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Polycystic ovary syndrome and Hashimoto's thyroiditis: An autoimmune relationship

Polikistik over sendromu ve Hashimoto tiroiditi: Otoimmün bir ilişki

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Abstract

Aim: Polycystic ovary syndrome (PCOS) and Hashimoto's thyroiditis (HT) are common and frequently comorbid diseases. A genetic predisposition and an inflammatory and autoimmune relationship have been posited between them. This study examines the role played by autoimmunity in the relation between PCOS and HT.

Methods: This case-control study was conducted at the Medical Park Hospital endocrinology and gynecology departments, Ordu, Turkey, from July 2015 to December 2018. Reproductive-age women diagnosed with PCOS based on the Rotterdam criteria, women diagnosed with HT, and healthy women with neither PCOS nor HT were included in the study. Thyroid function tests, thyroid autoantibodies, gonadotropins, androgen hormones, fasting glucose and insulin levels, and body mass index (BMI) were compared among the three groups. All patients also underwent pelvic and thyroid ultrasound examinations.

Results: Five hundred ninety-six women were included in the study, 254 in the PCOS group, 190 in the HT group, and 152 in the control group. BMI was significantly higher in the PCOS and HT groups than in the control group (P=0.012, and P=0.027, respectively). Menstrual and androgenic symptoms were also significantly higher in the patient groups than in the control group (P<0.001). The incidence of TPOAb and TgAb positivity was again significantly higher in the PCOS patients than in the controls (P<0.001).

Conclusion: This research demonstrated a higher prevalence of HT, together with elevated TSH, anti-TPO, and anti-Tg levels in PCOS patients. Our data suggest that thyroid functions and ovaries should be screened later in life in patients with PCOS and HT.

Keywords: Hashimoto's thyroiditis, Polycystic ovary syndrome, Thyroid autoantibodies, Autoimmunity

Öz

Amaç: Polikistik over sendromu (PKOS) ve Hashimoto tiroiditi (HT) sıklıkla birbirine eşlik eden yaygın hastalıklardır. Genetik, inflamasyon ve otoimmünite iki hastalığın arasındaki ilişkide mevcuttur. Bu çalışma otoimmünitenin PCOS ve HT arasındaki ilişkideki rolünü incelemektedir.

Yöntemler: Bu vaka-kontrol çalışması, Ordu Medical Park Hospital endokrinoloji ve jinekoloji bölümlerinde, Temmuz 2015 - Aralık 2018 arasında yapılmıştır. Rotterdam kriterlerine göre reprodüktif yaşlarda PKOS tanılı, HT tanılı kadınlar ve ne PCOS ne de HT tanısı olmayan sağlıklı gönüllüler çalışmaya dahil edildi. Üç grup arasında tiroid fonksiyon testleri, tiroid otoantikorları, gonadotropinler, androjen hormonları, açlık glukoz ve insülin düzeyleri ve vücut kitle indeksi (VKİ) karşılaştırıldı. Tüm hastalar ayrıca pelvik ve tiroid ultrason ile tarandı.

Bulgular: Çalışmaya toplamda beş yüz doksan altı kadın, PKOS grubunda 254, HT grubunda 190 ve kontrol grubunda 152 kişi dahil edildi. VKİ; PKOS ve HT grubunda kontrol grubundan anlamlı olarak daha yüksekti (sırasıyla P=0,012 ve P=0,027). Menstruel ve androjenik semptomlar hasta gruplarında kontrol grubundan anlamlı olarak daha yüksekti (P<0,001). TPOAb ve TgAb pozitifliği insidansı PKOS hastalarında kontrol grubuna göre anlamlı olarak yüksekti (P<0,001).

Sonuç: Bu araştırma PKOS hastalarında artmış TSH, anti-TPO ve anti-Tg düzeyleri ile birlikte HT sıklığının da yüksek olduğu gösterilmiştir. Çalışmamız, PKOS ya da HT hastalarının tiroid fonksiyonları ve overlerin ileri yaşamlarında taranması gerekliliğini göstermektedir.

