Serum retinol-binding protein 4 levels in nonobese women with polycystic ovary syndrome

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Objective: To test whether there was a difference in serum retinol-binding protein 4 (RBP4) levels between subjects with polycystic ovary syndrome (PCOS) and those with a healthy regular menstrual cycle and, in addition, to correlate serum RBP4 levels with a variety of parameters.
Design: Clinical study.
Setting: University hospital.
Patient(s): A total of 74 nonobese women were evaluated. Thirty-seven had PCOS, whereas the remaining 37 served as control subjects.
Intervention(s): Serum RBP4 levels were analyzed using ELISA.
Main Outcome Measure(s): Serum levels of FSH, LH, TSH, E_2, T, insulin, glucose, cholesterol, triglycerides, and RBP4.
Result(s): The women with PCOS had higher levels of serum RBP4, waist-to-hip ratio, LH, T, insulin, homeostatic model assessment of insulin resistance, cholesterol, and triglycerides. Logistic regression analyses revealed a significant association between odds ratio (OR) values of PCOS and both T (OR = 1.125; 95% confidence interval [CI] 1.050–1.205), and cholesterol levels (OR = 1.029; 95% CI 1.004–1.056). Age and triglycerides were significantly correlated to serum RBP4 levels by multiple linear regression analysis.
Conclusion(s): Our study has shown that [1] elevated RBP4 levels might arise from triglyceride metabolism, and that RBP4 levels might not be influenced by PCOS itself. [2] RBP4 might not be a useful marker of insulin resistance in subjects with PCOS. (Fertil Steril® 2010;93:869–73. ©2010 by American Society for Reproductive Medicine.)

Key Words: RBP4, polycystic ovary syndrome, triglycerides

Polycystic ovary syndrome (PCOS), expressed as chronic anovulation and hyperandrogenism, is a common reproductive disorder (1, 2). It is linked with insulin resistance and dyslipidemia (3). Insulin resistance is found in both lean and obese patients with PCOS, and PCOS may independently affect insulin resistance (4). Under conditions of insulin resistance, catecholamine-induced lipolysis is accelerated in visceral fat cells (5). Disturbances in fatty acid released from visceral adipose tissue through visceral adipocyte lipolysis may play a major pathophysiological role in causing hyperinsulinemia, dyslipidemia, glucose intolerance, and insulin resistance (6).

Retinol-binding protein 4 (RBP4) is known as a transporter for retinol (vitamin A) (7). Hepatocytes are considered the main source of circulating RBP4, but adipose tissue has the second highest expression level (20%–40% of levels in the liver) (8). RBP4 is regarded as an adipokine and has recently been shown to contribute to insulin resistance in mouse models (9). A decrease in glucose transporter 4 expression is accompanied by an increased expression and secretion of RBP4 in the fatty tissue of obese animals (10). RBP4 impairs insulin signaling in muscle, inhibiting glucose uptake, and interfering with insulin-mediated suppression of glucose production in the liver (10, 11). The RBP4 levels correlate with the magnitude of insulin resistance in subjects

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with obesity, impaired glucose tolerance, type 2 diabetes mellitus, or gestational diabetes mellitus, and metabolic syndrome (12, 13).

Because RBP4 is produced by adipose tissue and associated with insulin resistance, we investigated whether there was a difference in serum RBP4 levels between subjects with PCOS and those with a healthy regular menstrual cycle. We also set out to correlate serum RBP4 levels with a variety of parameters.

MATERIALS AND METHODS

Thirty-seven women with PCOS were enrolled into the study along with 37 healthy women with regular menstrual cycles to serve as control subjects. All women had visited the outpatient Department of Obstetrics of the Kaohsiung Medical University Hospital. Women with hyperprolactinemia, thyroid disease, hypertension, diabetes mellitus, and other chronic diseases were excluded. The approval of the institute review board (IRB) was obtained.

Women were diagnosed with PCOS based on the revised 2003 consensus on PCOS diagnostic criteria (14). They included clinical findings of hyperandrogenism of ovarian origin, chronic anovulation (both oligomenorrhea and amenorrhea), and a typical ovarian appearance on transvaginal ultrasound (2 of 3). A precise medical and obstetric history, including body mass index (BMI), was obtained. Nonobese subjects are defined as BMI less than 26 kg/m^2.

