# Validity of adiponectin-to-leptin and adiponectin-to-resistin ratios as predictors of polycystic ovary syndrome

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**Objective:** To evaluate the association of changes in adipokine ratios with polycystic ovary syndrome (PCOS) and related features as altered levels of the adipokines adiponectin, leptin, and resistin were linked with the pathogenesis of PCOS.
**Design:** Case-control retrospective study.
**Setting:** Outpatient obstetrics/gynecology and adult endocrinology clinics.
**Patient(s):** Unrelated women with PCOS (n = 211) and age-matched control women (n = 215).
**Intervention(s):** None.
**Main Outcome Measure(s):** Utility of adiponectin/leptin and adiponectin/resistin ratios as potential biomarkers of PCOS and associated features.
**Result(s):** Significant differences in adiponectin but not leptin or resistin serum levels were seen between women with PCOS and control women. Ratios of adiponectin/leptin and adiponectin/resistin, but not leptin/resistin ratios, were statistically significantly different between PCOS cases and control women. Receiver operated characteristics area under the curve demonstrated sensitivity and specificity for adiponectin/leptin and adiponectin/resistin but not leptin/resistin ratios or individual adipokines as predictors of PCOS. Adiponectin/leptin and adiponectin/resistin ratios negatively correlated with body mass index, homeostatic model assessment, insulin resistance, and free insulin, testosterone, and sex hormone-binding globulin. In addition, adiponectin/resistin ratio negatively correlated with menarche.
**Conclusion(s):** Ratios of adiponectin/leptin and adiponectin/resistin constitute novel predictor factors to explain PCOS and associated features and thus may present target for novel therapeutics in PCOS. (Fertil Steril® 2015;104:460–6. ©2015 by American Society for Reproductive Medicine.)
**Key Words:** Adipokines, adiponectin, leptin, polycystic ovary syndrome, resistin

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Polycystic ovary syndrome (PCOS), a common endocrinopathy that affects reproductive-aged women, is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries (1). The phenotype of PCOS is heterogeneous and includes oligomenorrhea/amenorrhea, hirsutism, and infertility, and is associated with the metabolic syndrome (1, 2). Also, PCOS is associated with obesity, central adiposity, and dyslipidemia (3–5), and an increased risk of type 2 diabetes (T2DM) (1, 5, 6), which have been linked to insulin resistance (IR) (7, 8). Insofar as adipose tissue secretes bioactive cytokines and adipokines, including adiponectin, leptin, and resistin (9), mounting evidence implicates dysregulated adipokine expression with the onset of obesity-related pathologies including PCOS (9–12).

Adiponectin is an abundant adipokine secreted by adipose tissues, with

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anti-inflammatory, antiatherogenic, cardioprotective, and insulin-sensitizing properties (2, 13, 14). Adiponectin is synthesized as 28–30 kDa monomer, which assembled into low-molecular-weight trimeric, medium-molecular-weight hexameric, and high-molecular-weight forms (14). Adiponectin levels are inversely related to IR, and reduced adiponectin levels are linked with IR-associated conditions, including obesity, T2DM, and PCOS (8, 15, 16).

The association between altered adiponectin levels and PCOS remains controversial, with some studies reporting comparable adiponectin levels in BMI-matched PCOS and control women (11, 12, 17), and others (8, 9, 11, 16), including two meta-analyses (18, 19), showing that women with PCOS have lower levels of adiponectin independent of body mass index (BMI).

Leptin is an anorexigenic peptide hormone secreted by white adipose tissue, which circulates in the plasma as a free or protein-bound adipokine (20). Circulating leptin levels have been positively correlated with body fat independent of PCOS according to some studies (21, 22) but not others; the latter did not document statistically significant differences in serum leptin levels in women with PCOS compared with age- and BMI-matched controls (23, 24), or between ovulatory and anovulatory women with PCOS (25).

