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CLINICAL ARTICLE

Thyroperoxidase antibodies and polycystic ovarian morphology

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ABSTRACT

Objective: To evaluate the association between polycystic ovarian morphology (PCOM) and thyroperoxidase antibody level. *Methods:* A cross-sectional study was undertaken of women aged 15–49 years living in one of four provinces in Iran recruited between February 2009 and November 2010. Eligible women did not have hirsutism and were eumenorrheic. All participants underwent a comprehensive interview, clinical examination, blood sampling, and ultrasonographic assessment. The serum concentration of thyroperoxidase antibodies was compared between women with and without PCOM. *Results:* Among 491 participants, 74 (15.1%) had PCOM. In total, 11 (14.9%) women with PCOM and 61 (14.6%) women with normal morphology tested positive for thyroperoxidase antibodies. The serum concentration of thyroperoxidase antibodies was higher among women with PCOM (48.45 ± 135.74 IU/mL) than among those with normal ovarian morphology (37.99 ± 96.49 IU/mL), but the difference was not significant ($P = 0.42$). *Conclusion:* Thyroperoxidase antibody levels were higher in Iranian women with PCOM than in women with normal morphology, although the difference was not significant. Larger longitudinal studies are needed to investigate whether the treatment of thyroid disorders can prevent the development of PCOM.

1. Introduction

Some endocrine disorders—such as hypothyroidism, Cushing syndrome, congenital adrenal hyperplasia, and hypothalamic amenorrhea—and some metabolic abnormalities are more prevalent among patients with polycystic ovary syndrome (PCOS) [1]. The endocrine environment, obesity, and insulin resistance in women with PCOS could contribute to an increase in the number of follicles or ovarian volume [2,3]—conditions that are considered as polycystic ovarian morphology (PCOM) [3,4]. An increased number of follicles might lead to irregular menstrual cycles and/or increased androgen production [5]. There is some evidence [6] that women with PCOS also have increased serum levels of autoimmune antibodies, including anti-ovarian and anti-thyroid antibodies, although the exact autoimmune mechanism of PCOS is still unclear. The autoantibodies have been hypothesized to activate follicular recruitment in the ovaries [7].

Autoimmune thyroiditis is characterized by chronic inflammation of the thyroid gland; it is caused by viral infections, stress, and sex hormone imbalances, and can lead to hypothyroidism [6]. Most patients with autoimmune thyroiditis test positive for thyroperoxidase antibodies (TPO-Abs) and/or thyroglobulin antibodies (Tg-Abs), and ultrasonography of the thyroid shows a typical echogenic pattern [8]. Among patients with PCOS, a significant correlation between antinuclear antibodies and thyroid-stimulating hormone (TSH) levels has been established [9], and TPO-Abs and/or Tg-Abs can be increased in these patients [8,10,11]. The prevalence of autoimmune thyroiditis among women with PCOS has been reported to be 42.3% on the basis of thyroid ultrasonography and 26.9% on the basis of an assessment of TPO-Abs and Tg-Abs [10].

Hypothyroidism is three times more prevalent among women with PCOS than in the general female population [7], and it can initiate, stabilize, or worsen PCOS. Both disorders independently influence fertility and reproduction [2,11–13]. Thyroid hormones have direct effects on the ovaries and indirectly affect reproduction by interacting with sex-hormone-binding proteins [14]. Human oocytes have thyroid hormone receptors, and cooperation between thyroid hormones and the follicle-stimulating hormone (FSH)-mediated luteinizing hormone/human chorionic gonadotropin receptor is needed to stimulate granulosa cells to differentiate and produce progesterone [2]. Moreover, hypothyroidism might interfere with the pulsatile secretion of gonadotropin-releasing hormone, which disturbs the normal path to follicular development and ovulation through delay of the luteinizing hormone response [15,16]. The achievement of euthyroidism in hypothyroid patients can result in a decrease in ovarian volume, the resolution of ovarian cysts, and the reversal of PCOM, and hormonal impairment can be ameliorated [17].

Given the lack of community-based data on the relationship between autoimmune thyroiditis and the development of PCOM, the present study aimed to assess the association between PCOM and the TPO-Ab titer as a marker of thyroid autoimmunity.