To make biochemical and hormonal determinations, blood samples were obtained directly from all subjects from a cannulated vein after overnight fasting. The serum was separated by centrifugation, and stored at -80°C until further analysis. FSH, LH, T, E_2, TSH, and insulin were measured with a Coat-A-count radioimmunoassay kit (Diagnostic Products Corp., Los Angeles, CA). Prolactin was measured with a RIA kit (DiaSorin, Saluggia, Italy). Insulin resistance was estimated by the homeostatic model assessment of insulin resistance (HOMA-IR), using the following formula: HOMA-IR = [fasting insulin (μIU/mL) × fasting glucose (mg/dL)/18]/22.5. Glucose, hemoglobin A_{1c}, cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol were analyzed by LX-20 pro chemistry analyzers (Beckman Coulter, Brea, CA). Serum RBP4 levels were analyzed by an ELISA kit according to the manufacturer's instructions (Immundiagnostik AG, Bensheim, Germany). The intra-assay and interassay coefficients of variation (CV) were 6.5% and 14.5%, respectively.

Data were evaluated with SPSS software for Windows (version 11.0; SPSS Inc., Chicago, IL). Data were presented

TABLE 1

Clinical data.

	PCOS (N = 37)	Control (N = 37)	*P* value
RBP4 (ng/mL)	4.4 ± 2.0	3.7 ± 1.3	.047[a]
Age (y)	27.9 ± 5.2	29.3 ± 4.8	.215
Body height (cm)	161.2 ± 6.3	160.0 ± 5.4	.391
Body weight (kg)	58.0 ± 12.3	53.4 ± 7.2	.055
Body mass index (kg/m^2)	22.2 ± 4.1	20.8 ± 2.9	.098
Waist-to-hip ratio	0.77 ± 0.06	0.74 ± 0.05	.039[a]
FSH (mIU/mL)	6.1 ± 1.9	5.9 ± 3.0	.728
LH (mIU/mL)	9.1 ± 4.3	5.6 ± 3.3	.000[a]
E_2 (pg/mL)	75.9 ± 30.9	74.5 ± 33.9	.847
T (ng/dL)	53.0 ± 25.3	33.1 ± 9.2	.000[a]
TSH (μIU/mL)	2.0 ± 1.0	1.9 ± 0.7	.527
Glucose (mg/dL)	88.2 ± 8.7	87.2 ± 7.7	.632
Insulin (μIU/mL)	6.4 ± 5.6	4.3 ± 2.4	.039[a]
HOMA-IR	1.4 ± 1.3	0.9 ± 0.6	.037[a]
Hemoglobin A_{1c} (%)	5.3 ± 0.3	5.2 ± 0.3	.070
Cholesterol (mg/dL)	188.8 ± 24.9	175.6 ± 31.5	.049[a]
Triglycerides (mg/dL)	67.9 ± 30.4	54.6 ± 26.3	.048[a]
HDL cholesterol (mg/dL)	56.5 ± 16.0	58.5 ± 13.2	.545
LDL cholesterol (mg/dL)	118.4 ± 22.1	106.3 ± 32.2	.064

Note: Values are expressed as mean ± SD. PCOS refers to women with polycystic ovary syndrome; Control refers to women in the control group.

RBP4 = retinol-binding protein 4; HOMA-IR = homeostatic model assessment of insulin resistance; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

[a] $P<.05$ (Student's *t* test).

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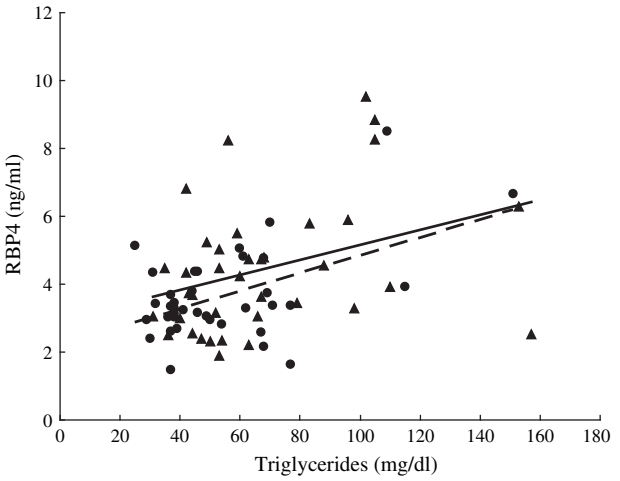
FIGURE 1

Serum retinol-binding protein 4 (RBP4) levels plotted against triglycerides levels for subjects with PCOS (*closed triangle*) and those in the control group (*closed circle*). The solid and dashed lines indicate the regression lines for the PCOS and control group, respectively. Total: $r = 0.438$, $r^2 = 0.192$, $P<.001$; PCOS: $r = 0.346$, $r^2 = 0.120$, $P=.036$; Control: $r = 0.514$, $r^2 = 0.264$, $P=.001$.



