

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/m²) 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 ≥ 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 × 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.

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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/m², 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* < .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)	<i>P</i> value
Fasting glucose (mg/dL)	85.0 \pm 7.9	87.2 \pm 6.9	NS
Fasting insulin (μ IU/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 \pm 0.2	0.34 \pm 0.3	< .001 ^a
FSH (mIU/mL)	5.1 \pm 1.16	5.4 \pm 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 (μ IU/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 (μ g/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 \pm 24	174 \pm 36	NS
LDL-C (mg/dL)	99 \pm 26	101 \pm 27	NS
HDL-C (mg/dL)	59 \pm 11	53 \pm 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 (μ mol/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 \pm 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.

$P=.024$; $r = -0.294$, $P=.022$; respectively). However, neither CIMT nor Hcy were correlated with baseline characteristics or the serum parameters.

During ischemia, acidosis and generation of superoxide free radicals occurs and the N-terminal portion of the human serum albumin becomes unable to bind metal ions. As a result of oxidative stress, IMA generation occurs, lacking tissue specificity (20). IMA is mostly studied in cardiac events. Ischemia in any organ before infarction can lead to IMA elevation within 6–10 minutes, remaining positive for up to 6 hours (20). Apart from acute coronary syndrome (20), chronically elevated levels of IMA have been detected in many clinical conditions, such as intrauterine pathologies and systemic sclerosis (21, 22). Confirming our results, high levels of IMA were recently reported in PCOS cases (15). In vivo and in vitro studies showing oxidative stress linked to IR might be an explanation for higher IMA levels in PCOS cases with IR in the present study (23–25). Supporting our data, higher IMA concentrations were reported in patients who have poor glycemic control than in patients with good glycemic control in type 2 DM (26). Furthermore, significant but weak correlation was found between IMA and fasting glucose in type 2 DM (27). High concentrations of IMA might indicate persistent ischemia in PCOS associated with metabolic complications. Additionally, when evaluating a PCOS patient with an acute ischemic condition, chronically increased IMA concentrations would be better kept in mind if it is to be used for clinical purpose.

The progression of atherosclerotic lesions is associated with lipid accumulation due to increased triglyceride biosynthesis, reduced beta-oxidation, and increased expression of the enzyme stearyl-coenzyme A desaturase in fatty acid synthesis (28). In the present study, oxidative stress and chronic ischemia detected

by higher concentrations of IMA in accordance with higher TG levels in PCOS cases might explain higher CIMT in our study subjects. As in our study, increased levels of CRP supporting chronic inflammation and elevated Hcy levels showing abnormal Hcy metabolism has been previously reported in PCOS women (29–31).

Previously, positive correlation between serum IMA and hyperandrogenism were reported and suggested as a possible cause of cardiovascular risk in PCOS (15). In the present study, lack of correlation of IMA with any of the parameters studied might be due to small sample size. No correlation between hs-CRP and clinical/biochemical parameters of PCOS confirms the earlier data that CRP levels are associated with obesity rather than the presence of PCOS per se (32). Even if the effect of obesity on hs-CRP levels was minimized by recruiting lean PCOS cases, higher WHR of PCOS subjects, indicating excessive visceral fat, might be the explanation for significantly elevated hs-CRP levels, because visceral fat correlates with CRP levels independently of total adiposity (33). Moreover, in the present study, higher levels of hs-CRP in cases with IR and correlation between IR, dyslipidemia (high levels of Total-C and LDL-C), and hs-CRP are in accordance with studies showing CRP as an independent predictor of type 2 DM development (33, 34). Although IR was suggested to be associated with Hcy levels (31), no difference in Hcy levels were found in cases with or without IR in the present study.

The high IMA levels in PCOS cases indicates chronic hypoxia and oxidative stress which needs to be confirmed in future studies with larger populations. The metabolic complications present in PCOS may predispose these cases to cardiovascular disease (CVD). However, further longitudinal studies are still needed to clarify the precise risk for CVD in PCOS cases.

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