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High prevalence of autoimmune thyroiditis in Polish PCOS women and its association with insulin resistance

Zwiększona częstość autoimmunizacyjnego zapalenia tarczycy u polskich kobiet z zespołem PCO i jej związek z insulinoopornością

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Keywords

PCOS, autoimmune thyroiditis, autoimmunity, insulin resistance

Słowa kluczowe

PCOS, autoimmunizacyjne zapalenie tarczycy, autoimmunologia, insulinooporność

Summary

Introduction. Both polycystic ovary syndrome (PCOS) and chronic autoimmune thyroiditis (AIT) are common endocrinopathies, are connected to infertility and cause the increase in miscarriage rate. In PCOS patients insulin resistance plays a significant role in pathogenesis. There is only limited data concerning prevalence of AIT in PCOS and its association with insulin resistance in PCOS.

Aim. To assess the prevalence of AIT and hypothyroidism in PCOS patients and to determine if the degree of insulin resistance, clinical symptoms and hyperandrogenism are connected with AIT presence.

Material and methods. We analyzed data of 195 PCOS women diagnosed based on Rotterdam criteria. TSH, thyroid antibodies, thyroid USG and OGTT were performed.

Results. AIT was present in 68 (34.9%) PCOS women while evident or subclinical hypothyroidism was present in 45 (23%) patients. PCOS women with AIT had higher HOMA (1.52 vs 1.18, p = 0.01) and fasting insulin than women without AIT. The androgen levels did not differ between both groups.

Conclusions. AIT and hypothyroidism are very common in patients with PCOS. PCOS patients with AIT do not differ in androgens level, but are more insulin resistant than the patients without AIT. All PCOS patients should be screened for AIT (Hashimoto disease) and hypothyroidism.

Streszczenie

Wstęp. Zarówno zespół policystycznych jajników (PCOS), jak i przewlekłe autoimmunizacyjne zapalenie tarczycy (AZT) są częstymi endokrynopatiami, wiążą się z niepłodnością i zwiększają ryzyko poronień. Insulinooporność odgrywa istotną rolę w patogenezie PCOS. Dane dotyczące częstości AZT i powiązań z insulinoopornością w PCOS są ograniczone.

Cel pracy. Ocena częstości AZT i niedoczynności tarczycy u pacjentek z PCOS oraz zbadanie, czy nasilenie insulinooporności, objawów klinicznych i hiperandrogenizmu wiąże się z obecnością AZT.

Materiał i metody. Przeanalizowano dane 195 kobiet z PCOS rozpoznanym zgodnie z kryteriami rotterdamskimi. Oznaczono TSH, przeciwciała przeciwtarczycowe, wykonano test OGTT i USG tarczycy.

Wyniki. AZT rozpoznano u 68 (34,9%) kobiet z PCOS, jawna bądź podkliniczna niedoczynność tarczycy występowała u 45 (23%) chorych. Kobiety z PCOS i AZT w porównaniu do kobiet bez AZT cechowały wyższe wartości wskaźnika HOMA (1,52 vs. 1,18, p = 0,01) i stężeń insuliny na czczo. Poziom androgenów w obu grupach nie różnił się istotnie.

Wnioski. AZT i niedoczynność tarczycy występują bardzo często u kobiet z PCOS. Pacjentki z PCOS i AZT nie mają istotnie innych poziomów androgenów niż pacjentki z PCOS bez AZT, ale mają bardziej nasiloną insulinooporność. Wszystkie pacjentki z PCOS powinny być badane w kierunku wykrycia AZT (choroby Hashimoto) i niedoczynności tarczycy.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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Abbreviations:

AIT – autoimmune thyroiditis
AUC ins – insulin area under the curve
DHEA-S – dehydroepiandrosterone sulphate
HOMA – homeostasis model assessment
OGTT – oral glucose tolerance test
PCOS – polycystic ovary syndrome
TSH – thyroid stimulating hormone
USG – ultrasonography

INTRODUCTION

Chronic autoimmune thyroiditis (AIT, Hashimoto's disease) is a common endocrinopathy. In areas with sufficient iodine intake it is the most prevalent cause of hypothyroidism. Women are five to ten-fold more susceptible to develop AIT in comparison with men (1). Both hypothyroidism and autoimmune process could cause infertility (ovulatory and menstrual disturbances and pregnancy complications including miscarriages).