In contrast, resistin is an adipocyte-derived polypeptide linked with obesity and IR (26, 27) as well as inflammation and cardiovascular risk (28). Resistin, produced by peripheral blood mononuclear cells (29) and adipose tissues (27), circulates as a high-molecular-weight hexamer and bioactive low-molecular-weight complex (26, 27). Most but not all studies have reported that serum or follicular fluid resistin levels are comparable between women with PCOS and control women (10, 15, 17,28–31) whereas others have shown that serum resistin levels are increased in overweight and obese compared with lean women irrespective of the presence of PCOS (10).

Adiponectin, and leptin and resistin have opposing effects on the course of PCOS. Adiponectin levels are low in PCOS, but leptin and resistin levels are elevated in PCOS; an inverse relationship between adiponectin on the one hand and leptin and resistin on the other has been documented. This points to the concerted interaction of adiponectin, leptin, and resistin in modulating PCOS risk. Previous studies suggested that adipokine ratios are a stronger indicator of IR than individual adipokines (32, 33), thus prompting speculation as to the utility of adipokine ratios as a measure of IR and as a marker of PCOS progression, especially in women undergoing treatment. Apart from a lone report on small number of subjects (50 women with PCOS and 50 control women) (34), the association of the adiponectin/leptin and adiponectin/resistin ratios with PCOS had not been previously examined until our study.

## MATERIALS AND METHODS

### Patients

In total, 457 unrelated women comprising 241 women with PCOS, and 216 ethnically matched and age-matched control women were recruited from outpatient obstetrics/gynecology and adult endocrinology clinics in Manama, Bahrain. The PCOS diagnosis was based on the 2003 Rotterdam criteria, in which a PCOS diagnosis is confirmed when two of three conditions are met: anovulation, hyperandrogenism, and the presence of polycystic ovaries on ultrasound examination. Before obtaining samples, we excluded one control woman for lack of a sufficient serum sample, and 30 women with PCOS: 12 had missing information for key covariates (BMI, testosterone), 11 who were not fasting for the homeostatic model assessment, insulin resistance (HOMA-IR) determination, and the remaining 7 were on metformin therapy. A final sample of 211 women with PCOS and 215 control women were included.

Among the women with PCOS, 185 (87.7%) had positive polycystic morphology on ultrasound, 156 (73.9%) had hirsutism (assessed by the modified Ferriman-Gallwey scale $>8$ with/without acne and/or androgen alopecia), and 145 (68.7%) were hyperandrogenic (elevated androgen levels beyond 95% confidence limits in controls). Of the 211 women with PCOS, 69 (32.7%) had regular menses, and irregular menses were seen in the remaining 142 women with PCOS, who were either oligomenorrheic with three to seven periods per year ($n = 103$; 72.5%) or amenorrheic with no menstrual period ($n = 39$; 27.5%). The menstrual status of the women with PCOS was assessed before initiation of any treatment. The exclusion criteria included androgen-producing tumors, 21-hydroxylase-deficiency, nonclassic adrenal hyperplasia, hyperprolactinemia, active thyroid disease, and Cushing syndrome. None of the women with PCOS or the control women was on medication known to affect carbohydrate metabolism or endocrine parameters for at least 3 months before entering the study.

The control group comprised eumenorrheic university students and employees, or otherwise healthy female volunteers with regular menses (27–35 days), circulating testosterone levels within the reference range (0.4–3.5 nmol/L), and modified Ferriman-Gallwey scores $\leq 6$. The control women were ethnically matched to women with PCOS, and they were studied in the follicular phase of their menstrual cycle. Demographic data and history of hypertension, diabetes, and hypercholesterolemia were recorded for all participants. In addition, data on physical activity (lack of, occasional, and frequent exercise), weight control (food restriction, diet pills), weight gain in the past 6-months (none, $<5$ kg, $\geq 5$ kg), and special dietary requirements (carbohydrate restriction, fat restriction, high protein, vegetarian, and macrobiotic) were collected from all participants through a unified questionnaire. Local ethics committees approved the study protocol, and written informed consent was obtained from all participants.

### Biochemical Analysis

Blood samples were collected after an overnight ($>12$ hours) fast for measurement of glucose, insulin, triglycerides, total cholesterol, and high-density lipoprotein levels. The levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone, progesterone, 17$\alpha$-hydroxyprogesterone, and thyroid-stimulating hormone (TSH) were