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as mean ± SD. Differences between groups were evaluated with a Student's *t* test. Pearson correlation, multiple linear regression analysis, and logistic regression analysis were carried out to determine the relationships between the variables. All tests were two-tailed, and the significance level was defined as $P<.05$.

RESULTS

Table 1 shows the clinical characteristics of our subjects, those with PCOS and those in the healthy control group. Subjects were of similar age, with the mean being 27.9 years for PCOS cases and 29.3 years for the control group. There were no major differences between the two groups with respect to BMI, FSH, E_2, and TSH, glucose, hemoglobin A_{1c}, HDL cholesterol, and LDL cholesterol. However, PCOS cases had higher levels of serum RBP4, waist-to-hip ratio, LH, T, insulin, HOMA-IR, cholesterol, and triglycerides. A correlation figure with serum RPB4 levels plotted against triglyceride levels is shown in Figure 1.

Additional logistic regression analyses were performed to evaluate possible determinants of PCOS, with adjustments being made for age and BMI. We calculated odds ratio (OR) values for RBP4, E_2, T, TSH, hemoglobin A_{1c}, HOMA-IR, cholesterol and triglycerides levels, BMI, and age to compare and evaluate their contribution to PCOS. There was a significant association between OR values of PCOS and both T (OR = 1.125; 95% confidence interval [CI] 1.050–1.205) and cholesterol levels (OR = 1.029; 95% CI 1.004–1.056) (Table 2).

TABLE 2

Logistic regression analysis of the possible determinants of PCOS.

Variable	Exp(B)	Exp(B) 95% CI	*P* value
RBP4	1.335	0.824–2.163	.240
Age	0.936	0.806–1.087	.389
BMI	0.955	0.743–1.228	.720
E_2	1.006	0.986–1.027	.537
T	1.125	1.050–1.205	.001[a]
TSH	1.218	0.567–2.619	.614
Hemoglobin A_{1c}	2.338	0.206–26.497	.493
HOMA-IR	1.124	0.401–3.149	.824
Cholesterol	1.029	1.004–1.056	.024[a]
Triglycerides	0.992	0.961–1.023	.602

PCOS = polycystic ovary syndrome; RBP4 = retinol-binding protein 4; CI = confidence interval; BMI = body mass index; HOMA-IR = homeostatic model assessment of insulin resistance.

[a] $P<.05$.

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Multiple linear regression analysis was performed to study the relationship between serum RBP4 levels and demographic characteristics and biochemical markers. Serum RBP4 level was used as the dependent variable, whereas age, BMI, waist-to-hip ratio, T, E_2, TSH, HOMA-IR, hemoglobin A_{1c}, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and the dichotomy variable PCOS/control were used as independent variables. Age ($P=.044$) and triglycerides ($P=.003$) were significantly correlated to serum RBP4 levels (Table 3).

DISCUSSION

Patients with PCOS often display an impairment of insulin-stimulated glucose utilization in peripheral tissue (15). In our study, we found increased RBP4 levels, hyperandrogenemia, hypercholesterolemia, and increased insulin resistance, all prominent features of PCOS (Table 1). This is consistent with a recent study by Weiping et al. (16), which suggests that RBP4 may be a linking factor between adipose tissue and insulin resistance in PCOS. Furthermore, Hahn et al. (17) found that RBP4 levels were elevated in PCOS women with obesity and impaired glucose metabolism. Tan et al. (18) found increased serum RBP4 in overweight women with PCOS. After adjustment for TSH, E_2, glucose, insulin, triglycerides levels, age, and BMI, logistic regression analysis found that cholesterol and T, but not RBP4 levels, were increased in women with PCOS (Table 2). This is consistent with two recent studies: one conducted by Hahn et al. (17), which did not detect a difference between lean PCOS and controls, and the other carried out by Hutchison et al. (19),

TABLE 3

Multiple linear regression analysis of the possible determinants for serum retinol-binding protein 4 level.