Polycystic ovary syndrome (PCOS) is a heterogeneous condition, affecting 5-19% of women of reproductive age (2, 3), making it the most prevalent endocrine disorder among premenopausal women and the main cause of infertility. There is a strong relationship of PCOS to obesity, insulin resistance, diabetes, chronic inflammation and other metabolic disturbances. Oligo- or anovulation in PCOS women causes low progesterone secretion and thus, high estrogen-to-progesterone ratio, resulting in increased likelihood of developing autoimmune diseases (4, 5), including AIT.

Pathogenesis of both AIT and PCOS is thought to be a combination of genetic susceptibility and environmental factors. Sex steroid hormones and another factors such as stress and viral infections, contribute to the development of AIT and the hormones play probably the most important role (6).

There are some studies in which coexistence of PCOS and autoimmune diseases, like AIT (1, 7), rheumatoid diseases (8), APS2, and other, are described (9-13). In some studies (14, 15) the higher than in general population prevalence of AIT in PCOS women was not confirmed. However, there is no population data and no recommendations are available for diagnosis of Hashimoto's disease in all PCOS patients.

AIM

In our study we assessed the prevalence of AIT and subclinical or evident hypothyroidism in our PCOS population and the correlations of the AIT with insulin resistance and clinical manifestations and different phenotypes of PCOS (16).

MATERIAL AND METHODS

Subjects

We analyzed data of 195 young (aged 18-40) PCOS women, admitted to our Endocrinology Department, and diagnosed based on Rotterdam criteria.

The institutional ethics committee gave the opinion that, because of retrospective character of the study, their consent is not necessary.

Protocol

All subjects underwent a physical examination and detailed past and present medical history including menstrual history, fertility, thyroid dysfunction in the past, taken drugs esp. thyroxin.

All hormonal and biochemical measurements were performed in the early follicular phase of spontaneous or progestin-induced menstrual cycle.

Hashimoto disease was recognized if thyroid antibodies were present and there were changes in ultrasonography typical for AIT, or if thyroid antibodies were present with concurrent hypothyroidism.

Hormonal measurements

Venous blood samples were collected in the morning (between 7-9 a.m.) following an overnight fast.

Blood samples were collected into plane tube with clot activator and centrifuged (3500 rpm, 10 minutes).

Routine determinations included: TSH, thyroid antibodies (anti-TPO and anti-TG), testosterone, androstenedione and DHEA-S.

Oral glucose tolerance test

After an overnight fast, all subjects underwent OGTT with a load of 75 g glucose; glucose and insulin at 0, 30, 60 and 120 min were determined, insulin resistance indexes: HOMA and AUC for insulin were calculated as previously described.

Assays

Insulin levels were determined by immunoradiometric (IRMA) assay (BI-INSULIN IRMA, CIS bio International, France).

Levels of thyroid stimulating hormone (TSH-3rd generation), thyroid autoantibodies (anti-TPO and anti-TG), androstenedione, DHEA-S and total testosterone were measured by chemiluminescent immunometric assay on Immulite 2000 (Siemens Healthcare Diagnostics, USA).

Plasma glucose concentrations were determined by an oxydase method (Cobas Integra 400, Roche, Switzerland).

Thyroid ultrasound

Ultrasound of the thyroid was performed using a 7.5 MHz transducer with Duplex sonography. The thyroid was considered hypoechogenic when its signal was equal or below the echogenicity of the surrounding neck muscles.

Statistical analysis

The calculations were done using the statistica analysis package.

Normality of distribution was assessed by Shapiro-Wilk test.

In the case of variables deviating from the normal distribution, the median values with interquartile ranges were calculated.

Because of the absence of normality, nonparametric testing U-Mann Whitney was used.

For further analysis Fisher's exact test and logistic regression were used.

The limit of statistical significance was set at $P < 0.05$.

RESULTS

In the group of 195 PCOS women, AIT was recognized in 68 women (the prevalence of 34.9%). Markedly increased thyroid antibodies (anti-TPO or anti-TG or both) were present in 62 patients (31.8%) and the ultrasound changes typical for AIT were found in 86 women (44.1%).

TSH level in the whole group was 1.81 mU/l (mean value), the TSH values for subgroups with and without AIT are presented in the table 1.

