IS THERE A RELATIONSHIP BETWEEN SERUM IGF-1 AND THYROID NODULE, THYROID OR OVARIAN VOLUME IN POLYCYSTIC OVARIAN SYNDROME?

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Abstract

Context. Studies investigating the association between serum IGF-1, and thyroid nodule, ovarian or thyroid volume in polycystic ovarian syndrome (PCOS) are limited.

Objective. We aimed to analyze the association between serum IGF-1 level, and ovarian or thyroid volume, or thyroid nodule in PCOS.

Design. The study was performed between June 2017 and August 2019 as prospective design.

Subjects and Methods. Adult females with new-onset PCOS were included. The patients having comorbid illness, or using medication were excluded. Basic tests, thyroid and ovarian sonography were performed. The patients were grouped according to thyroid nodule(absent/present) and ovarian volume (<10mL/≥10mL). We planned to find a positive association between IGF-1, and thyroid nodule, thyroid or ovarian volume in PCOS.

Results. Of total 118 patients, 11(9%) had thyroid nodule. The patients with thyroid nodule had a higher ovarian volume (p=0.006). No correlation was found between GH or IGF-1, and thyroid or ovarian volume. IGF-1 was not a predictor for thyroid nodule or higher ovarian volume. Thyroid nodule was a significant predictor for higher ovarian volume.

Conclusion. Our study is the first to analyze the association between IGF-1 and thyroid nodule in PCOS. We found that thyroid nodule was associated with thyroid and ovarian volume, but IGF-1 was not associated with thyroid nodule, thyroid or ovarian volume.

Keywords: polycystic ovarian syndrome, IGF 1, thyroid nodule, PCOS, ovarian volume, thyroid volume.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a complex heterogeneous disorder consisting of several clinical symptoms and signs such as ovulatory dysfunction, menstrual irregularity, hyperandrogenism and sonographic evidence of polycystic ovaries (PCO) (1). It was first described by Stein and Leventhal (2). In a meta-analysis, the rate of PCOS was found in a range of 6-10% depending on the criteria used for diagnosis (1). According to the presence of clinical features, PCOS can be classified into four phenotypes: A, B, C, D (3, 4). PCOS was found to be associated with obesity, insulin resistance, type 2 diabetes mellitus (T2D) and metabolic syndrome (5-7). These adverse outcomes were more frequently defined in phenotype A (8-10).

Hyperinsulinemia decreases insulin-like growth factor binding protein (IGFBP), and hence, insulin-like growth factor 1 (IGF-1) was shown to be elevated in the patients with PCOS (11,12). Several studies indicated that therapeutic advances targeting IGF-1 system would be important in the management of PCOS (13,14). miRNAs were studied and implicated in the development of PCOS in rat models, via interacting with IGF-1 system (14). Again, targeting miRNAs, such as overexpression of miR-19b was shown to be a good therapeutic choice in PCOS (15). In one study, improvement in clinical findings of PCOS after rosiglitazone was proposed to be associated with a decrease in IGF-1 levels (16).

There is a limited number of studies investigating the association between serum IGF-1 levels and ovarian or thyroid volume in the patients with PCOS. In one study, there was no correlation between ovarian volume and IGF-1 level in the patients with central precocious puberty (17). Frequency of thyroid nodule and volume of thyroid gland was shown to be similar in PCOS and control groups in a Turkish population (18). No correlation was found between thyroid volume and IGF-1 level in the patients with PCOS in another study (19). We aimed to analyze the association between serum IGF-1 level, and ovarian volume, thyroid volume, or presence of thyroid nodule in the patients with PCOS.

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MATERIALS AND METHODS

Adult female patients who were admitted to our clinics and diagnosed as new-onset PCOS between June 2017 and August 2019 were included in our study. The diagnosis of PCOS was based on Rotterdam criteria (20). The patients younger than 18-year-old were not included in our study. The patients with a known history of thyroid dysfunction, hypertension, diabetes mellitus, cardiovascular disease, ovarian mass or surgery, or any other comorbid illnesses were excluded. The patients with a history of using thyroid or antithyroid medication, antidiabetic drug, oral contraceptive, metformin or any PCOS-related medication for a past history of PCOS were also excluded. The patients lacking data of thyroid or ovarian sonographic analyses were not included.

Our study was designed as prospective manner and approved by the Ethics Committee of our university, and we performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was taken from each participant.

