.1 ± 11.2	69.1 ± 8.6	<0.05
ALT (U l^{-1})	30.9 ± 40.3	18.9 ± 13.2	<0.05

ALT, alanine aminotransferase; DBP, diastolic blood pressure; FAI, free androgen index; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β cell, homeostasis model assessment of β cell function; NS, not significant at $P \geq 0.1$; SHBG, sex hormone-binding globulin; SBP, systolic blood pressure.
Values are expressed as mean ± SD.

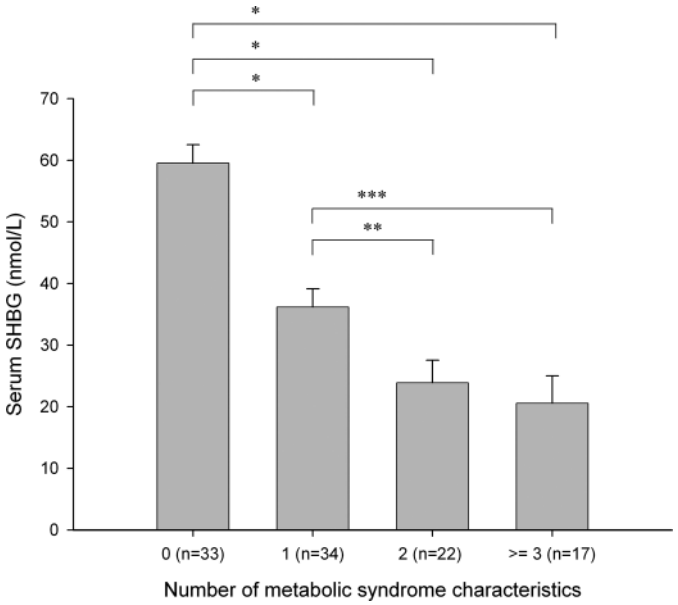

Figure 1. The serum sex hormone-binding globulin (SHBG) level (least square mean ± SE) after adjustment for age among PCOS women with different numbers of metabolic syndrome components. *P < 0.0001; **P < 0.01; ***P < 0.005 by ANOVA.

total testosterone, triglycerides, insulin, glucose, HOMA-IR, ALT and total cholesterol. In the final multivariable model, the HDL-C level remained significantly (P < 0.0001) related to the SHBG level after adjustment for age, BMI, total testosterone and triglyceride levels, HOMA-IR, ALT and total cholesterol levels. Utilizing logistic regression analysis with adjustment for age, testosterone, triglyceride and ALT levels, HOMA-IR and BMI, the increased SHBG level per nmol l^{-1} was associated with a higher probability of an HDL-C level greater than 50 mg dl^{-1}, with an odds ratio of 1.054 (95% confidence interval 1.02, 1.09; P = 0.0025). If waist circumference was used instead of BMI in the same logistic model, the increased SHBG level per nmol l^{-1} was still significantly associated with a higher probability of an HDL-C level >50 mg dl^{-1}, with an odds ratio of 1.059 (95% confidence interval 1.02, 1.10; P = 0.0014).

The age-adjusted LS means of SHBG levels were the highest in women with PCOS without metabolic syndrome characteristics and was significantly higher than that of the subjects exhibiting one, two and greater than two components of the metabolic syndrome (P < 0.0001, Figure 1). The LS means of SHBG levels were also significantly higher in women with PCOS with only one characteristic of the metabolic syndrome in comparison with those with two or more characteristics of the metabolic syndrome (P < 0.01 and P < 0.005 separately, Figure 1). With logistic regression adjusted for age, the increased SHBG concentration per nmol l^{-1} was associated with a decreased probability of having the metabolic syndrome, with an odds ratio of 0.92 (95% confidence interval 0.87, 0.97; P = 0.003).

Discussion

Women with PCOS have been well characterized as having a high FAI, decreased HDL-C and SHBG levels and a high susceptibility to cardiovascular disease (Rajkhowa *et al*., 1997; Talbott *et al*., 2000; Xita *et al*., 2003; Ehrmann, 2005; Ehrmann *et al*., 2006). In this study, we found a positive correlation between HDL-C and SHBG levels after adjusting for many anthropometric and metabolic factors. Decreased HDL-C and SHBG levels have been reported to be associated with insulin resistance and obesity in women with PCOS (Jayagopal *et al*., 2003; Xita *et al*., 2003; Ehrmann, 2005). Our data showed that decreased levels of SHBG in women with PCOS were associated with decreased levels of HDL-C, independent of insulin resistance and obesity. SHBG is a blood-transport protein for testosterone and estradiol, and its concentration is regulated by testosterone and estradiol (Petra, 1991). In addition, the genetic influence of SHBG on the phenotype of women with PCOS has been reported in several studies (Xita *et al*., 2003; Cousin *et al*., 2004). Both SHBG and HDL-C are secreted by the liver, and their blood concentrations are negatively correlated with hepatic lipase activity (von Eckardstein *et al*., 2000; Kahn *et al*., 2002; Desmeules *et al*., 2003). Our results suggest that the HDL-C level is independently correlated with the SHBG level after controlling for sex steroid level and liver function.

