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Circulating levels of obestatin and copeptin in obese and nonobese women with polycystic ovary syndrome

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5–8% of reproductive-age women. It is associated with insulin resistance, central obesity, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases. The current study was undertaken to evaluate serum copeptin and obestatin levels, carotid artery intima-media thickness, and brachial artery flow mediated dilatation in obese and nonobese women with PCOS and age-matched healthy controls and to investigate their relationship with each other and with clinical, metabolic, and hormonal parameters and cardiovascular risk factors.

Method: In the study population, we analyzed 60 patients with PCOS and 30 age-matched healthy women as controls. The patients with PCOS were divided into two groups based on body mass index (BMI): obese group (BMI > 30 kg/m^2, $n = 30$) or nonobese group (BMI < 30 kg/m^2, $n = 30$). History was obtained and a physical examination, peripheral venous blood sampling, and carotid and brachial artery ultrasonography were performed. Serum copeptin and obestatin levels, total testosterone, C-reactive protein (CRP), glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, homeostasis model assessment for insulin resistance (HOMA-IR), carotid artery intima-media thickness (CIMT), and brachial artery flow-mediated vasodilation (FMD) were determined and compared among the groups.

Results: Women with PCOS, especially obese ones, had higher triglycerides, HOMA-IR, total testosterone, CRP, systolic and diastolic blood pressure, and waist-to-hip ratio (WHR), and lower HDL. Serum obestatin levels were significantly lower in the obese PCOS group than they were in the nonobese and control groups ($p < 0.001$). Serum copeptin levels were significantly higher in the obese PCOS group than they were in the nonobese PCOS and control groups ($p < 0.001$). CIMT values were similar among the groups ($p > 0.05$). Brachial artery FMD was lower in the PCOS groups than it was in the control group ($p < 0.001$). Obestatin and FMD values were negatively correlated with cardiovascular risk factors, whereas copeptin was positively correlated. A significant positive correlation was found between copeptin, BMI, WHR, hirsutism score, total testosterone, and HOMA-IR. There was no correlation between CIMT, copeptin, obestatin, and FMD. A positive correlation was seen between CIMT, BMI, triglycerides, and HOMA-IR.

Conclusion: Copeptin and obestatin may provide useful information regarding future cardiovascular risk in PCOS patients as copeptin was positively correlated and obestatin was negatively correlated with cardiovascular risk factors.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies; it affects 5–8% of reproductive-age women [1]. It is characterized by chronic oligo-ovulation or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries

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[2]. PCOS is also associated with insulin resistance, central obesity, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases [3]. Women with PCOS are more likely than other women to have increased blood pressure, endothelial dysfunction, reduced arterial compliance, low grade chronic inflammation, and increased endothelin-1 and homocysteine [4]. They have a 2–4-fold increased risk of metabolic syndrome compared to healthy controls [5].

Ghrelin is a 28-amino-acid peptide that is the posttranslation product of the peptide preproghrelin [6]. Ghrelin is an orexigenic hormone and has effects on energy balance, appetite, and weight gain [7]. Obestatin is peptide hormone secreted by the cells of the stomach and small intestine of several mammals including humans. Although obestatin and ghrelin are both encoded by the same gene and derived from the precursor protein proghrelin, obestatin behaves as a physiological opponent to ghrelin in inhibiting food intake, body weight gain, and gastric emptying [8]. Arginine vasopressin, which is also named antidiuretic hormone, is released from the posterior pituitary gland in conditions of chronic psychosocial stress via inducing the hypothalamic–pituitary–adrenal (HPA) axis along with corticotropin-releasing hormone [9]. Several studies suggest that stress-mediated activation of the HPA axis may have a role in the pathogenesis of insulin resistance and metabolic syndrome [10]. Copeptin is a C-terminal provasopressin fragment, directly mirroring vasopressin level and more stable in the plasma and serum [11]. Saleem et al. [9] have shown a cross-sectional association between plasma copeptin and measures of insulin resistance and metabolic syndrome. There are recent studies that associate diabetes mellitus, cardiovascular risk, central obesity, and copeptin levels [12–14]. Karbel et al. [13] have recently reported that copeptin is associated with cardiovascular risk in women with PCOS.