Basic demographic (age) and clinical (height, weight, body mass index, waist and hip circumference, phenotype of PCOS, symptoms such as menstrual irregularity, hirsutism, acne, alopecia, weight gain, age at menarche, Ferriman-Gallwey score) features were recorded and analyzed. Body weight (kg) and height (m) were measured with patient barefoot and having light clothes. Body mass index (BMI) was calculated as weight/square of height (kg/m^2), waist to hip ratio (WHR) as waist(cm) divided by hip (cm). Ferriman-Gallwey score (FGS) was evaluated by physical examination of the patients. For all 9 androgen sensitive areas, 0 to 4 points were given to quantify hair growth. More than 6 points were accepted as abnormal (1).

Baseline laboratory findings were measured and analyzed. All laboratory tests were measured at morning fasting in early follicular phase, or in a random day if menstrual cycle was absent. Fasting blood glucose (FBG), low-density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (Tchol), triglyceride (TG) were designated as mg/dL; insulin was designated as mIU/L, C-peptide (Cp) ng/mL, HbA1c %, TSH mIU/L, free T4 (fT4) ng/dL, free T3 (fT3) pg/mL, anti-thyroid peroxidase (ATPO) IU/mL, 25(OH)D3 ng/mL. Dehydroepiandrosterone sulfate (DHEAS) mcg/dL, total testosterone (Ttest) ng/dL, luteinizing hormone (LH) IU/L, follicle stimulating hormone (FSH) IU/L, prolactin (PRL) ng/mL, estradiol (E2) pg/mL, progesterone ng/mL, adrenocorticotropic hormone (ACTH) pg/mL, cortisol mcg/dL, growth hormone (GH) ng/mL, IGF-1 ng/mL. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as FBG (mg/dL) × fasting insulin(U/L)/405, and LH/FSH ratio as LH divided by FSH. HOMA-IR of >2.7 was accepted as insulin resistance (21).

IGF-1 and GH were measured with chemiluminescence method by a tool marked Immulite 2000 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Normal reference range of IGF-1 in age group of 18-20, 21-23, 24-25, 26-30, 31-40, 41-50, >50 year-old females was determined as 193-575, 110-521, 129-480, 96-502, 100-494, 101-303, and 78-258 ng/mL in our laboratory, respectively. Glucose was measured by a glucose oxidase method with the Olympus AU-2700 analyzer. TG, Tchol and HDL were measured by an enzymatic method with Olympus AU-2700 analyzer using reagents from Olympus Diagnostics (Gmbh, Hamburg, Germany). LDL was calculated with the Friedewald's equation method. Insulin, PRL, E2, progesterone, Ttest, DHEAS, FSH, LH, ACTH, total cortisol, TSH, fT4, fT3, and ATPO were measured with the chemiluminescence method by using the Beckman Coulter marked and DxI 800 model device (Beckman Coulter, Inc. 4300 N. Harbor Blvd., Fullerton, CA 92835 U.S.A.). HbA1c was measured as NGSP (National Glycohemoglobin Standardization Program) units by HPLC method (high purification liquid chromatography). Basal Cp were measured early in the morning after an overnight fasting with chemiluminescence method by a tool marked Siemens Immulite 2000 (Siemens Medical Solutions Diagnostics 5210 Pacific Concourse Drive, Los Angeles, CA 90045-6900, USA). We measured 25(OH) D3 level (ng/mL) by immunoassay. The reference range of our laboratory was used to determine the upper and lower limit of normal for all laboratory parameters.

Differential diagnosis such as nonclassical congenital adrenal hyperplasia (NCCAH), hypothyroidism, Cushing's syndrome or hyperprolactinemia were excluded for all patients after basal tests. Basal morning serum 17(OH) progesterone measurement in early follicular phase, and 1mg overnight dexamethasone suppression test were performed for all patients to exclude NCCAH and Cushing's syndrome, respectively. The patients having 17(OH)progesterone level greater than 200 ng/dL in the early follicular phase were excluded from the study. The patients having cortisol level of ≥1.8mcg/dL after overnight 1 mg dexamethasone underwent confirmation tests for Cushing syndrome, such as 2-day

2 mg dexamethasone suppression test. The patients whose Cushing syndrome could not be ruled out were excluded from the study.