Tab. 1. Analysis of continuous variables between two groups. Data are presented as medians (quarters I-III in the brackets). P value of < 0.05 is considered statistically significant

	non-AIT group	AIT group	P[a]
TSH, mIU/l	1.35 (0.99-1.84)	2.15 (1.18-2.61)	0.0002
HOMA	1.18 (0.69-1.71)	1,52 (0.87-2.92)	0.01
AUC ins	4297.5 (3135-6390)	5640 (3330-11 430)	0.05
Fasting insulin, mIU/l	6.0 (3.0-8.0)	7.0 (4.0-13.0)	0.03
DHEA-S, ng/ml	3230 (2330-4040)	2810 (2140-3620)	0.06
Testosterone, ng/ml	0.61 (0.4-0.9)	0.6 (0.47-0.84)	0.6

Conversion factors to SI units are as follows: for DHEA-S, 0.00271
[a]nonparametric Mann-Whitney U test was used in the analysis

Evident (TSH above 4 uIU/ml or within normal range in patients taking levothyroxine) or subclinical hypothyroidism (TSH > 2.5 and < 4 uIU/ml with normal level of fT4) were present in 45 women (23% of the whole group).

PCOS women with AIT were more insulin resistant than non-AIT group; the results are presented in the table 1 and on the figures 1 and 2.

The concentration of testosterone, androstenedione and DHEA-S did not differ between both groups (tab. 1, 2). Alopecia was statistically more frequent in AIT group, while hirsutism was more frequent in non-AIT group (tab. 2).

The most severe phenotype (the four phenotypes are shown in the table 3) of PCOS, which consists of coexisting hyperandrogenism, menstrual disturbances and polycystic morphology of ovaries on ultrasonography (the phenotype A), was observed most frequently in the AIT group.

DISCUSSION

Risk of AIT is much higher in women than in men; it is correlated to high estrogen levels, which enhance humoral immunity (17, 18). Progesterone and androgens are thought to be protective, being natural immune suppressors (19). It is unclear why in PCOS,

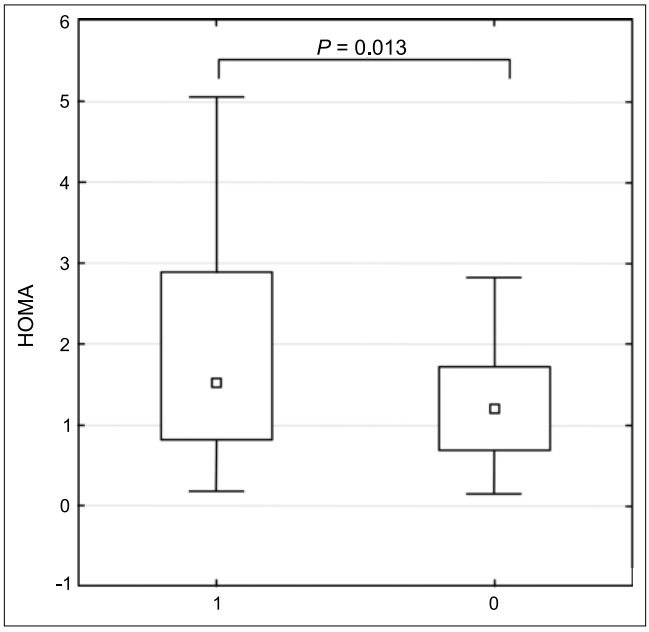

Fig. 1. Median value of HOMA in analyzed groups. 1 – AIT group; 0 – non-AIT group

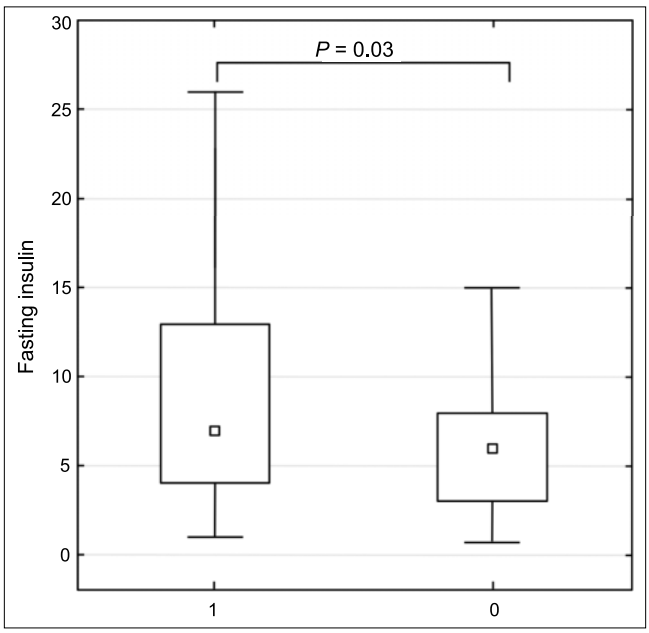

Fig. 2. Fasting insulin levels in analyzed groups. 1 – AIT group; 0 – non-AIT group

