Ischemia-modified albumin and cardiovascular risk markers in polycystic ovary syndrome with or without insulin resistance

The aim of this study was to evaluate ischemia-modified albumin levels (IMA) in polycystic ovary syndrome (PCOS) cases with and without insulin resistance and the correlation of IMA with carotid intima media thickness, homocysteine, and high-sensitivity C-reactive protein levels. Significantly higher levels of IMA in young lean PCOS cases, more relevant in insulin resistant cases, indicates chronic hypoxia and oxidative stress which might play a role in the metabolic consequences in PCOS. (Fertil Steril® 2011;95:310–3. ©2011 by American Society for Reproductive Medicine.)

Key Words: Ovary syndrome, ischemia modified albumin, cardiovascular risk, insulin resistance

Polycystic ovary syndrome (PCOS) is associated with hypertension, dyslipidemia, metabolic syndrome, impaired glucose tolerance, and type 2 diabetes mellitus (DM) (1–4). Women with PCOS have 50%–70% insulin resistance (IR) (5–6). IR and compensatory hyperinsulinemia not only causes hyperglycemia but also have been proposed as key factor leading to cardiometabolic comorbidities, such as early endothelial dysfunction (7–8). Significantly higher carotid intima media thickness (CIMT) was confirmed in PCOS compared with control subjects (9–12). PCOS women may have 4–5-fold increased risk for coronary and cerebrovascular atherosclerosis (13).

Among the inflammatory biomarkers, C-reactive protein (CRP) and fibrinogen seem to be the best for cardiovascular risk detection, which relies on evidence suggesting atherosclerosis as chronic inflammatory process (14). Oxidative stress may also contribute to the inflammatory state in atherosclerosis. Ischemia-modified albumin (IMA) is new marker of oxidative stress, and there is only one study measuring IMA levels in PCOS women (15). In the present study high-sensitivity (hs) CRP, CIMT, homocysteine (Hcy), and IMA levels were analyzed in PCOS cases with and without IR and compared with control subjects. The association of IMA levels with other markers was also evaluated.

Sixty-one PCOS patients with written informed consent were enrolled in this study approved by the Institutional Review Board. The diagnosis of PCOS was made as proposed at the Rotterdam Consensus Meeting (16). Exclusion criteria were hyperprolactinemia, thyroid and adrenal dysfunction, DM, hypertension, pregnancy, any history of cardiac symptoms, angina, myocardial infarction, coronary artery disease, vascular disease, and inflammatory disease. Subjects receiving vitamins/drugs that may effect Hcy levels or drugs known to interfere with hormonal levels, smokers and alcohol consumers, and cases with abnormal albumin levels ($<$3.5 g/dL and $>$5.5 g/dL) and body mass index (BMI) ($>$30 kg/m^2) were excluded. The control subjects (n = 21) had no signs/symptoms of hyperandrogenism or menstrual dysfunction. Blood samples were collected after an overnight fast for $\geq$12 hours on the second or third day of menstrual cycle. Fasting glucose–to-insulin ratio (FIGR), homeostasis model assessment of IR (17) (HOMA-IR; insulin $\times$ glycemia [μmol/L]/22.5), and quantitative insulin sensitivity check index (18) (QUICKI; 1/log insulin + log glycemia [mg/dL]) were all estimated and used as indicators of IR.

IMA concentrations were analyzed by measuring the complex composed of dithiothreitol and cobalt unbound from albumin by the colorimetric method as described by Guven et al. (15). The analyses in the Human Humalyzer 2000 spectrophotometer (Human Diagnostics, Wiesbaden, Germany) were performed at 470 nm and the results given as absorbance units (ABSU). Imaging was conducted using a high-resolution ultrasound machine (Logic Q7; General Electric, Fairfield, CT) with a 7.5-MHz mechanical sector transducer in all cases. The carotid artery was explored in B-mode by visual assessment of the distance between the lumen-intima and intima-adventitia interphases in longitudinal frames acquired during arterial diastole (19). The means of greatest thicknesses on both sides were used for statistical analyses.

Gamze S. Caglar, M.D.[a]
Efser Oztas, M.D.[a]
Demet Karadag, M.D.[b]
Recai Pabuccu, M.D.[a]
Selda Demirtas, M.D.[c]

[a] *Department of Obstetrics and Gynecology, Faculty of Medicine, University of Ufuk, Ankara, Turkey*
[b] *Department of Radiology, Faculty of Medicine, University of Ufuk, Ankara, Turkey*
[c] *Department of Biochemistry, Faculty of Medicine, University of Ufuk, Ankara, Turkey*

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Reprint requests: Gamze S. Caglar, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, University of Ufuk, 06530, Ankara, Turkey (FAX: +90-312-4355770; E-mail: gamzesinem@hotmail.com).

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Data analyses were performed with SPSS for Windows, version 11.5 (SPSS, Chicago, IL). The distributions of continuous variables were determined by Shapiro-Wilk test. The mean differences between groups were compared by Student *t* test. Mann-Whitney *U* test was applied for comparisons of median values. Importance of the degrees of association between continuous variables was analyzed by Spearman correlation test. In the PCOS group, statistically significant effects of cardiovascular risk factors on higher HOMA-IR levels were evaluated by multiple logistic regression analyses adjustment for age and BMI. Odds ratios and 95% confidence intervals for each independent variable were calculated. A *P* value $<.05$ was considered to be statistically significant.