Several studies in post-menopausal women have shown that although the total testosterone level does not change significantly during the menopausal transition, there is a significant fall in circulating SHBG, together with an increase in the free testosterone level, as indicated by the FAI (Burger *et al*., 2000; Rexrode *et al*., 2003). These may explain the coincidental decrease of HDL-C and the increased risk of cardiovascular disease after the menopause (Haffner *et al*., 1992). On the contrary, hormone replacement therapy in post-menopausal women has been shown to increase the circulating SHBG level accompanied by an elevation in HDL-C (Abbas *et al*., 2004).

The current study was cross-sectional, and a causal relationship between HDL-C and SHBG levels was not established. It has been reported that SHBG, like HDL-C, has a strong negative association with hepatic lipase activity (Desmeules *et al*., 2003). The biologic mechanism underlying the correlation between HDL-C and SHBG is not clear but may involve a regulatory effect of androgen on hepatic lipase activity. However, we speculate that SHBG might exert some direct or indirect effects on HDL-C metabolism.

SHBG may mediate its effect on HDL-C by regulating bioavailable testosterone. Because SHBG binds preferentially to testosterone, a decrease in SHBG increases the amount of circulating free testosterone. A high FAI in women was reported to contribute to a low HDL-C level (Korytkowski *et al*., 2005). In men, testosterone substitution increases the activity of hepatic lipase (Sorva *et al*., 1988). However, it is possible that SHBG has metabolic actions of its own. SHBG may act not only as a plasma carrier protein but also as a part of the signal transduction pathway that mediates the signalling of androgen and estrogen at the cell membrane (Rosner *et al*., 1999; Kahn *et al*., 2002). Furthermore, there are reports directly linking low SHBG levels to a high risk of cardiovascular disease (Bataille *et al*., 2005; Joffe *et al*., 2005; Sutton-Tyrrell *et al*., 2005). Low SHBG levels may also lead to a low HDL-C level.

Middle-aged women with PCOS have been found to have a greater prevalence of carotid artery atherosclerosis and coronary artery disease than age-matched women without PCOS (Talbott *et al*., 2000; Christian *et al*., 2003). Orio *et al*. (2004) reported that women with PCOS may undergo asymptomatic adverse alterations in the cardiovascular system at an early age. In this study, we also found that a low SHBG level was strongly associated with the occurrence of the metabolic syndrome. Both low SHBG levels and the metabolic syndrome were reported to indicate a severe degree of insulin resistance (Cikim *et al*., 2004). The low SHBG status in young women with PCOS is associated with low HDL-C levels and the metabolic syndrome, which may increase the risk of cardiovascular disease in later years. This finding is consistent with previous reports.

Because of different dietary, genetic and environmental factors, the prevalence of insulin resistance in women with PCOS, presenting as obesity and metabolic syndrome, is quite different among different ethnicities (Carmina *et al*., 1992; Wijeyaratne *et al*., 2002). Carmina *et al*. (1992) proposed that obesity and hirsutism, but not the level of androgens, were less common in women with PCOS from Japan than in women from the United States and Italy. In a recent large multi-centre study, the high prevalence of metabolic syndrome (33.4%) in women with PCOS was noted in South American and Caucasian women associated with a high BMI after adjusting for age, in which the prevalence of a decreased HDL-C level (<50 mg dl^{-1}) was about 66% (Ehrmann *et al*., 2006). The criteria for metabolic syndrome in that study were the same as in this study, except that they utilized a waist circumference greater than 88 cm as the criterion for abdominal obesity and a fasting glucose >110 mg dl^{-1} as the definition of glucose intolerance. Because our subjects were younger and had a lower BMI than that in the previous study (Ehrmann *et al*., 2006), a relatively low prevalence of metabolic syndrome (16.0%) was acceptable in this study. However, the prevalence of a low HDL-C level (<50 mg dl^{-1}) was high (65.1%), similar to that in the previous report (Ehrmann *et al*., 2006), implying that the level of HDL-C may play an important role in women with PCOS, even though of a different ethnicity.

Several studies (Pinheiro *et al*., 2005; Sowers *et al*., 2005; Sutton-Tyrrell *et al*., 2005) conducted in middle-aged women showed that Asian women, especially Chinese and Japanese women, had markedly lower SHBG levels associated with a higher FAI, in comparison with women of other ethnicities. In some studies conducted in the breast cancer population, it was revealed that even living in the same geographic area, Asian-American women were noted to have lower SHBG levels than Caucasians (Pinheiro *et al*., 2005), but the level of SHBG in Asian offspring did not differ significantly regardless of birthplace (Falk *et al*., 2002). The association between SHBG and HDL-C levels are particularly stronger in Chinese and Japanese women (Sutton-Tyrrell *et al*., 2005). Although the mechanisms that link SHBG to HDL-C are still unclear, the racial differences imply a possible genetic background; however, the impact from nutrition, exercise and other parameters should also be considered.

In conclusion, a high prevalence of decreased HDL-C levels was found in Taiwanese women with PCOS, although they had a lower prevalence of obesity and the metabolic syndrome. A low SHBG level is independently associated with a low level of HDL-C and is associated with the occurrence of the metabolic syndrome, implying that a low SHBG level might increase the risk of cardiovascular disease in women with PCOS.

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