where hyperandrogenism is present, there is such a high prevalence of AIT. One possible explanation is related to the overbalance of estrogen over progesterone and the crucial role of relative hyperestrogenism. In our study we assessed androgens' concentrations and didn't find the differences between AIT group and non-AIT group. This suggests that the role of androgens is not crucial. Many endogenous substances, like cytokines, are strictly involved in the process of autoimmune reactivity. It was revealed, that interleukin-6, which is a strong mediator of autoimmune reactions, correlates positively with estrogens and negatively with progesterone levels in normal menstruating young women (20).

Tab. 2. Qualitative variables (nominal)

		non-AIT group	AIT group	P[b]
Androstendione levels	Normal	69 (53.1)	32 (47.1)	0.4
	Elevated	61 (46.9)	36 (52.9)	
Dysmenorrhea	Not present	25 (19.2)	7 (10.4)	0.2
	Present	105 (80.8)	60 (89.5)	
Hirsutism	No	19 (14.7)	24 (36.4)	0.001
	Yes	110 (85.3)	42 (63.6)	
Acne	No	88 (68.2)	46 (68.7)	1
	Yes	41 (31.8)	21 (31.3)	
Alopecia	No	125 (96.9)	58 (89.2)	0.05
	Yes	4 (3.1)	7 (10.8)	
Features of PCOS in transvaginal ultrasound	No	21 (16.7)	14 (21.2)	0.4
	Yes	105 (83.3)	52 (78.8)	

Analysis of the relationship between percent variables depending on the function of thyroid. Data are presented as number of patients (% of patients). P value of < 0.05 is considered statistically significant
[b]each time Fisher's exact test was used

Tab. 3. PCOS phenotypes according to the Rotterdam criteria

Characteristics	Phenotype			
	A	B	C	D
Hirsutism/hyperandrogenemia	✓	✓	✓	
Ovulation disorders	✓	✓		✓
Polycystic ovaries on USG	✓		✓	✓

Our results are similar to that published by Janssen et al. (1) and Petrikova et al. (11). High prevalence of PCOS in euthyroid girls with Hashimoto disease was described by Ganie et al. (21). In our study we did not compare the AIT prevalence in PCOS group to the healthy control group, but according to the population morbidity and data from control group from Janssen et al. study (1), we can assess that AIT is present in about 5-8% of whole population in reproductive age, so this almost 35% AIT prevalence in PCOS women is very high and surely much higher than in general population.

Autoimmunity, in general, decreases female fertility and infertility treatment success and increases miscarriage risks (22, 23). Some data shows elevated different antibodies in PCOS women (24), what suspects PCOS as autoimmunologic origin. In our study alopecia was more then threefold higher in patients with AIT (10.8 vs 3.1%), while hirsutism was more frequent in patients without AIT. Alopecia could have autoimmunologic origin, while hirsutism not and it could explain this observation.

It is interesting, that PCOS women with AIT were more insulin-resistant: HOMA and fasting insulin were statistically higher in AIT-group. What is more, when we have analyzed different phenotypes (16) of PCOS (tab. 3), it was revealed, that the phenotype in which there are together menstrual disturbances, hyperandrogenism and polycystic ovaries on ultrasonography is the most frequent phenotype in AIT group. This phenotype is believed to be the most severe one and in the discussion about the criteria of PCOS seems to be the surely proper PCOS phenotype.

In our study we showed very high prevalence of AIT and subclinical or evident hypothyroidism in PCOS women. What is more, thyroid antibodies or ultrasonography changes typical for AIT as a single sign were much higher than are usually observed in general population.

According to our results the coexistence of AIT and PCOS seems to be connected with worse insulin resistance and clinical phenotype of PCOS.

CONCLUSIONS

We can conclude, that all patients, who are recognized as having PCOS should be diagnosed for Hashimoto disease and hypothyroidism, because the prevalence of coexistence of AIT and PCOS is very high. PCOS patients with AIT do not differ in androgens level, but are more insulin resistant than the patients without AIT. Proper treatment for hypothyroidism and insulin resistance could be crucial for fertility outcomes.

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