Clinical Nutrition ESPEN 13 (2016) e33–e38

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

The high-molecular weight multimer form of adiponectin is a useful marker of polycystic ovary syndrome in Bahraini Arab women

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ARTICLE INFO

Article history:
Received 7 July 2015
Accepted 22 March 2016

Keywords:
Adiponectin
Androgens
ELISA
Insulin resistance
Polycystic ovary syndrome

SUMMARY

Background & aims: We tested if decreased total and high molecular weight (HMW)-adiponectin, and altered HMW/total adiponectin ratio (HMWR) constitute reliable markers of polycystic ovary syndrome (PCOS) among Bahraini Arab women.
Methods: Case–control study involving 122 Bahraini Arab women with PCOS and 89 ethnically-matched control women. PCOS was evaluated according to 2003 Rotterdam criteria. Total and HMW-adiponectin were measured by ELISA.
Results: Compared to controls, women with PCOS had significantly reduced plasma HMW-adiponectin, and HMWR, more so than total adiponectin. Logistic regression analysis revealed that HMW-adiponectin and HMWR, more than total adiponectin, were negatively associated with PCOS. ROC area-under-the-curve for predicting PCOS were larger for HMW-adiponectin (0.679 ± 0.037), and HMWR (0.653 ± 0.039), than total adiponectin (0.537 ± 0.041). Regression analysis confirmed the association of low HMW-adiponectin and HMWR with PCOS. HMW-adiponectin and HMWR inversely correlated with age, BMI, hirsutism, insulin, HOMA-IR, and positively correlated with serum LDL-cholesterol. Total adiponectin was negatively correlated with waist–hip ratio and serum LH levels.
Conclusions: Reduction in adiponectin plasma levels is an independent risk factor for PCOS. Changes in HMW-adiponectin serum levels and HMW/total adiponectin ratio are better markers for the presence of PCOS, when compared with total adiponectin.
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1. Background

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, and is a leading cause of female infertility [1]. It affects 5–25% of women in the reproductive age, depending on the population and the diagnostic criteria adopted (National Institutes of Health criteria, Androgen Excess and PCOS Society criteria, Rotterdam criteria) [2,3]. PCOS is multi-factorial in nature, and genetic and environmental factors contribute to its development [1]. PCOS is characterized by obesity, anovulation, clinical or biochemical hyperandrogenism and acne, which vary in intensity between affected women. PCOS is also associated with insulin resistance (IR) and hyperinsulinemia, which are exacerbated by obesity according to some [4,5], but not other [6,7] studies. The presence of IR and the resultant hyperinsulinemia increase the risk of diabetes, dyslipidemia, and atherosclerosis in women with PCOS [8].

Adiponectin is an abundant adipocytes-secreted serum protein, and its serum levels are reduced in conditions associated with obesity, including PCOS [1,4]. Growing evidence implicate insulin resistance and hyperinsulinemia with PCOS [5], evidenced by the altered secretion of adiponectin in women with PCOS [7]. Adiponectin circulates in serum as high molecular weight (HMW), medium molecular weight hexamer, and low molecular weight trimer complexes [9]. Adiponectin activity appears to be mediated by HMW-adiponectin, as serum HMW/total adiponectin ratio (HMWR) correlates better than total adiponectin with insulin resistance, and other measures of the metabolic syndrome [10,11], and with the response to thiazolidinediones in type 2 diabetes

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http://dx.doi.org/10.1016/j.clnesp.2016.03.078
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(T2DM) [9]. In addition, low levels of circulating adiponectin, in particular HMW-adiponectin, constituted a risk marker for the development of the metabolic syndrome and T2DM [6,10].

Recent reports demonstrated that basal [12,13], and TNF-α triggered [14] adiponectin secretion is reduced in women with PCOS compared to BMI-matched control women. In addition, adiponectin levels were inversely related to insulin resistance associated with metabolic syndrome, T2DM and PCOS [7,11,13]. However, the relationship between altered adiponectin levels and the risk of PCOS remains controversial [15,16], and whether reduction in adiponectin levels is a direct consequence of, or occurs independently of insulin resistance remains to be seen [15,17,18]. In the present study, we investigated the relationship between serum total and HMW-adiponectin concentrations with PCOS and its associated features among Bahraini Arab women.

2. Subjects and methods

2.1. Subjects

This retrospective case–control study was performed at outpatient OB/GYN and endocrinology clinics in Manama and Rifaa, Bahrain. Between January 2012–February 2014 a total of 211 unrelated women comprising 122 women with PCOS (mean age: 29.0 ± 5.7 yr) and 89 ethnically-matched control women (mean age: 26.3 ± 8.9 yr) were recruited into the study. PCOS diagnosis was based on the 2003 Rotterdam Criteria, in which PCOS diagnosis was confirmed when two of three conditions were met: (1) oligo- and/or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) a polycystic ovary assessed by ultrasonography [1,3]. Among women with PCOS, 107 (87.7%) had positive polycystic morphology on ultrasound, 90 (73.8%) had hirsutism (assessed by the modified modified Ferriman-Gallwey (mF-G) scale >8 with/without acne and/or androgen alopecia), while 83 (68.0%) were hyperandrogenic (elevated androgen levels beyond 95% confidence limits in controls). Oligomenorrhoea was defined as ≤8 periods/year or ≥35 cycles days, while amenorrhoea was defined as lack of menstruation ≥3 months without pregnancy.