Anahtar kelimeler: Hashimato Tiroiditi, Polikistik over sendromu, Tiroid antikorları, Otoimmunite

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disease. Various chronic diseases are associated with PCOS, such as diabetes mellitus and metabolic syndrome [1]. The etiology of PCOS remains unclear, although the evidence indicates a multifactorial origin on the basis of genetic predisposition [2]. Hashimoto's thyroiditis (HT) is characterized by elevated thyroid autoantibodies, leading to various degrees of thyroid dysfunction. Hypoechogenicity is seen at thyroid ultrasound due to lymphocytic infiltration, resulting in thyroid fibrosis. A relationship between HT and recurrent miscarriage, pregnancy loss and PCOS has been confirmed in many studies, but the adverse effects caused by thyroid autoantibodies in women of reproductive age are still an important problem [3, 4].

Thyroid hormone abnormalities can also be seen in PCOS. Thyroid hormone dysfunction in PCOS further complicates the clinical picture and may result in significant effects on comorbidity. The incidence of PCOS is increasing every year. Effective diagnostic and therapeutic methods need to be discovered for a better understanding of the causes of PCOS. The aim of our study was to determine the clinical and laboratory similarities between PCOS and HT, to identify the incidence of thyroid autoantibodies in PCOS cases, and to establish whether autoimmunity constitutes a risk factor for the transmissibility between the two diseases.

Materials and methods

This study was conducted at the Medical Park Hospital endocrinology and gynecology departments, Ordu, Turkey from July 2015 to December 2018. The study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Ordu University (10.01.2019-91120269-000-E.00000031).

Participants, data collection and processing

The study population consisted of 596 women, those diagnosed with HT in our endocrinology and general surgery clinics, those diagnosed with PCOS in our endocrinology and gynecology clinics, and healthy volunteers. PCOS was diagnosed based on the ESHRE / ASRM (Rotterdam) 2004 criteria [5]. Subjects with ovulation disorder (oligo-ovulation or anovulation), clinical and / or biochemical hyperandrogenism, or those meeting the criteria for polycystic ovarian morphology were included in the study. Patients with a history of other autoimmune diseases, diabetes mellitus, coronary heart disease, hyperlipidemia, malignancy, or liver or kidney failure, women aged under 18 years or older than 52, or with menopausal status were excluded. Serum fasting glucose (70-100 mg/dl), TSH (0.35-4.94 mIU/L), free T4 (fT4) (9.01-19.05 pmol/L), TgAb (0-4.11 IU/mL), TPOAb (0-5.61 IU/mL), FSH (1.5-12.4 mlU/mL), LH (2.00-15.00 mlU/mL), serum testosterone (3,5-8.6 ng/ml), DHEA-S (82-338 ng/dL), and PRL (2-20 ng/mL) were studied using automated chemiluminescence immunoassay (ICMA) kits (Abbott, IL, USA). Pelvic ultrasonography was performed with a high-resolution apparatus equipped with a 5-1 MHz broadband convex array probe (Philips Affiniti 70 ultrasound; Philips North America Corporation, MA 01810, USA).

Statistical analysis

Data were analyzed on SPSS version 20.0 software [SPSS Inc., Chicago, IL, USA]. Mean standard deviation (SD) values for descriptive analysis were calculated with one-way ANOVA for intergroup comparisons. The Kruskal Wallis, chi-square, and independent samples t tests were used for further analysis. Categorical variables were evaluated using Pearson's chi-square test. Statistical data were considered significant if $P<0.05$.

Results

The PCOS group consisted of 254 patients, the HT group of 190 patients, and the control group, 152 healthy women. Mean (Standard Deviation) ages were 26.7 (8.2) years in the PCOS group, 25.4 (7.8) years in the HT group, and 24.1 (6.9) years in the control group.