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2. Materials and methods

The participants of the present cross-sectional study were selected from 1126 women aged 18–45 years who had participated in the Iranian PCOS prevalence study conducted from February 1, 2009, to November 15, 2010, in various geographical regions of Iran. The study design, recruitment process, and data collection for the PCOS prevalence study have been described elsewhere [18]. Briefly, the participants were selected from Iranian household lists prepared by the Iranian Ministry of Health and Medical Education using a stratified, multistage probability cluster sampling method. The PCOS prevalence study was approved by the ethics committee of the Iranian Ministry of Health and Medical Education and all participants provided written informed consent.

All participants in the PCOS prevalence study underwent comprehensive interviews and blood pressure, anthropometric, hormonal, and metabolic assessments, except for 97 who did not attend the clinics and 25 women for whom no hormonal and metabolic profiles were available. For the present analysis, only women without hirsutism and menstrual irregularity were included. Pregnant (n = 43) and menopausal (n = 37) women, and those with PCOS according to the Rotterdam definition (n = 136), anovulation (n = 77), hyperandrogenism (n = 205), or hyperprolactinemia (n = 5) were excluded, as were women for whom data were missing (n = 10). The final analysis included 491 non-hirsute eumenorrheic women.

A blood sample was obtained from all participants on the second or third day of their spontaneous menstrual cycles. All serum samples were stored at −80°C until the time of measurement. Additionally, each participant underwent a transvaginal or transabdominal ultrasonographic examination of the ovaries on the same day as the blood samples were collected. The ultrasonographic examinations were performed by an experienced sonographer (one sonographer in each of the four provinces) using a 3.5-MHz transabdominal transducer or a 5-MHz transvaginal transducer.

Dehydroepiandrosterone sulfate (DHEAS) was measured by enzyme immunoassay (EIA) with a commercial kit from DRG Instruments (Marburg, Germany). Total testosterone, 17-hydroxyprogestrone, and androstenedione were also measured by EIA and sex-hormone-binding globulin (SHBG) was measured by immunoenzymometric assay (IEMA), all with commercial kits from Diagnostic Biochem Canada (Dorchester, ON, Canada). Insulin was measured using an IEMA kit from Mercodia (Uppsala, Sweden), and TPO-Abs were determined using an IEMA kit from Monobind (Costa Mesa, CA, USA). Glucose, triglycerides, total cholesterol, low density lipoprotein, and high density lipoprotein were measured by enzymatic colorimetry using a kit from Pars Amazon (Tehran, Iran). All enzyme-linked immunosorbent assays were read on a Sunrise reader (Tecan, Salzburg, Austria). Luteinizing hormone, FSH, prolactin, and TSH were measured by immunoradiometric assay using a commercial kit from Izotop (Budapest, Hungary) and the Dream Gamma-10 gamma counter (Shin Jin Medics, Seoul, South Korea).

The intra-assay and interassay coefficients of variation were 1.9% and 2.5%, respectively, for DHEAS; 1.7% and 2.3% for total testosterone; 4.8% and 6.8% for 17-hydroxyprogestrone; 4.5% and 6.8% for androstenedione; 0.8% and 2.4% for SHBG; 0.9% and 1.1% for insulin; 2.5% and 5.3% for anti-TPO; 1.3% and 2.9% for glucose; 1.8% and 2.7% for triglycerides; 0.8% and 2.8% for total cholesterol; 0.7% and 2.9% for low density lipoprotein; 0.9% and 3.3% for high density lipoprotein; 1.6% and 4.2% for luteinizing hormone; 1.4% and 2.0% for FSH; 2.3% and 3.5% for prolactin; and 2.1% and 3.1% for TSH.

PCOM was defined as the presence of 12 or more follicles with a diameter of 2–9 mm and/or an increased ovarian volume of 10 cm^3 or more on ultrasonography [3,4]. A TPO-Ab titer of 40 IU/mL or more was considered a positive test result for autoimmune thyroiditis. The homeostatic model assessment for insulin resistance (HOMA-IR) index was used to quantify insulin resistance and was calculated as fasting insulin (mIU/L) multiplied by fasting blood sugar (mg/dL), divided by 405. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters; a BMI of 25.0–29.9 was defined as overweight and a BMI of 30.0 or more was defined as obese.

The data were analyzed with SPSS version 15 (SPSS Inc, Chicago, IL, USA). The unpaired *t* test was used to compare distributions between the two groups. Linear regression models adjusted for independent variables including age, BMI, insulin, HOMA-IR, luteinizing hormone, FSH, and TSH were used to evaluate the association of TPO-Abs with ovarian follicular number and with ovarian volume in separate models. $P<0.05$ was considered statistically significant.

