Lower serum apelin levels in women with polycystic ovary syndrome

We tested differences in serum apelin levels between women with polycystic ovary syndrome (PCOS) and those with a healthy regular menstrual cycle, finding that apelin levels were higher in normal women and that apelin was positively correlated with apolipoprotein A levels. (Fertil Steril® 2011;95:2520–3. ©2011 by American Society for Reproductive Medicine.)

Key Words: Apelin, polycystic ovary syndrome, apoA

Polycystic ovary syndrome (PCOS), expressed as irregular menses and androgen excess, is a common reproductive endocrinologic disorder (1) which affects approximately 7%–8% of women of reproductive age (2). Apart from chronic oligo/anovulation and elevated levels of circulating androgens and/or clinical hyperandrogenism, the main features of the condition include polycystic ovary morphology, increased LH secretion, insulin resistance, hyperinsulinemia, and obesity (3, 4). Women affected by PCOS have a higher risk of type 2 diabetes, dyslipidemia, hypertension, and cardiovascular diseases (5).

Apelin is a bioactive peptide originally identified from bovine stomach extracts as the endogenous ligand of the G protein–coupled receptor APJ (6, 7). Apelin and its receptor are widely expressed in the central nervous system and peripheral tissues (8) and are involved in the regulation of certain pathophysiologic functions, including the cardiovascular system, fluid homeostasis, and endothelial cells (9–11). Recently, apelin has been identified as a new adipokine expressed and secreted by mature adipocytes in both humans and mice (12, 13). Insulin directly regulates apelin expression in human adipocytes via phosphatidylinositol 3-kinase and protein kinase C (13). A positive correlation has been observed between apelin serum levels and body mass index (BMI) (14). Obesity associated with hyperinsulinemia has been shown to cause a large increase in both the expression of apelin in fat cells and the plasma level of apelin in animal models (13). Apelin expression in adipose tissue is regulated by nutritional status, tumor necrosis factor α, growth hormone, and glucocorticoids (15–17). The apelinergic system has been demonstrated to be involved in the pathogenesis of a number of conditions, such as hypertension, heart failure, obesity, glucose intolerance, and diabetes mellitus (DM) (12, 18–20). Apelin also shows strong antiatherogenic action in animal models (21).

Because apelin seems to be a key regulator in normal glucose and lipid metabolism and may be associated with insulin resistance, we wanted to investigate whether there was a difference in serum apelin levels between women with PCOS and women with a healthy and regular menstrual cycle. We also set out to correlate serum apelin levels with hormone and metabolic parameters to investigate the associations between apelin and several markers related to cardiovascular disease to explore the possible properties of apelin.

Fifty women with PCOS were enrolled in the study along with 34 healthy women with regular menstrual cycles to serve as control subjects. All women had visited the outpatient Department of Obstetrics and Gynecology of the Kaohsiung Medical University Hospital. Women with hyperprolactinemia, thyroid disease, hypertension, DM, and other chronic diseases were excluded from the study. A precise medical history, including BMI, was obtained. The approval of the Institute Review Board was obtained. The diagnosis of PCOS was based on the revised 2003 consensus on PCOS diagnostic criteria (22). These included clinical findings of hyperandrogenism, chronic anovulation (both oligomenorrhea and amenorrhea), and a typical ovarian appearance on transvaginal ultrasound (two out of three).

Blood samples were obtained directly from all subjects from a cannulated vein after overnight fasting. FSH, LH, T, E_2, TSH,

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and insulin were measured by using a Coat-a-Count RIA kit (Diagnostic Products). PRL was measured by using a radioimmunoassay kit (Diasorin). 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, glycated hemoglobin, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), apolipoprotein A (apoA), and apolipoprotein B (apoB) were analyzed by LX-20 Pro chemistry analyzers (Beckman Coulter). Serum apelin levels were analyzed by an ELISA kit according to the manufacturer's instructions (Immundiagnostik). The intraassay and interassay coefficients of variation were 5.3% and 12.0%, respectively. Data were evaluated with SPSS software for Windows (version 12.0) and presented as mean ± SD. Differences between groups were evaluated with a Student *t* test. Pearson correlation analysis was carried out to determine the relationships between the variables. All tests were two tailed, and the significance level was defined as $P<.05$.