BMI was significantly higher in the PCOS and HT than in the control group ($P=0.012$, and $P=0.027$, respectively). HOMA-IR was also significantly higher than in the control group ($P<0.001$, and $P=0.031$, respectively). Patients' menstrual and hyperandrogenic symptoms were also greater compared with the control group ($P<0.001$). The number of patients with polycystic ovary detected via ultrasound was significantly higher in the HT group than in the control group ($P<0.001$). The patient groups' clinical and biochemical data are summarized in Table 1.

Comparison of hormone levels between PCOS and HT groups and the control group revealed significantly higher testosterone levels ($P=0.002$, and $P=0.328$, respectively) and DHEA-S levels ($P<0.001$, and $P=0.016$, respectively) than in the control group. FSH, LH and PRL values were also significantly higher than in the control group ($P<0.001$). TSH values were significantly higher in the PCOS group than in the control group ($P=0.059$). Comparison of thyroid autoantibodies among the groups revealed significantly higher TgAb in the PCOS and HT groups than in the control group ($P<0.001$). TPOAb was significantly higher in both patient groups than in the control group ($P=0.043$, and $P<0.001$, respectively). A comparison of the patient groups' hormone levels with those of the control group is summarized in Table 2.

Table 1: Clinical and biochemical data for the study groups

Parameters	Control group (n=152)	PCOS group (n=254)	*P*-value (PCOS vs. Control)	HT group (n=190)	*P*-value (HT vs. Control)
Age (years) mean (SD)	24.1 (6.9)	26.7 (8.2)	0.647	25.4 (7.8)	0.853
BMI (kg/m^2)	23.8 (2.1)	28.6 (4.1)	0.012	25.9 (2.9)	0.027
Fasting glucose (mg/dl)	76.1 (24)	89.5 (22)	0.004	82.3 (18)	0.007
HOMA-IR	1.86 (0.4)	3.2 (1.2)	<0.001	2.73 (0.8)	0.031
Oligomenorrhea & amenorrhea n (%)	34 (22.3)	167 (65.7)	<0.001	94 (49.4)	<0.001
Hirsutism & acne n (%)	30 (19.7)	190 (74.8)	<0.001	85 (44.7)	<0.001
USG for polycystic ovaries n (%)	38 (25.2)	198 (77.9)	<0.001	89 (46.8)	<0.001

BMI: body mass index, HOMA-IR: homeostasis model assessment insulin resistance index, SD: Standard deviation

Table 2: Hormonal data for the patients and control group

Parameters	Control group (n=152)	PCOS group (n=254)	*P*-value (PCOS vs. Control)	HT group (n=194)	*P*-value (HT vs. Control)
Serum TE (ng/ml) mean (SD)	4.1 (1.2)	6.8 (1.9)	0.002	5.2 (2.2)	0.328
DHEA-S (ng/dL)	168.5 (65)	278.7 (107)	<0.001	253.9 (93)	0.016
FSH (mlU/mL)	4.6 (0.6)	9.2 (2.5)	<0.001	8.8 (2.1)	<0.001
LH (mlU/mL)	5.7 (2.1)	14.1 (4.1)	<0.001	10.3 (3.2)	<0.001
PRL (ng/mL)	12.9 (3.4)	35.7 (6.2)	<0.001	42.8 (7.3)	<0.001
TSH (μIU/L)	1.8 (0.6)	2.6 (1.1)	0.059	4.9 (2.1)	<0.001
fT4 (pmol/L)	15.8 (3.3)	13.6 (3.8)	0.383	11.2 (2.9)	0.032
TgAb (lU/mL)	1.2 (0.2)	3.5 (0.6)	<0.001	51.4 (12.1)	<0.001
TPOAb (lU/mL)	2.5 (0.5)	3.7 (1.2)	0.043	64.9 (28.4)	<0.001

TE: Testosterone, DHEA-S: Dehydroepiandrosterone-Sulfate, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PRL: Prolactin, TSH: Thyroid-Stimulating Hormone, fT4: Free thyroxine, TgAb: Thyroglobulin antibody, TPOAb: Thyroid peroxidase anti-body, SD: Standard deviation

TgAb and TPOAb antibody positivity rates in the PCOS group were 15.7% for TgAb and 38.5% for TPO, both being significantly higher than the corresponding values in the control group (P<0.001). The results are shown in Table 3.

