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Is AMH Really Related to Hyperandrogenism and Insulin Resistance? A Study in Young Women With PCOS

AMH Gerçekten Hiperandrojenizm ve İnsülin Direnci ile İlişkili mi? PKOS'lu Genç Kadınlarda Bir Araştırma

HALİLZADE İNCİ [1] Orcid ID: 0000-0002-3078-8420
HALİLZADE MOHAMMAD İBRAHİM [1] Orcid ID: 0000-0002-5946-6302
KILIÇKIRAN HARUN [1] Orcid ID: 0000-0002-6097-6350
KAHYAOĞLU SERKAN [1] Orcid ID: 0000-0001-8964-3552

[1] University of Health Sciences Ankara City Hospital, Gynecology and Obstetrics Department, Ankara, Turkey.

ÖZ

Amaç: Polikistik over sendromu (PKOS), hiperandrojenizm ve insülin direnci ile ilişkili endokrinolojik bir hastalıktır. Son zamanlarda yayınlanan kılavuzla AMH'nin polikistik over sendromundaki yeri kabul edilse de altta yatan mekanizmalar halen belirsizliğini koruyor. Bu çalışmanın amacı PKOS'ta A ve D fenotiplerini kullanarak hiperandrojenizm ile AMH arasındaki ilişkiyi araştırmak ve hiperandrojenizm olmayan PKOS fenotipinin tanısında AMH'nin yerini göstermektir. Ayrıca insülin direnci ile AMH arasındaki ilişkiyi ortaya koymaktır.

Gereç ve Yöntem: Bu çalışmaya 102 PKOS'lu hasta dahil edildi. Hastalar Fenotip A ve D olarak iki gruba ayrıldı. Ayrıca hastalar 2 gruba ayrıldı; insülin direnci olan (HOMA-IR ≥2,5) ve insülin direnci olmayan (IR). Birincil sonuç, iki grup arasındaki serum AMH seviyelerini ölçmekti. İkincil sonuç ise demografik ve klinik özelliklerin karşılaştırılmasıydı (yaş, BMI, laboratuvar değerleri).

Bulgular: AMH değerleri açısından A ve D fenotipleri arasında anlamlı fark yoktu. Hastalar insülin dirençli ve insülin direnci olmayan PKOS'lu olarak 2 gruba ayrıldığında insülin dirençli PKOS'lularda AMH anlamlı olarak düşük bulundu (p=0,006). AMH için kesme değeri %70,4 duyarlılık ve %62,5 özgüllük ile 6,26 ng/ml idi.

Sonuç: Çalışmamız sonucunda AMH'nin PKOS'ta A ve D fenotipleri arasında belirleyici bir gösterge olmaması nedeniyle hiperandrojenizm ile ilişkisinin net ve güvenilir olmadığını ancak PKOS'ta insülin direncinin belirlenmesinde bir gösterge olabileceğini düşünüyoruz.

Anahtar kelimeler: hiperandrojenizm, polikistik over sendromu, amh, insülin direnci, fenotipler

ABSTRACT

Aims: Polycystic ovary syndrome (PCOS) is an endocrinological disease associated with hyperandrogenism and insulin resistance. Although the place of AMH in polycystic ovary syndrome has been accepted with the recently published guideline, the underlying mechanisms still remain unclear. The aim of this study is to investigate the relationship between hyperandrogenism and AMH using phenotypes A and D in PCOS and to show the place of AMH in the diagnosis of PCOS phenotype without hyperandrogenism. In addition, to reveal the relationship between insulin resistance and AMH.

Material and Method: One hundred two patients with PCOS were included in this study. The patients were divided into two groups as Phenotype A and D. In addition, the patients were divided into 2 groups; with (HOMA-IR ≥2.5) and without insulin resistance (IR). The primary outcome was to measure the serum AMH levels between two groups. The secondary outcome was to compare demographic and clinical caracterics (age, BMI, laboratory values).

Results: There was no significant difference in AMH values between phenotypes A and D. When patients are divided into 2 groups as PCOS with insulin resistant and without insulin resistant, AMH was found to be significantly lower in the insulin resistant PCOS (p=0.006). The cut-off value for AMH was 6.26 ng/ml, with a sensitivity of 70.4% and a specificity of 62.5%.

Conclusion: As a result of our study, we think that the relationship of AMH with hyperandrogenism is not clear and reliable, as it is not a defining indicator between A and D phenotypes in PCOS, but it could be an indicator in determining insülin resistance in PCOS.

Key words: hyperandrogenism, policistic ovary sendrom, amh, insulin resistance, phenotypes

Sorumlu Yazar/ Corresponding Author: İnci Halilzade
Adres: University of Health Sciences Ankara City Hospital, Gynecology and Obstetrics Department, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya/ANKARA/ TURKEY
E-mail: fanuscuinci@gmail.com

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INTRODUCTION

PCOS is an endocrinological disorder commonly seen in women of reproductive age (1). The hormonal imbalance in PCOS manifests itself as hyperandrogenism and hyperinsulinemia and leads to clinical effects such as menstrual irregularity, chronic anovulation, infertility and hyperandrogenism (2). Most patients also have metabolic disorders such as insulin resistance, obesity, and dyslipidemia (3). Early diagnosis and treatment of this disease, which has a multisystemic involvement, is also important. Four different phenotypes have been recognized in PCOS: phenotype A (Oligo/anovulation + Hyperandrogenism + Polycystic ovaries) (OA+HA+PCO); phenotype B (HA+OA), phenotype C (HA+PCO), and phenotype D (OA+PCO) (4). A few studies have been conducted on the difference in AMH, FSH, LH and homa ır levels among these phenotypes, but clear results have not yet been shown (5-7).