The participants were subgrouped according to BMI (<30 *vs.* ≥30 kg/m²), FGS (<6 *vs.* ≥6), FBG (<100 *vs.* 100-125 mg/dL), HbA1c (<5.7 *vs.* 5.7-6.4%), presence of prediabetes according to both HbA1c (5.7-6.4%) and FBG (100-125 mg/dL), Cp (1-2 *vs.* ≥2 ng/mL), HOMA-IR (<2.7 *vs.* ≥2.7), DHEAS (normal *vs.* increased), T test (normal *vs.* increased), LH/FSH ratio (<1 *vs.* ≥1), ATPO positivity, 25(OH)D3 (<10 *vs.* ≥10 ng/mL), IGF1 (normal *vs.* decreased), presence of hypertriglyceridemia, hypercholesterolemia or low HDL level.

Thyroid sonography and suprapubic ovarian sonography were performed for all patients, by the same skilled endocrinologist and the same radiologist, respectively. Thyroid sonography was performed with the 7.5 MHz linear transducer of an SONOACE R3 ultrasound machine (Samsung Medison Co., Korea 2015). The patients were divided into two groups according to the presence of thyroid nodule on thyroid sonography. Thyroid echogenicity (normal *vs.* decreased) and vascularity (normal *vs.* increased) were also assessed by sonography (22). After measuring thickness, width, and length, the volume of each thyroid lobe was calculated by the formula: Volume = Anteroposterior (thickness) × Mediolateral (width) × Craniocaudal (length) × 0.49 (conversion factor) (23). Total thyroid volume (TTV) was calculated by the sum of the volume of each thyroid lobe.

Ovarian sonography was performed in all participants with Voluson P6 (General Electric Ultrasound, Seongnam, Korea) equipped with a 2-5 MHz transducer. After measuring the width, length and thickness, the volume of each ovary was calculated by the formula: d1×d2×d3×0.523 (24). Mean ovarian volume was calculated by the sum of volume of each ovary divided by two. Both the mean ovarian volume (MOV) and the volume of larger ovary were recorded and analyzed. If 12 follicles or more in each ovary measuring 2 to 9 mm in diameter were detected, sonographic criterion of PCO was accepted. The patients were divided into two groups by ovarian volume: > 10 mL *vs.* <10 mL, or presence or absence of PCO.

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of data. We used Shapiro-Wilk test to assess data with normal distribution. Homogeneity of variance was evaluated by Levene test. When comparing independent two groups according to quantitative data, Independent-Samples T test was used. In comparison of categorical variables each other, Pearson Chi-Square test was used. To determine the risk groups for parameters affecting thyroid nodule, we used univariate logistic regression analysis. Odds Ratio (OR) was used with 95% confidence intervals (CI) to show that risk groups had a higher risk than the other subjects. To analyze the correlations of variables with each other, Spearman's correlation(r) analysis was used. Quantitative variables were defined as mean (X) ±standard deviation (SD) in the tables. Categorical variables were demonstrated as number (n) and percent (%), and p value of <0.05 was accepted as statistically significant.

RESULTS

A total of 118 patients with PCOS was included; 11 (9%) of total had a thyroid nodule detected on thyroid sonography. Mean age was 22.38(±4.35), and similar in two groups (p=0.532). The patients with thyroid nodule had a lower mean TSH (p=0.044), and a higher mean thyroid and ovarian volume (p=0.026, p=0.006, respectively). Mean IGF-1 levels were similar in both groups (p=0.337). There were no differences according to other clinical and laboratory findings between two groups. Distribution of PCOS phenotypes was similar in both groups (p=0.957) (Table 1).

There was a significant negative correlation between GH, and BMI or TSH (p=0.002 and p=0.013, respectively), and a positive correlation between GH and IGF-1 (p=0.029). There was a positive correlation between IGF-1 and DHEAS (p=0.035). A positive correlation was found between thyroid volume and WHR (p=0.045). Mean and larger ovarian volumes were positively correlated with testosterone or LH, and negatively correlated with prolactin or progesterone. No significant correlation was found between GH or IGF-1, and thyroid or ovarian volume (p>0.05) (Table 2). There was no significant correlation between HOMAIR, and thyroid volume (p=0.265, r=-0.103) or ovarian volume (p=0.248, r=0.140). If analyzing the patients with thyroid nodule alone, again, no significant correlation was found between GH or IGF-1, and thyroid or ovarian volume (p>0.05).

Hypercholesterolemia was found as a significant predictor for the presence of thyroid nodule. The presence of oligomenorrhea and higher DHEAS were shown as significant predictors for a higher ovarian volume (Table 3).