Table 3: Thyroid autoantibody positivity in the PCOS and control groups

Parameters	Control group (n=152)	PCOS group (n=254)	*P*-value
TgAb, n (%)	10 (6.5)	40 (15.7)	<0.001
TPOAb, n (%)	19 (12.5)	98 (38.5)	<0.001

TgAb: Thyroglobulin antibody, TPOAb: Thyroid peroxidase anti-body

Discussion

As the prevalence of endocrinological diseases increases, the relationship between PCOS and autoimmune thyroid disease is becoming increasingly recognized. However, the reason for this relationship is still unclear, and the exact nature of the connection has not yet been elucidated. In polycystic morphology, the ovaries are also a clinical feature of hypothyroidism [6]. Thyroid function tests play an important role in the investigation of ovulatory dysfunction. Thyroid dysfunction should be ruled out before a diagnosis of PCOS, and correct diagnosis is particularly important in this patient group since PCOS can be treated medically.

A connection between PCOS and HT has been reported in several studies. However, the true pathogenesis has not yet been clarified [7]. Although there is no clear link between the underlying causes of hypothyroidism PCOS, studies have shown that the two conditions share many common features, such as chronic anovulation, decreased serum sex hormone binding globulin levels, and increased serum testosterone, LH and cholesterol [8]. We observed a significant increase in ovulatory dysfunction, and in serum testosterone and LH levels in the PCOS and HT groups compared to the control group. BMI, fasting glucose levels, and prevalences of ovulatory dysfunction, hirsutism and acne were also higher in both disease groups compared to the control group. Similarly, high fasting insulin and fasting glucose, and the presence of HOMA-IR in the PCOS and HT group mays indicate a pathogenic link between autoimmunity and insulin resistance [9]. Hormonal, clinical and ultrasonographic similarities have been reported in PCOS patients and in patients with thyroid dysfunction and thyroid antibody [10]. The results of these studies and our own research clearly show the connection between them.

TSH levels in this study were higher in the PCOS group compared to the control group, while fT4 levels were lower, although the differences were not statistically significant. While some studies have reported a significant increase in TSH levels, the increase is more generally reported to be slight [11,12]. The National Academy of Clinical Biochemistry (NACB) recommends the use of 2.5 μIU/mL instead of 4 μIU/mL for TSH levels [13]. In our study, the mean TSH level was 2.6 IU / mL. Occult hypothyroidism is seen in PCOS cases based on the NACB reference range definition.

In our study, the incidence of polycystic ovarian morphology in the HT group was 48.8% (n=89). Studies have shown that ovarian morphology becomes polycystic in the presence of hypothyroidism. Thyroid disorders should be excluded before PCOS is diagnosed [14]. The incidence of the characteristic ultrasonic characteristics of HT in a previous study was 42.3% in a PCOS group and 6.5% in the control group [15]. The presence of similar findings in the two diseases supports the idea of a connection between them.

Autoimmune thyroiditis is three times more common in patients with PCOS among women of reproductive age [16]. Statistically significant increases have been shown in TPOAb and TgAb positivity in PCOS cases [17-19]. In our study, TPOAb and TgAb levels were higher than in the control group. The incidence of TPOAb positivity was 3 times higher and that of TgAb positivity 2.4 times higher compared to the control group. The pathophysiological pathway that connects thyroid disorder with PCOS may thus involve autoimmunity.

There are several limitations to this study, including the small sample size and the population consisting of women from a single center.

Conclusion

Studies indicate a clear connection between PCOS and HT. There is sufficient evidence in the literature to suggest that one of the two diseases increases the prevalence of the other. The current unclear nature of the link between them may possibly be due to the complexity of the etiology of both diseases. We believe that autoimmune susceptibility contributes to the development of the two conditions. Our findings indicate a higher prevalence of TPOAb and TgAb in patients with PCOS. Our data also suggest that thyroid functions and the ovaries should be screened later in life in patients with PCOS and HT.

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