The clinical features and serum apelin levels are shown in Table 1 for the PCOS and control groups. The PCOS subjects had lower levels of serum apelin (490.6 ± 169.8 ng/mL vs. 616.8 ± 178.9 ng/mL; $P=.002$). The correlations between apelin and T, E_2, P, FSH, LH, insulin, glucose, HOMA-IR, HDL, and LDL were not statistically significant. For the association between serum apelin and markers of lipid metabolism, significant associations were found between apelin and apoA ($r = 0.250$; $P=.022$), TC/HDL ($r = -0.233$; $P=.033$), LDL/HDL ($r = -0.226$; $P=.039$), apoB/apoA ($r = -0.217$; $P=.047$), and the dichotomy variable PCOS/control ($r = -0.340$; $P=.002$; Supplemental Table 1, available online at www.fertstert.org). Multiple linear regression analysis was performed to study the relationship between serum apelin levels and demographic characteristics and biochemical markers. Serum apelin level was the dependent variable, and age, BMI, apoA, AST, ALT, P, HOMA-IR and, the dichotomy variable PCOS/control were used as independent variables. ApoA ($P=.005$), the dichotomy variable PCOS/control ($P=.003$), AST ($P=.015$), and ALT ($P=.039$) were found to be significantly associated with serum apelin levels (Supplemental Table 2, available online at www.fertstert.org).

Our comparison of PCOS and non-PCOS normal subjects found that apelin levels were significantly lower in PCOS subjects. There have been no studies showing the relationship between apelin levels and reproductive function in humans. Recent research on the bovine ovary suggests that the apelin-APJ system is involved in the mechanism that regulates angiogenesis during follicle maturation as well as during corpus luteum formation (23, 24). It has been found that LH induced the expression of apelin and APJ receptor mRNAs in cultured theca cells (25). Apelin mRNA maintains high levels in the early and midluteal stages, declining at the

TABLE 1

Clinical data.

	PCOS (n = 50)	Control (n = 34)	*P* value[a]
Apelin (ng/mL)	490.6 ± 169.8	616.8 ± 178.9	.002[a]
Age (y)	24.8 ± 5.0	28.9 ± 5.0	<.001
FSH (mIU/mL)	6.0 ± 2.0	6.1 ± 1.7	.757
LH (mIU/mL)	9.7 ± 7.5	8.5 ± 6.8	.471
P (ng/mL)	1.5 ± 2.2	2.0 ± 2.6	.414
E_2 (pg/mL)	59.9 ± 35.1	62.6 ± 58.6	.004
T (ng/dL)	46.9 ± 20.2	38.9 ± 13.1	.044
Glucose (mg/dL)	89.4 ± 7.5	87.2 ± 5.8	.155
Insulin (μIU/mL)	5.4 ± 3.2	3.4 ± 1.7	.002
AST (IU/L)	21.2 ± 6.4	19.1 ± 3.9	.088
ALT (IU/L)	21.9 ± 13.7	16.3 ± 4.8	.024
BUN (mg/dL)	10.0 ± 3.1	8.7 ± 2.0	.040
Creatinine (mg/dL)	0.7 ± 0.1	0.7 ± 0.1	.249
Cholesterol (mg/dL)	194.7 ± 30.2	182.1 ± 34.4	.079
Triglycerides (mg/dL)	72.6 ± 33.7	57.7 ± 24.3	.030
HDL (mg/dL)	55.2 ± 17.4	61.8 ± 14.9	.078
LDL (mg/dL)	117.7 ± 27.5	102.4 ± 27.7	.015
ApoA (mg/dL)	164.2 ± 34.0	171.7 ± 27.4	.287
ApoB (mg/dL)	84.7 ± 17.1	74.8 ± 17.6	.012
TC/HDL	3.7 ± 1.0	3.2 ± 0.8	.010
LDL/HDL	2.4 ± 1.0	1.9 ± 0.7	.018
Hemoglobin (g/dL)	13.4 ± 0.9	13.2 ± 1.2	.272
Glycated hemoglobin (%)	5.3 ± 0.3	5.1 ± 0.2	.007
Body mass index (kg/m^2)	22.2 ± 4.1	21.0 ± 2.7	.129
HOMA-IR	1.2 ± 0.8	0.7 ± 0.4	.001

Note: Values are expressed as mean ± SD. ALT = alanine aminotransferase; ApoA = apolipoprotein A; ApoB = apolipoprotein B; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein cholesterol; PCOS = polycystic ovary syndrome; TC = total cholesterol.

[a] Student *t* test.

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end of the luteal phase and then dropping steeply during corpus luteum regression (24). However, the apelin-APJ system is unlikely to be directly involved in the synthesis of P (24). Neither P nor FSH was found to stimulate the expression of apelin in cultured granulosa cells (25). This is consistent with the present study, where we did not find any correlations between apelin and estrogen and P levels.

