ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

# High-molecular-weight adiponectin is inversely associated with sympathetic activity in polycystic ovary syndrome

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**Objective:** To examine the role of high-molecular-weight (HMW) adiponectin and its relationship to sympathetic activity in women with polycystic ovary syndrome (PCOS).
**Design:** Cross sectional study using biobanked samples.
**Setting:** Not applicable.
**Patient(s):** Premenopausal women with PCOS (n = 46, Rotterdam diagnostic criteria) and without PCOS (n = 22).
**Intervention(s):** None.
**Main Outcome Measure(s):** High-molecular-weight adiponectin levels with secondary outcomes of sympathetic activity and leptin levels.
**Result(s):** The high-molecular-weight adiponectin level was lower in women with PCOS (median 2.2 [interquartile range (IQR)2.3] μg/mL) than in controls (median 3 [IQR2.5] μg/mL) (age and BMI adjusted), and it correlated inversely with the values measured for homeostatic model of assessment of insulin resistance (HOMA-IR), fasting insulin, triglycerides, and free androgen index and positively with sex hormone-binding globulin (SHBG) and high-density lipoprotein cholesterol in all participants and in the PCOS group. In the PCOS group, sympathetic activity (burst frequency) was statistically significantly higher than in controls (median 26 [IQR11] vs. median 22 [IQR14], respectively) and correlated inversely with HMW adiponectin (r = −0.230). The leptin levels were similar between the women with PCOS and controls and did not statistically significantly correlate with HMW adiponectin or sympathetic activity. On multiple regression analysis, burst frequency and SHBG explained 40% of the HMW adiponectin variability (B = −0.7; 95% CI −1.2 to −0.2; and B = 0.01; 95% CI 0.004–0.01) in PCOS.
**Conclusion(s):** Alongside insulin resistance, increased sympathetic activity is associated with and may modulate HMW adiponectin levels in women with PCOS. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
**Key Words:** HMW adiponectin, insulin resistance, leptin, polycystic ovary syndrome, sympathetic nervous system

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Polycystic ovary syndrome (PCOS) is a common and complex endocrinopathy affecting 12% to 18% of reproductive-aged women (1). Hyperinsulinemia and hyperandrogenism are the key hormone disturbances underpinning the pathophysiology of PCOS. In addition to its reproductive features, PCOS is associated with worsened metabolic risk factors and increased cardiovascular morbidity (2, 3). The increased adverse cardiometabolic outcome in PCOS is attributed at least in part to the interrelated effects of insulin resistance (IR), hyperandrogenism, sympathetic nervous system (SNS) dysfunction, and chronic low grade inflammation (4).

A potential role of adipose tissue dysfunction is emerging as contributing to PCOS pathophysiology. Women with PCOS have dysfunctional hypertrophied adipocytes associated with dysregulated production of adipocytokines (4). Despite the contradictory data, lower adiponectin levels and lower expression of adiponectin and its receptors in the ovarian granulosa cells have been reported in women with PCOS compared with controls (5, 6), and adiponectin gene (*ADIPOQ*) polymorphism has been associated with PCOS (7). Adiponectin is an adipokine with known insulin sensitizing, antioxidant, and antiatherogenic effects (8–10). Adiponectin also modulates follicular growth and maturation, early embryo development, and androgen synthesis in the ovaries (11, 12). Adiponectin mediates the effects of hyperandrogenism and central adiposity on IR (13). Lower adiponectin levels are associated with obesity, IR, dyslipidemia, and the metabolic syndrome in women with PCOS (14–16); enlarged adipocytes, low adiponectin levels, and increased waist circumference have been demonstrated as potential drivers of IR in PCOS (17). Previous studies have suggested an association of low adiponectin levels with PCOS that is independent of obesity, and adiponectin has been proposed as a biomarker to distinguish women with PCOS at a higher risk of diabetes and cardiovascular morbidity (5,18–20).

Adiponectin is related to sympathetic function and may regulate sympathetic activity directly via central mechanisms or indirectly via an effect on leptin, and sympathetic overactivity may suppress adiponectin production in adipose tissue (21–25). Consistently low adiponectin levels may link sympathetic overactivity and metabolic dysfunction in obesity (26). Despite a paucity of studies, higher muscle sympathetic activity measured by microneurography has been reported in women with PCOS (27, 28). However, the exact role of sympathetic dysfunction in PCOS and its interactions with dysregulated adipocytokine production, including adiponectin, are not fully understood.

We studied high-molecular-weight (HMW) adiponectin (primary outcome) and leptin (secondary outcome) in women with and without PCOS and explored the association of HMW adiponectin with anthropometric, metabolic, reproductive, and sympathetic parameters in each group (secondary outcomes). We hypothesized that women with PCOS have lower levels of HMW adiponectin compared with controls and that the altered sympathetic activity in PCOS is a potential contributor to the lower HMW adiponectin levels in these women. In a secondary analysis we also explored the potential role for leptin in mediating the association of HMW adiponectin and sympathetic function.

## MATERIALS AND METHODS

### Study Population and Design

This observational study focused on baseline data from a double-blind, randomized, controlled trial (NCT01504321). Premenopausal women with PCOS were recruited by advertisement from the community between January 2013 and March 2015. We diagnosed PCOS according to the Rotterdam criteria as the presence of at least two of the following three criteria: irregular menstruation (cycle length $<21$ days or $>35$ days), clinical hirsutism or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound (presence of $\geq 12$ follicles measuring 2–9 mm in each or both ovaries) (29). Hirsutism was evaluated using a modified Ferriman-Gallwey scoring system (30). A diagnosis of biochemical hyperandrogenism was guided by local laboratory results (Monash Health) compared with validated reference ranges for testosterone (0.1–1.7 nmol/L) and free androgen index (0.7–10.9). Clinical hyperandrogenism was defined as a modified Ferriman-Gallwey score above 8 in Caucasian and above 6 in Asian women.

The control participants (overweight and obese) were recruited through community advertisement. They reported regular menstrual cycles, had no history of menstrual dysfunction, and demonstrated no evidence of hirsutism or hyperandrogenism based on biochemical analysis of their testosterone, sex hormone-binding globulin (SHBG), and free androgen levels.

The study's exclusion criteria included pregnancy, diabetes, use of any medication that could interfere with SNS activity, insulin resistance within the 3 months before recruitment, a history of secondary hypertension, cardiovascular, cerebrovascular, renal, liver, thyroid, or lung disease, or severe mental illness. Women who were taking oral contraceptive pills or metformin were asked to stop the medication and use barrier contraception instead if there were no contraindications; they went through a 3-month washout period for oral contraceptive pills or 1-month washout period for metformin before recruitment. The study was approved by local ethics committees at Alfred Hospital and Monash Health. All women gave written informed consent before participation.

The blood tests included total testosterone, SHBG, highly sensitive C-reactive protein (hs-CRP), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. An oral glucose tolerance test (OGTT) was performed, and the serum glucose and insulin levels were measured after fasting and 2 hours after ingestion of 75 g of glucose.

### Anthropometric Measurements

Body weight was measured in underclothes without shoes, using a digital scale. The body mass index (BMI) was calculated as weight (kg)/height squared ($m^2$). Waist circumference was measured at the midpoint between the iliac crest and the lowest rib.