The mean ages of the case and control subjects (range 18–30 years) were 22.6 ± 4 years and 23.4 ± 4 years, respectively ($P>.05$). Although the BMIs of the case and control subjects were similar (22.7 ± 3.9 vs. 21.1 ± 1.6 kg/m^2, respectively; $P>.05$), PCOS cases had significantly higher waist-to-hip ratio (WHR) compared with control subjects (0.74 vs. 0.70, respectively; $P<.05$). IR indexes were also significantly different in PCOS cases ($P<.05$). The hormone profile of PCOS cases and control subjects are presented in Table 1. In lipid profile, significantly higher levels of triglycerides (TG) and TG/high-density lipoprotein (HDL) ratio were detected in PCOS cases compared with control subjects ($P<.05$). IMA, hs-CRP, Hcy, and CIMT were significantly higher in PCOS cases ($P<0.05$; Table 1).

PCOS cases are categorized according to calculated HOMA-IR index. There were 31 cases with HOMA-IR ≥2.1 and 30 cases with HOMA-IR index <2.1. In the group with HOMA-IR ≥2.1, fasting glucose, fasting insulin, and HOMA-IR were significantly elevated and FIGR and QUICKI were significantly lower compared with the HOMA-IR <2.1 group ($P<.05$). None of the hormone parameters differed between the two groups. Although higher levels of total cholesterol (C), low-density lipoprotein (LDL) C, and TG were found in the HOMA-IR ≥2.1 group, only TG/HDL ratio showed statistical significance (median TG/HDL 1.7 in HOMA-IR ≥2.1 vs. 1.4 in HOMA-IR <2.1; $P<.05$). In addition, hs-CRP and IMA levels were significantly elevated in cases with HOMA-IR ≥2.1 (median hs-CRP 2.03 in HOMA-IR ≥2.1 vs. 1.09 in HOMA-IR <2.1 [$P<.05$]; median IMA 1.04 in HOMA-IR ≥2.1 vs. 0.84 in HOMA-IR <2.1 [$P<.05$]). In correlation analysis, neither the baseline characteristics (age, BMI, WHR) nor the serum parameters (hormone levels, lipid profile, indicators of IR) were found to have any correlation with IMA levels in PCOS cases. In addition, fasting insulin, HOMA-IR, Total-C, and LDL-C levels were found to be positively correlated ($r = 0.0299$, $P=.019$; $r = 0.318$, $P=.013$; $r = 0.457$, $P<.001$; $r = 0.383$, $P=.002$; respectively) and FIGR and QUICKI index were negatively correlated with hs-CRP levels ($r = -0.288$,

TABLE 1

Parameters of insulin sensitivity, hormone and lipid profile, and cardiovascular disease risk markers in polycystic ovary syndrome (PCOS) cases and control subjects.

Parameter	Control (n = 21)	PCOS (n = 61)	*P* value
Fasting glucose (mg/dL)	85.0 ± 7.9	87.2 ± 6.9	NS
Fasting insulin (μIU/mL)	6.6 (2.5–9.0)	9.7 (3.3–57.4)	<.001[a]
FIGR	12.9 (9.5–35.1)	9.0 (1.7–25.4)	<.001[a]
HOMA-IR	1.2 (0.5–1.9)	2.1 (0.5–14.03)	<.001[a]
QUICKI	0.37 ± 0.2	0.34 ± 0.3	<.001[a]
FSH (mIU/mL)	5.1 ± 1.16	5.4 ± 1.2	NS
LH (mIU/mL)	5.8 (1.1–9.7)	6.5 (1.7–23.8)	NS
E_2 (pg/mL)	36 (5–147)	59 (14–230)	<.05[a]
PRL (ng/mL)	10.3 (5.6–24.4)	12.7 (1.3–51.7)	NS
TSH (μIU/mL)	1.9 (0.4–5)	1.2 (0.5–4)	NS
Total T (ng/dL)	0.29 (0.1–0.6)	0.30 (0.1–1.3)	NS
Free T (pg/dL)	1.6 (1.0–3.0)	2.4 (0.8–5.5)	<.05[a]
DHEAS (μg/dL)	199 (55–526)	232 (64–677)	NS
17OH-P (ng/dL)	1.34 (0.2–2.6)	1.80 (0.4–4.4)	NS
Total-C (mg/dL)	166 ± 24	174 ± 36	NS
LDL-C (mg/dL)	99 ± 26	101 ± 27	NS
HDL-C (mg/dL)	59 ± 11	53 ± 11	NS
TG (mg/dL)	67 (33–137)	82 (30–272)	<.05[a]
TG/HDL	1.08 (0.3–3.1)	1.5 (0.5–6.8)	<.05[a]
IMA (ABSU)	0.78 (0.5–1.4)	0.94 (0.6–1.2)	<.05[a]
Hcy (μmol/L)	7.6 (5.2–9.6)	9.1 (5.0–18)	<.05[a]
hs-CRP (mg/L)	0.6 (0.2–4.6)	1.3 (0.2–18.6)	<.05[a]
CIMT (mm)	0.5 (0.5–0.7)	0.6 (0.4–0.9)	<.001[a]

Note: Values are expressed as either mean ± SD or median (range). ABSU = absorbance units; CIMT = carotid intima media thickness; FIGR = fasting glucose to insulin ratio; Hcy = homocysteine; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IMA = ischemia-modified albumin; LDL-C = low-density lipoprotein cholesterol; NS = not significant; QUICKI = quantitative insulin sensitivity check index; TG = triglycerides; Total-C = total cholesterol.

[a] Statistically significant.

Caglar. Correspondence. Fertil Steril 2011.