Table 1. Baseline clinical and laboratory findings of the patients

| | Nodule | | | |
	Present (n=11)	Absent (n=107) Mean(±SD)	Total (n=118)	p value
Age (year)	23.27(4.98)	22.29(4.30)	22.38(4.35)	0.532
Menarche age (year)	13.36(1.20)	12.78(1.22)	12.83(1.22)	0.111
Height (cm)	160.64(66.22)	163.49(5.58)	163.22(5.72)	0.065
Body weight (kg)	64.32(12.62)	71.13(16.04)	70.49(15.83)	0.259
BMI (kg/m²)	24.89(4.60)	26.64(6.09)	26.48(5.98)	0.423
Waist (cm)	76.82(9.09)	80.37(12.00)	80.04(11.77)	0.415
Hip (cm)	100.55(10.40)	102.79(12.35)	102.58(12.16)	0.544
WHR	0.76(0.06)	0.78(0.09)	0.78(0.09)	0.667
FGS	10.91(5.82)	11.16(5.12)	11.14(5.17)	0.896
FBG (mg/dL)	86.72(5.33)	88(8.51)	87.88(8.25)	0.633
Insulin (mIU/L)	10.39(6.24)	12.65(7.90)	12.44(7.76)	0.557
HOMA-IR	2.26(1.39)	2.79(1.85)	2.74(1.82)	0.508
Cp (ng/mL)	1.85(0.78)	2.22(1.00)	2.19(0.98)	0.265
HbA1c (%)	5.20(0.40)	5.30(0.32)	5.29(0.33)	0.707
DHEAS (mcg/dL)	296.95(154.45)	274.44(135.35)	276.54(136.67)	0.547
Ttest (ng/dL)	57.57(15.53)	64.29(23.71)	63.66(23.10)	0.343
FSH (IU/L)	5.96(1.41)	6.36(2.33)	6.33(2.26)	0.680
LH (IU/L)	9.53(4.47)	13.17(11.06)	12.83(10.66)	0.554
LH/FSH	1.64(0.72)	2.06(1.28)	2.02(1.24)	0.413
PRL (ng/mL)	12.47(8.32)	18.17(22.52)	17.63(21.64)	0.072
E2 (pg/mL)	64.55(34.50)	94.58(86.02)	91.78(82.96)	0.505
Progesterone (ng/mL)	0.79(0.51)	1.51(2.26)	1.44(2.17)	0.426
TSH (mIU/L)	1.50(0.74)	2.13(1.18)	2.07(1.16)	0.044
fT4 (ng/dL)	1.03(0.12)	1.02(0.19)	1.02(0.18)	0.890
fT3 (pg/mL)	3.06(0.36)	3.29(0.46)	3.27(0.46)	0.243
GH (ng/mL)	3.20(3.56)	2.86(3.75)	2.90(3.71)	0.059
IGF-1 (ng/mL)	207.46(90.78)	185.58(67.93)	188.06(70.61)	0.337
25(OH)D3 (ng/mL)	19.02(9.90)	15.14(11.73)	15.50(11.59)	0.107
TG (mg/dL)	76.27(25.77)	99.70(49.73)	97.51(48.41)	0.054
LDL (mg/dL)	116.11(40.53)	97.90(26.27)	99.59(28.17)	0.147
Tchol (mg/dL)	189.81(44.11)	170.99(31.65)	172.74(33.23)	0.134
HDL (mg/dL)	58.34(11.93)	52.97(12.23)	53.47(12.25)	0.166
TTV (cm³)	8106.65(2464.93)	6623.92(3116.59)	6762.14(3083.29)	0.026
MOV (cm³)	17622.48(9800.24)	10129.29(6667.42)	11092.70(7494.91)	0.006
Larger ovarian volume (cm³)	20073.84(10541.83)	12052.56(8576.85)	13083.87(9174.16)	0.008
Phenotype		**N**		**p value**
A	8	82	90	
B	2	14	16	0.957
C	1	10	11	
D	0	1	1	

DISCUSSION

PCOS is the most common endocrinopathy in the women of reproductive age who may be presented with diverse clinical phenotypes (25). We performed our study based on the paucity of data concerning the association among IGF-1, thyroid, and ovary in PCOS. And, we found that the patients with thyroid nodule had a higher thyroid and ovarian volume; however, IGF-1 level was similar in the patients having thyroid nodule or not. No correlation was detected among IGF-1, thyroid or ovarian volume.