3. Results

The mean age of the 491 study participants was 35.2 ± 7.5 years. The mean serum concentration of TPO-Abs was 39.6 ± 103.3 IU/mL. More than one-third (n = 192 [39.1%]) of the participants were overweight and more than one-fifth (n = 110 [22.4%]) were obese.

Of the 491 women, 417 (84.9%) did not have hyperandrogenism/PCOS, whereas 74 (15.1%) women had PCOM. Positive results for TPO-Abs were recorded for 11 (14.9%) women with PCOM and 61 (14.6%) without PCOM. The serum level of TPO-Abs was higher in the PCOM group, but the difference was not significant ($P = 0.42$) (Table 1). The level of androstenedione was significantly higher in women with PCOM than in those without ($P = 0.004$) (Table 1).

Overall, 72 (14.7%) women tested positive for TPO-Abs, and these women were significantly older than women with a normal TPO-Ab titer ($P = 0.02$) (Table 2). Women who tested positive for TPO-Abs had a higher weight, waist circumference, hip circumference, BMI, blood pressure, insulin level, and HOMA-IR than did those with normal antibody levels, but the differences between the groups were not significant (Table 2). Compared with women with normal TPO-Abs results,

Table 1
Demographic, metabolic, and hormonal features, by ovarian morphology.[a]

Feature	Polycystic ovarian morphology (n = 74)	Normal morphology (n = 417)	*P* value
Age, y	34.41 ± 7.73	35.36 ± 7.47	0.32
Weight, kg	67.50 ± 11.68	66.84 ± 12.43	0.67
Height, cm	159.24 ± 6.48	158.24 ± 6.16	0.20
Waist circumference, cm	85.78 ± 13.67	84.72 ± 11.99	0.49
Hip circumference, cm	105.08 ± 11.93	104.86 ± 11.19	0.87
Body mass index[b]	26.66 ± 4.64	26.74 ± 5.04	0.90
Systolic blood pressure, mm Hg	111.22 ± 13.54	109.11 ± 13.73	0.22
Diastolic blood pressure, mm Hg	70.27 ± 11.70	68.78 ± 10.86	0.28
Fasting blood sugar, mmol/L	4.81 ± 1.92	4.90 ± 1.19	0.56
Insulin, pmol/L	61.05 ± 52.30	57.57 ± 43.89	0.54
HOMA-IR	2.16 ± 3.17	1.89 ± 1.96	0.33
Total cholesterol, mmol/L	4.73 ± 1.05	4.81 ± 1.12	0.54
Triglycerides, mmol/L	1.66 ± 1.36	1.60 ± 1.09	0.70
High density lipoprotein, mmol/L	1.21 ± 0.35	1.16 ± 0.34	0.25
Low density lipoprotein, mmol/L	2.77 ± 0.84	2.92 ± 0.97	0.19
Thyroxine, nmol/L	8.00 ± 2.23	8.21 ± 2.00	0.41
TPO-Abs, IU/mL	48.45 ± 135.74	37.99 ± 96.49	0.42
Thyroid-stimulating hormone, IU/L	3.36 ± 3.09	3.38 ± 2.83	0.95
FSH, IU/L	7.02 ± 3.22	8.27 ± 6.73	0.01
LH, IU/L	4.79 ± 2.41	5.37 ± 4.78	0.31
LH/FSH ratio	0.76 ± 0.45	1.03 ± 5.01	0.65
Total testosterone, nmol/L	1.70 ± 0.73	1.74 ± 0.80	0.65
Dehydroepiandrosterone sulfate, μmol/L	6.94 ± 3.55	6.71 ± 3.88	0.64
17-hydroxyprogesterone, ng/dL	1.64 ± 0.77	1.66 ± 0.99	0.85
Androstenedione, nmol/L	10.36 ± 3.70	8.88 ± 2.96	0.004
Sex-hormone-binding globulin, nmol/L	72.85 ± 23.39	72.52 ± 24.03	0.91
Free androgen index	2.62 ± 1.42	2.68 ± 1.45	0.72

Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; TPO-Abs, thyroid peroxidase antibodies; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

[a] Values are given as mean ± SD unless indicated otherwise.

[b] Calculated as weight in kilograms divided by the square of height in meters.

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