	Coefficients				
	Unstandardized coefficients		Standardized coefficients		
	β	SE	*β*	*t*	*P* value
Independent variables					
(constant)	−4.147	4.506		−0.920	.361
Age	0.084	0.041	0.248	2.061	.044[a]
BMI	0.060	0.083	0.126	0.720	.474
Waist-to-hip ratio	−6.228	4.728	−0.208	−1.317	.193
T	0.010	0.012	0.127	0.868	.389
E_2	−0.003	0.006	−0.054	−0.467	.642
TSH	0.257	0.221	0.128	1.165	.249
HOMA-IR	−0.406	0.281	−0.247	−1.447	.153
Hemoglobin A_{1c}	1.041	0.663	0.191	1.570	.122
Cholesterol	0.006	0.014	0.097	0.404	.688
Triglycerides	0.029	0.009	0.499	3.131	.003[a]
HDL cholesterol	0.006	0.021	0.053	0.296	.768
LDL cholesterol	0.001	0.014	0.016	0.068	.946
PCOS/control	0.359	0.432	0.106	0.832	.409

Note: The dependent variable is serum RBP4 level. The model ($r = 0.607$, $r^2 = 0.368$, $P = .006$). Dichotomy variable (PCOS = 1/control = 0); PCOS refers to women with polycystic ovary syndrome, and control refers to women in the control group.

HOMA-IR = homeostatic model assessment of insulin resistance; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

[a] $P < .05$.

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which found no difference in RBP4 between overweight PCOS and controls. And Möhlig et al. (20) suggested that RBP4 appeared unsuited for metabolic screening in women with PCOS.

Some reports had shown RBP4 to be associated with fatty acid metabolism (21, 22) and that the association between RBP4 and hypertriglyceridemia was particularly strong (12, 17, 22–25). However, the study by Choi et al. (26) detected no significant correlation between triglycerides and RBP4 levels. Our study showed that triglycerides levels are strongly associated with RBP4 levels (Table 3), a finding that is consistent with a previous study where RBP4 levels correlated with hypertriglyceridemia independently of insulin resistance (12). This suggested that impaired fatty acid metabolism may play an important role in regulating RBP4. Triglyceride can accumulate in the liver as ectopic fat (27). Hypertriglyceridemia accompanied by hyperinsulinemia may trigger RBP4 synthesis and secretion in the liver or ectopic fat (23), and RBP4 has been found to be closely related to liver fat (28). Taken together, these results suggested that RBP4 might be a marker for fatty acid metabolism, and that RBP4 levels might not be influenced by PCOS itself.

The results of research into the correlation of RBP4 levels and insulin resistance have been inconsistent. Recent studies have shown positive correlations between circulating RBP4 and insulin resistance assessed by HOMA-IR (12, 23, 28, 29). However, other studies found no such significant relationships (18, 30, 31). This study failed to find any significant correlations between RBP4 and HOMA-IR. Some studies have shown that high plasma RBP4 levels also correlate with low insulin clearance (28) and a negative relationship between RBP4 and insulin secretion has been observed (32). Our results might suggest that RBP4 might not directly affect glucose metabolism or insulin resistance and therefore that it might not be a useful marker of insulin resistance and glucose metabolism in subjects without PCOS.

Because relative hyperestrogenemia, as well as elevated androgen levels, are key features of many patients with PCOS, we investigated the correlation of E_2 and T with RBP4 levels. Our findings showed that RPB4 levels were not directly affected by T and E_2 (Table 3). This is in line with other studies, in which no association was found between RBP4 and systemic gonadal steroids (20) and in which the oral contraceptive pill was shown not to affect RBP4 levels (19). However, a recent study had

shown that RBP4 expression and secretion from adipose tissue was enhanced by 17β-E_2 (18). These results suggested that E_2 and T might not be associated with increased RBP4 levels.

The strength of this study is that it took several significant determinants into account, such as biochemical and hormonal determinations. Especially for TSH, the research by Choi et al. (26) had suggested that RBP4 levels were associated with subclinical hypothyroidism. The retinol-binding protein is easily filtered through the kidney, forming a complex with transthyretin, a transport protein for T_4, and this complex can prevent retinol-binding protein from being cleared by the kidney (33, 34). It is possible that thyroid function could influence the excretion of RBP4 from the kidney. We suggest that TSH should be taken into account as a confounding factor in any analysis model of RBP4. In addition, this study excluded subjects who are overweight to investigate whether PCOS itself would have impact on RBP4 levels. However, the findings did not necessarily apply to the obese subjects with PCOS.

In conclusion, our study showed that [1] elevated RBP4 levels might arise from triglycerides metabolism, and that RBP4 levels might not be influenced by PCOS itself; and [2] RBP4 might not be a useful marker of insulin resistance and glucose metabolism in subjects with PCOS.

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