The presence of thyroid nodule, thyroid function or volume have been investigated in various endocrinopathies. For example; the frequency of thyroid nodule, and thyroid volume were found to be higher in the patients with DM or prediabetes (26). We knew that insulin/IGF-1 stimulate cell cycle progression and cell proliferation in thyrocyte culture systems and they stimulated the growth of thyroid cancer precursors (27,28). It was also demonstrated that the individuals with insulin resistance had a higher frequency of thyroid nodule (29). Insulin resistance may be accepted as the major pathophysiological mechanism in PCOS

Table 2. Correlation of the clinical and laboratory parameters

Variables	GH	IGF-1	Thyroid volume	Mean ovarian volume	Larger ovarian volume
			r (p)		
Age (year)	-0.123 (0.253)	-0.179 (0.095)	-0.174 (0.059)	0.000 (0.995)	0.000 (0.998)
BMI (kg/m²)	-0.320 (0.002)	-0.107 (0.319)	0.008 (0.129)	0.131 (0.280)	0.139 (0.253)
WHR	-0.135 (0.211)	0.064 (0.551)	0.185(0.045)	0.114 (0.346)	0.115 (0.345)
FBG (mg/dL)	-0.104 (0.336)	-0.048 (0.659)	-0.116 (0.213)	0.135 (0.266)	0.118 (0.333)
Cp (ng/mL)	-0.160 (0.135)	0.097 (0.368)	-0.105 (0.256)	-0.005 (0.967)	-0.030 (0.807)
HOMA IR	-0.156 (0.147)	0.007 (0.947)	-0.080 (0.391)	0.079 (0.517)	0.066 (0.589)
HbA1c (%)	-0.015 (0.886)	0.047 (0.663)	-0.059 (0.528)	0.276 (0.021)	0.264 (0.027)
DHEAS (mcg/dL)	0.088 (0.417)	0.225 (0.035)	0.119(0.199)	-0.051 (0.672)	-0.047 (0.698)
Ttest (ng/dL)	-0.107 (0.323)	0.197 (0.066)	0.117(0.206)	0.327 (0.006)	0.317 (0.007)
FSH (IU/L)	0.175 (0.102)	0.090 (0.403)	-0.056(0.545)	0.182 (0.132)	0.182 (0.132)
LH (IU/L)	0.107 (0.321)	0.011 (0.918)	-0.102(0.270)	0.330 (0.005)	0.333 (0.005)
PRL (ng/mL)	-0.017 (0.875)	0.043 (0.693)	0.095(0.307)	-0.247 (0.040)	-0.254 (0.034)
E2 (pg/mL)	-0.085 (0.429)	-0.054 (0.616)	-0.140(0.130)	-0.019 (0.877)	-0.021 (0.864)
Progesterone (ng/mL)	-0.084 (0.437)	0.085 (0.434)	-0.038(0.685)	-0.270 (0.024)	-0.260 (0.030)
TSH (mIU/L)	-0.263 (0.013)	-0.099 (0.358)	-0.178(0.054)	-0.011 (0.927)	-0.016 (0.894)
fT4 (ng/dL)	-0.037 (0.730)	0.096 (0.373)	-0.056(0.548)	-0.164 (0.174)	-0.152 (0.209)
fT3 (pg/mL)	0.094 (0.383)	-0.011 (0.917)	-0.063(0.500)	0.246 (0.040)	0.228 (0.058)
25(OH)D3 (ng/mL)	0.107 (0.322)	-0.078 (0.470)	0.102(0.272)	0.049 (0.689)	0.051 (0.676)
GH (ng/mL)	1	0.233 (0.029)	-0.064(0.555)	-0.040 (0.742)	-0.087 (0.474)
IGF-1 (ng/mL)	0.233 (0.029)	1	0.117 (0.279)	-0.078 (0.520)	-0.059 (0.626)
TTV (cm³)	-0.064 (0.555)	0.117 (0.279)	1	0.050 (0.683)	0.105 (0.389)
MOV (cm³)	-0.040 (0.742)	-0.078 (0.520)	0.050(0.683)	1	0.985 (0.001)
Larger ovarian volume (cm³)	-0.087 (0.474)	-0.059 (0.626)	0.105(0.389)	0.985 (0.001)	1

Table 3. Clinical predictors for the presence of thyroid nodule and higher MOV (≥10 mL) (Univariate)