Apelin has been suggested to play a role in antiatherogenic action (21). It was suggested that lower apelin concentrations were associated with the severity and the acute phase of cardiovascular disease and that apelin was involved in the progression and destabilization of coronary atherosclerotic plaques (26). Individuals with a high total cholesterol/HDL or LDL/HDL ratio and apoB/apoAI ratio had greater cardiovascular risk (27). This ratio reflected the balance between two completely opposite processes: transport of cholesterol to peripheral tissues, and reverse transport to the liver (28). A negative correlation between apelin and cardiovascular risk parameters was found in our study. ApoA, the major structural protein for HDL, has been regarded to be the atheroprotective side of lipid metabolism (29). The present study demonstrated a positive correlation between apoA and apelin levels. Our study revealed that PCOS patients had low apelin and high atherosclerosis markers when they were relatively young. These findings might suggest that PCOS women possess additional risk factors of cardiovascular diseases. Early recognition, proper intervention, and long-term monitoring were therefore necessary, and apelin is a candidate target for treatment and follow-up. Because there seems to be association between apelin and ovulation, whether apelin can be increased by stimulating ovulation, thereby reducing the occurrence of atherosclerosis, can be further investigated. For example, weight loss, altered diet, and exercise have been shown to be effective in the management of PCOS, including correct specific clinical consequences of anovulation, subsequently reducing cardiovascular disease risk factors (30).

PCOS may independently affect insulin resistance (3). Apelin has a glucose-lowering effect associated with enhanced glucose utilization in skeletal muscle and adipose tissue (31). The results of research into the correlation of apelin levels and insulin resistance have been inconsistent (20, 32, 33–38). The present study failed to find any significant correlation between apelin and HOMA-IR. HOMA-IR based on fasting glucose and insulin levels primarily reflects hepatic sensitivity (39). Apelin improves in vivo glucose metabolism by increasing glucose utilization in insulin-sensitive tissues, most likely in an insulin-independent manner rather than through inhibition of hepatic glucose output (31). These facts might be behind the lack of correlation between apelin levels and HOMA-IR.

Principe et al. (40) stated that patients with cirrhosis showed a marked increase in apelin levels and that the hepatic apelin system was markedly and selectively activated. It is possible that liver function could influence the secretion of apelin from liver. We suggest that liver function markers should be taken into account as a confounding factor in the analysis model of apelin. The PCOS group were younger than the control group. Because the risk of cardiovascular diseases and glucose metabolism impairment increased with age, the lower apelin levels and higher atherosclerotic marker seemed not to be attributed to age-related factors.

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SUPPLEMENTAL TABLE 1

Pearson correlation analysis of the possible determinants for serum apelin levels.

	BMI	Age	T	E_2	P	FSH	LH	Insulin	Glucose	HOMA–IR	PCOS	ApoA	ApoB	TC	TG	HDL-C	LDL-C	TC/HDL	LDL/HDL	ApoB/ApoA
r	0.004	0.130	0.099	0.076	0.004	0.059	−0.076	−0.092	0.135	−0.062	−0.340[a]	0.250[a]	−0.103	−0.082	−0.109	0.169	−0.162	−0.233[a]	−0.226[a]	−0.217[a]
P	.970	.237	.372	.490	.970	.594	.489	.403	.222	.574	.002	.022	.350	.458	.325	.125	.141	.033	.039	.047

Note: For dichotomy variable of PCOS: PCOS = 1; control = 0. ALT = alanine aminotransferase; ApoA = apolipoprotein A; Apo B = apolipoprotein B; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein cholesterol; PCOS = polycystic ovary syndrome; TC = total cholesterol.

[a] $P < .05$.

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SUPPLEMENTAL TABLE 2

Multiple linear regression analysis of the possible determinants for serum apelin levels.

	Coefficient				
	Unstandardized		Standardized		
Independent variable	β	SE	β	*t*	*P* value
(constant)	208.305	246.028		0.847	.400
PCOS	−128.502	41.765	−0.346	−3.077	.003[a]
Age	−1.002	3.996	−0.029	−0.251	.803
BMI	12.821	6.594	0.255	1.944	.056
HOMA-IR	−17.960	40.733	−0.065	−0.441	.661
AST	−14.819	5.946	−0.450	−2.492	.015[a]
ALT	6.932	3.307	0.426	2.096	.039[a]
ApoA	2.007	0.691	0.345	2.904	.005[a]
P	3.793	8.309	0.049	0.456	.649

Note: The dependent variable is serum apelin level. For dichotomy variable of PCOS: PCOS = 1; control = 0. For the model: $r = 0.508$; $r^2 = 0.258$; $P = .003$.
Abbreviations as in Supplemental Table 1.

[a] $P < .05$.

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