Carotid intima-media thickness (CIMT) is a morphologic marker of subclinical cardiovascular lesions in the early stage and a powerful predictor of future cardiovascular risk [15]. In a large community-based study, brachial artery flow-mediated vasodilation (FMD) was also found to be a potential marker for future cardiovascular risk [16]. The current study was undertaken to evaluate serum copeptin and obestatin levels, carotid artery intima-media thickness, and brachial artery flow mediated dilatation in obese and nonobese women with PCOS and age-matched healthy controls, and to investigate their relationship with each other and with clinical, metabolic, and hormonal parameters and cardiovascular risk factors.

Materials and methods

In this prospective study we analyzed 60 patients with PCOS and 30 age-matched healthy women as controls. The patients with PCOS were divided into two groups based on body mass index (BMI): obese group (BMI $> 30\ kg/m^2$, $n = 30$) or nonobese group (BMI $< 30\ kg/m^2$, $n = 30$). Patients were recruited from the outpatient clinics of the Department of Obstetrics and Gynecology, Balikesir University School of Medicine (Balikesir, Turkey) over an 8-month period between January and August 2014. The study protocol was in accordance with the Helsinki Committee requirements and was approved by the Ethics Committee of 18 Mart University. All patients gave written consent before the study. The diagnosis of PCOS was made based on the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) criteria [2], when two out of the following three features were present: oligoovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination (the presence of 12 or more follicles measuring 2–9 mm in diameter and/or ovarian volume $>10\ cm^3$). Oligoanovulation was defined as the presence of oligomenorrhea (menstrual cycles of >35 days) or amenorrhea (lack of menstrual period for 6 months or more). The control group consisted of 30 healthy women with regular menses. A pelvic ultrasound examination was performed on the same day as blood sampling (the early follicular phase of the menstrual cycle or progesterone induced early follicular phase in subjects with amenorrhea) with a 7.0 MHz vaginal transducer (Voluson 730, GE Healthcare, USA). All women were examined by the same physician. Patients who had taken oral contraceptive agents, antilipidemic or antihypertensive drugs, glucocorticoids, antiandrogens, insulin sensitizers, anticoagulants, or antiplatelet agents at least 3 months before the study were excluded. Hirsutism was determined by the Ferriman–Gallwey score [17]. Waist-to-hip ratio (WHR), which indicated visceral fat accumulation, was calculated. The body mass index (BMI) was calculated as weight (in kilograms)/height squared (meters squared). The BMI, WHR, and hirsutism scores were assessed by the same physician.

Measurement of carotid artery intima-media thickness and brachial artery flow-mediated vasodilation

Ultrasonographic measurement of the CIMT and FMD was performed with the use of a high-resolution ultrasound machine (Philips HD11 XE; Philips Medical Systems, Bothell, WA, USA). Women were examined in the supine position, with the head hyperextended and turned away from the side being scanned. Intima-media thickness was defined as the distance between the lumen intima and the media interfaces. Images for intima-media thickness at each carotid artery were made from the distal portion of both common carotid arteries. Five measurements from the right and left sides were taken and the mean value was determined.

After all patients had rested in the left lateral decubitus position for 10 min in a room with stable temperature, the brachial artery diameter was measured manually with electronic calipers from the intima-blood interface on the near wall to the blood-intima interface on the far wall. The right brachial artery was scanned above the antecubital fossa in the longitudinal plane. After measuring the baseline brachial artery diameter, a blood pressure cuff was placed over the patient's upper arm and inflated to 250–300 mmHg for 5 min. The brachial artery diastolic diameter was measured again 60 s after sudden deflation of the cuff (reactive hyperemia). FMD was calculated as brachial artery diameter during hyperemia-baseline diastolic diameter, and FMD% was calculated as 100X FMD/baseline diastolic diameter. All measurements were performed by the same investigator, who was blinded to the groups.

Biochemical evaluation

Venous blood samples were taken from all patients following a fast of one night between the hours of 09 and 10 AM for hormonal and biochemical analyses. Following centrifugation at $825 \times g$ for 10 min, serum samples were collected and stored $-80\ ^\circ C$ until assessment. The levels of glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using commercially available kits on a chemistry autoanalyzer (Cobas Integra 800; Roche Diagnostics GmbH; Mannheim, Germany). Serum C-reactive protein (CRP) was measured with chemiluminescent immunoassay using an ADVIA Centaur XP (Siemens Healthcare Diagnostics, NY, USA). The levels of fasting insulin were determined using Access kits on a hormone autoanalyzer (Beckman Coulter; Unicel DXI 600; Access Immunoassay System).

The serum levels of copeptin, obestatin, and testosterone were determined by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (eBioscience, Austria) on a diagnostic instrument (BioTek, ELx 800, USA).