Variables	Thyroid nodule		MOV	
	OR (95% CI)	p value	OR (95% CI)	p value
Amenorrhea (absence/presence)	0.898 (0.843-0.957)	0.289	0.040 (0.000-3.955)	0.169
Oligomenorrhea (absence/presence)	0.815 (0.223-2.973)	0.756	0.032 (0.002-0.580)	0.020
Menometrorrhagia (absence/presence)	1.230 (0.303-4.990)	0.772	0.116 (0.006-2.327)	0.159
Hirsutism (absence/presence)	0.464 (0.088-2.451)	0.356	13.19 (0.268-649.8)	0.195
Acne (absence/presence)	0.461 (0.116-1.833)	0.262	4.022 (0.307-52.64)	0.289
Alopecia (absence/presence)	1.318 (0.379-4.581)	0.664	0.419 (0.048-3.673)	0.432
Weight gain (absence/presence)	0.306 (0.063-1.486)	0.124	0.415 (0.046-3.730)	0.432
BMI (<30/≥30)	0.769 (0.155-3.799)	0.746	0.375 (0.010-1.410)	0.596
FGS (<6/≥6)	0.918 (0.105-8.011)	0.939	0.372 (0.003-43.82)	0.685
HOMAIR (<2.7/≥2.7)	1.786 (0.513-6.222)	0.357	2.806 (0.323-24.39)	0.350
FBG (<100/≥100)	0.899 (0.844-0.957)	0.317	57.92 (0.052-63.92)	0.256
Cp (<2/≥2)	0.375 (0.094-1.491)	0.151	0.500 (0.188-1.332)	0.163
HbA1c (<5.7/≥5.7)	0.897 (0.841-0.957)	0.264	40.90 (0.015-11.51)	0.360
Prediabetes (absence/presence)	0.890 (0.831-0.953)	0.139	0.013 (0.000-144.8)	0.363
DHEAS (normal/increased)	2.043 (0.581-7.189)	0.258	11.36 (1.204-107.1)	0.034
Ttest (normal/increased)	0.468 (0.133-1.648)	0.228	0.005 (0.000-0.181)	0.004
LH/FSH ratio (<1/≥1)	0.576 (0.140-2.374)	0.440	0.895 (0.053-14.99)	0.939
AntiTPO (normal/increased)	0.901 (0.847-0.958)	0.382	4.593 (0.071-296.4)	0.473
25(OH)D3 (<10/≥10)	3.023 (0.623-14.68)	0.152	1.036 (0.389-2.762)	0.943
IGF-1 (decreased/normal)	1.109 (1.043-1.179)	0.420	0.163 (0.001-36.23)	0.511
Hypertriglyceridemia (absence/presence)	0.893 (0.836-0.955)	0.184	2.467 (0.540-11.26)	0.233
Hypercholesterolemia (absence/presence)	13.67 (3.323-51.37)	0.001	1.653 (0.079-34.54)	0.746
HDL (low/normal)	0.758 (0.209-2.744)	0.672	0.494 (0.070-3.467)	0.478
Thyroid echogenicity (decreased/normal)	0.692 (0.141-3.411)	0.650	1.007 (0.088-11.56)	0.996
Thyroid vascularity (normal/increased)	2.420 (0.452-12.94)	0.289	1.457 (0.014-150.9)	0.874
PCO (absence/presence)	0.677 (0.132-3.464)	0.638	1.863 (0.175-19.79)	0.606
MOV (<10/≥10)	14.18 (1.663-120.9)	0.003	NA	NA

and may contribute to phenotype (6). Hyperinsulinemia with insulin resistance leads to a mitogenic stimulus for ovarian theca cells, so that they expand, and increase the production of androgens, increasing ovarian volume (30). By decreasing sex hormone binding globulin, hyperinsulinism may also contribute to increased levels of free androgen. Moreover, resulting hyperandrogenemia may increase insulin resistance (6). Hyperinsulinemia and insulin resistance have been proposed to contribute to nodule formation and increased thyroid volume via insulin/IGF-1 signalling system, at least partially (27,31). It was well defined that the central mechanism of metabolic syndrome was insulin resistance (32). As expected, a higher frequency of thyroid nodule was found in the patients with metabolic syndrome in one study (p<0.001) (33). However, in our study, we could not show that HOMAIR or BMI were as significant predictor for thyroid nodule. Moreover, hyperandrogenemia, LH/FSH ratio, or prediabetes were not found as predictor for thyroid nodule. Therefore, we could not explain which hormonal factors might be associated with thyroid nodule in PCOS. Besides, in one study including PCOS patients, thyroid nodule prevalence was shown to be higher (30.1%) in the patients with PCOS comparing to our findings (18). The prevalence of thyroid nodule was 20% in age-matched controls in that study, and it also was higher than the prevalence of thyroid nodule in our PCOS patients. Thyroid volume was also found as higher in the patients with metabolic syndrome; and it may be associated with IR (p<0.01) (33). However, we could not show any correlation between HOMAIR and thyroid volume, similar to findings in the study done by Anaforoglu *et al.* (34). WHR is known to be associated with insulin resistance in adults with or without DM (35); however, we showed that it was positively correlated with thyroid volume, but not associated with ovarian volume or thyroid nodule.