Exclusion criteria included androgen-producing tumors, 21-hydroxylase-deficiency, non-classical adrenal hyperplasia, hyperprolactinemia, active thyroid disease, and Cushing's syndrome. Additional exclusion criteria for women with PCOS and the control group included extremes of body mass index (BMI) (<18 kg/m^2 or >45 kg/m^2), recent/current illness, medications likely to affect carbohydrate metabolism or endocrine parameters for at least three months before entering the study. The latter include oral contraceptive, anti-hypertensive, lipid-lowering, and anti-inflammatory agents.

Control group comprised eumenorrheic university students and employees, or otherwise healthy female volunteers with regular menses (27–35 day), circulating testosterone levels within the reference range (0.4–3.5 nmol/l), and mF-G scores ≤6. Control women were ethnically-matched to women with PCOS, and were studied in the follicular phase of their menstrual cycle. Demographic data and history of hypertension, diabetes, and hypercholesterolemia were recorded for all subjects. Study participants gave written informed consent prior to entering the study, which was approved by research and ethics committees of Arabian Gulf University and Salmaniya Medical Complex.

2.2. Biochemical analysis

Peripheral venous blood samples were obtained at 7:00–9:00 am during the early follicular phase of the menstrual cycle (days 2–5) for control subjects, or any day for women with PCOS, after an overnight (>12 h) fast. FSH, LH, PRL, total testosterone, progesterone, 17α-hydroxyprogesterone, and TSH were determined using immunofluorometric assay or radioimmunoassay (coefficients of variation (CV) < 5% for all tests). Insulin was measured by enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions (R&D Systems, Minneapolis, MN). Indices of insulin resistance included homeostasis model assessment of insulin resistance (HOMA-IR: (fasting glucose (mmol/l)/fasting insulin (μIU/ml))/22.5), and revised QUICKI, the latter used as cases and controls spanned several BMI categories.

2.3. Serum adiponectin measurement

Peripheral venous blood was collected into plain tubes (no anticoagulants). Serum was prepared by centrifugation of coagulated blood at 2000*g* for 10 min at 4 °C, and was stored in aliquots at or below −30 °C. Samples were tested in duplicates for total (Cat. No. DRP300) and HMW (Cat. No. DHWADO) adiponectin levels by sandwich enzyme-linked immunosorbent assay (R&D Systems). For total adiponectin, assay sensitivity was 0.891 ng/ml, and inter-assay and intra-assay precision (CV%) were 6.5% and 3.5%, respectively. For HMW-adiponectin, assay sensitivity was 0.989 ng/ml, and inter-assay and intra-assay precision (CV%) were 8.5% and 3.0%, respectively.

2.4. Statistical analyses

Statistical analyses were performed using SPSS (version 21; IBM, Armonk, New York). Categorical variables were expressed as percentages of total, while continuous variables were presented as mean ± SD. Student's *t*-test was used to determine differences in means, and Pearson χ^2 or Fisher's exact test was used to assess inter-group significance. For continuous variables that did not follow a normal distribution, we used nonparametric analysis: Mann–Whitney *U*-test for two group comparisons, or Kruskal–Wallis test for multiple group comparisons; quantitative data described as medians and range values. Correlation among continuous variables was determined by Spearman correlation coefficient (*r*). The risk of PCOS was estimated in women with PCOS relative to control women by calculating the odds ratios (OR) and 95% confidence interval (CI), according to the method of Woolf.

3. Results

3.1. Study subjects

The characteristics of women with PCOS and control women are shown in Table 1. Compared to controls, women with PCOS were younger ($P = 0.022$), had higher BMI ($P = 0.001$), but comparable waist–hip ratio (WHR). Since age and obesity influence metabolic profile, all further comparisons were adjusted for age and BMI. Relative to control women, women with PCOS had significantly higher LH ($P = 0.032$), fasting plasma insulin ($P = 0.002$) and glucose ($P = 0.020$), but decreased insulin sensitivity (assessed by HOMA-IR ($P = 0.001$) and QUICKI ($P = 0.004$)), and SHBG ($P < 0.001$). No significant inter-group differences were recorded for FSH ($P = 0.825$), testosterone ($P = 0.590$), or serum lipids ($P > 0.050$). In view of their contribution to adiposity and insulin sensitivity, we also assessed lifestyle factors in PCOS women and control subjects, Weight control ($P = 0.491$), physical activity levels ($P = 0.853$), and special dietary requirements ($P = 0.075$) did not differ between women with and without PCOS (data not shown). However, weight gain of ≥5 kg over a 6-months period was more pronounced in women with PCOS than control women.

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