In the literature, similar rates of thyroid nodule, autoimmune thyroid disease, and similar thyroid volume were detected in the patients with PCOS comparing to controls; however, contrast findings had also been reported (18,34,36,37). LH has been known to bind TSH receptor, and found to be positively correlated with thyroid volume in PCOS (19,38,39). Together with this, there is a limited number of studies according to the association between ovarian volume, and thyroid nodule or volume in PCOS. We found that mean ovarian volume was not correlated with thyroid volume, but it was a strong predictor for thyroid nodule. Higher ovarian and thyroid volume in

our patients with thyroid nodule could be explained by that insulin resistance might have an important role in all of them (29). However, in our study, HOMAIR or BMI was similar in the patients having thyroid nodule or not, and they were not correlated with thyroid or ovarian volume. HbA1c, albeit in non-diabetic range, was positively correlated with ovarian volume. It may be thought that increasing HbA1c is an indicator of worse metabolic profile and may be associated with phenotypic features of PCOS independently of HOMAIR. Some other factors, such as LH, were also shown to be correlated with thyroid and ovarian volume (19,40). We detected a positive correlation between ovarian volume and LH, but no correlation between thyroid volume and LH. Moreover, LH/FSH ratio was not a predictor for thyroid nodule. Based on these findings, we may conclude that complex interactions might explain the association between the thyroid and ovaries in PCOS, rather than each hormone or parameter alone. Although thyroid autoimmunity was frequently seen in the patients with PCOS comparing to controls in some studies, we showed that ATPO positivity, decreased thyroid echogenicity, and increased thyroid vascularity were not shown as significant predictors for increased ovarian volume. We may think that autoimmune process in thyroid gland may not correlate or occur concurrently with the pathogenetic process in polycystic ovaries.

There is a limited number of studies investigating the association between IGF-1 and thyroid nodule. Dogansen *et al.* showed that a higher IGF-1 was associated with the development of thyroid nodule in the patients with acromegaly (p=0.01) (41). However, thyroid nodule was not linked to a higher IGF-1 in another study including the patients with metabolic syndrome (42). Liu *et al.* showed that an increased serum IGF-1 level was found in the patients with thyroid nodule (p<0.05) (43). In another report of the same author, they evaluated IGF-1 and IGF-1 receptor protein and mRNA expression by immunohistochemistry and quantitative reverse transcriptase PCR (polymerase chain reaction) in surgically excised thyroid nodules (44). They found that both staining and mRNA expression of IGF-1 and IGF-1 receptor were higher in the patients with follicular adenoma, nodular thyroid disease, and papillary thyroid carcinoma. The expression of IGF-1 was higher in papillary thyroid carcinoma than in nodular thyroid disease. To our knowledge, there is no report demonstrating the association between serum IGF-1 level and thyroid nodule in PCOS in the literature.

We found that IGF-1 level was similar in the patients having thyroid nodule or not; and a lower level of IGF-1 was not a significant predictor for thyroid nodule. Based on this finding, we may propose that lower IGF-1 may not have a protective role in the development of thyroid nodule in PCOS, in contrast to acromegaly.

There is a limited number of studies showing the association between serum IGF-1 level within normal reference range and thyroid volume. In one study from Turkey, no correlation was found between IGF-1 and thyroid volume in the patients with PCOS (19). In another study, thyroid volume was found to be positively correlated with serum IGF-1 in the patients with acromegaly (r=0.375, p=0.05)(45). They also showed that a decrease in IGF-1 levels was a significant predictor for the decrease in thyroid nodule volume. Völzke *et al.* showed that serum IGF-1 level higher than upper tertile was associated with higher thyroid volume (OR 1.73 for women, 1.63 for men), and increased frequency of thyroid nodule (OR 1.27 for women, 1.58 for men) in a population-based study (46). Besides, we could not show any association between IGF-1 and thyroid volume. There is also limited evidence about the possible link between serum IGF-1 levels and ovarian volume in the patients with PCOS or without any chronic illnesses. In one study, no significant correlation was detected between ovarian volume and IGF-1 level in the patients with central precocious puberty (17). Increased fasting insulin and higher HOMAIR were found to be associated with higher ovarian volume in the patients with PCOS (47). Similarly, in another study, higher HOMAIR, fasting insulin, and testosterone levels were found to be associated with larger ovaries in adolescents with PCOS (48) Therefore, besides LH, insulin resistance may be thought as a more important factor to explain larger ovaries in PCOS. Based on the knowledge that insulin resistance and hyperinsulinemia lead to activation of insulin/IGF-1 system, we propose that serum IGF-1 level might be correlated with thyroid and ovarian volume in PCOS. However, we detected that there was no correlation between ovarian volume, and serum IGF-1 or HOMAIR, BMI, or WHR. We showed that ovarian volume was positively correlated with LH, testosterone, HbA1c, or fT3, and negatively correlated with PRL. Mild elevation in prolactin or DHEAS may be detected in the patients with PCOS (49). And, mild hyperprolactinemia causes inhibition of LH via central inhibition of GnRH. For this reason, prolactin is expected to be negatively associated with ovarian volume in PCOS, as in our study. The association

between DHEAS and insulin was confusing (50,51). Similar to our findings, DHEAS was negatively correlated with ovarian volume in the patients with PCOS in one study (52).

So, there was an effect of complex interaction of multiple hormones and clinical parameters on the ovarian or thyroid volume in PCOS. Kaltsas *et al.* investigated PCOS phenotype in women with active acromegaly (53). They found a positive correlation between IGF-1 and ovarian volume in the patients with PCOS phenotype (r = 0.851, P < 0.05). Besides IGF-1 level higher than normal range, some of the patients in that study had also an increased LH and/or testosterone level. We knew that acromegaly triggers hyperinsulinemia and insulin resistance, and may be associated with hyperandrogenemia (54). Therefore, the net effect of the multihormonal alterations observed in acromegaly on ovarian volume might not be adapted for PCOS. Otherwise, we evaluated the effect of serum IGF-1 level on ovarian volume in our patients with PCOS who did not have any other comorbid illnesses or used any medication.

Cp is co-secreted with insulin from beta cells at equimolar level, and indicator of endogenous insulin secretion. Cp secretion may be altered in several conditions such as insulin resistance, prediabetes or DM. In one study, mean basal fasting Cp level was found to be similar in patients with PCOS and controls (55). There is no report regarding any association between Cp and thyroid nodule or thyroid or ovarian volume in the literature. We found that Cp was not an indicator for thyroid nodule or increased ovarian volume, and it was also not correlated with GH, IGF-1, thyroid or ovarian volume. We assumed that higher Cp might present in individuals with hyperinsulinemia and insulin resistance, because of co-secretion of insulin and Cp. Therefore, we proposed that Cp would be associated with thyroid or ovarian volume. However, even HOMAIR was not correlated with these parameters, so Cp was not surprised.

There is a limited number of studies according to the association between thyroid nodule or volume, and ovarian volume in PCOS. Again, the number of studies investigating the association between IGF-1 and thyroid nodule is limited. Indeed, there is no report demonstrating the association between serum IGF-1 level and thyroid nodule in PCOS in the literature. The strength of our study is that we evaluated the association of serum IGF-1 with thyroid nodule, thyroid volume and ovarian volume in our patients with PCOS who did not have any other comorbid illnesses or used any medication. The effect of

treatment for PCOS on the association between IGF-1, thyroid and ovaries should be evaluated in the further studies including larger cohorts.

In conclusion, our findings suggest that there is a complex interaction between IGF-1, and thyroid nodule, thyroid or ovarian volume in PCOS. We found that thyroid nodule was associated with thyroid and ovarian volume, but not with IGF-1. If supported by future reports, it may be proposed that the patients with larger ovaries would be screened by sonography to detect a possible thyroid nodule. No correlation was detected between IGF-1, and thyroid or ovarian volume. It should be kept in mind that metabolic screening is essential in managing PCOS but we do not recommend routine measurement of IGF-1 in PCOS.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

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