Anti-Müllerian hormone (AMH) is an important hormone that is secreted from ovarian granulosa cells, and indicates ovarian reserve because it is related to the number of follicles (8). Previous studies have shown that serum AMH levels increase in adult women with PCOS, and that there is a potential relationship between values >3.2 ng/mL and the diagnosis of PCOS (9). In addition, AMH is thought to contribute to hyperandrogenism in women PCOS due to its inhibitory effect on FSH-induced aromatase production (10). Therefore, hyperandrogenism in PCOS is thought to be associated with AMH. However, in phenotype D PCOS without hyperandrogenism, the difference of AMH levels from other phenotypes has not been clearly demonstrated. In addition, it is unclear whether there is a relationship between insulin resistance and AMH levels in patients with PCOS (11). While there are studies showing that AMH levels cannot be associated with insulin resistance (12), there are also studies that say they have a positive relationship (13). Studies on AMH have revealed that its place in PCOS is still not clearly demonstrated.

The aim of this study is to investigate the relationship between hyperandrogenism and AMH using phenotypes A and D in PCOS and to show the place of AMH in the diagnosis of PCOS phenotype without hyperandrogenism. In addition, to reveal the relationship between insulin resistance and AMH.

MATERİAL AND METHOD

All patients (One hundred two patients) with phenotypes A and D, aged 18-25 years, who applied to the City Hospital Polycystic Ovary Outpatient Clinic with the diagnosis of PCOS were recruited as a mixed group between September 2019 and February 2022. The Local Ethics Committee approval was obtained from the same hospital (21/1030). Patients had the Roterdam criteria (menstrual irregularity (chronic anovulation and oligomenorrhea), ultrasonographic polycystic ovaries, biochemical or clinical hyperandrogenism) recommended by the last Amsterdam ESHRE/ASRM. Ultrasonographic measurements were made by a single physician using Voluson S10 BT18, KOREA ultrasound. The ovaries were considered polycystic on ultrasound if each ovary had 12 or more follicles with a diameter of 2-9 mm and/or an enlarged ovarian volume (>10 mm3). Oligomenorrhea was defined as menstrual cycles longer than 35 days, while amenorrhea was defined as the absence of a menstrual period for three consecutive months. Hirsutism was defined as a modified Ferriman and Gallwey score ≥8 (14). Biochemical hyperandrogenemia was defined as free testosterone (fT) level ≥2.4 ng/mL and/or dehydroepiandrosteronesulfate (DHEA-S) level ≥358 µg/mL (15). Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared (kg/m2). BMI 18.5-24.9 kg/m2 was considered as normal weight >25.0 kg/m2 as overweight and >30 kg/m2 was considered as obese.

All of the patients were new admissions and there were no patients who had received hormone therapy within the last 3 months. All patients were of the same ethnicity. Gynecological and general history, demographic characteristics, BMI and laboratory values of each patient were recorded. Laboratory values included basal FSH, LH, E2, TSH, prolactin, androstedione, DHEA-S, FAI (free androjen index), total and free testosterone, SHBG, AMH, 75gr OGTT, HOMA-IR, fasting insulin, HbA1c. With these values, the patients were divided into 2 groups, A and D, according to the phenotypes defined by ESHRE/ASRM. Phenotype A: Oligo/anovulation + hyperandrogenism + polycystic ovaries, Phenotype D: Oligo/anovulation + polycystic ovaries. These patients were compared in terms of serum AMH values. Exclusion criteria included use of drugs known to alter insulin secretion or action, hypertension, smoking, Cushing's syndrome, androgen-secreting tumors, late-onset 21-hydroxylase deficiency, thyroid dysfunction, endocrinopathies including hyperprolactinemia, and autoimmune diseases.

The primary outcome of this study was to measure the serum AMH levels between phenotype A and D. The secondary outcome was to compare demographic and clinical caracterics (age, BMI, FSH, LH, E2, TSH, prolactin, 75gr fasting and 2nd hour glucose, HOMA-IR, fasting insulin, HbA1c) between phe-

notype A and D. In addition, the patients were divided into 2 groups; with (HOMA-IR ≥2.5) and without insulin resistance (IR). The primary outcome was to measure the serum AMH levels between two groups. The secondary outcome was to compare demographic and clinical caracterics (age, BMI, FSH, LH, E2, TSH, prolactin, FAI, androstenedione, DHEA-S, free testosterone, total testosterone, SHBG) between women with and without IR in PCOS.

Statistical analyses were performed using SPSS version 22. The conformity of the variables to the normal distribution was examined using Kolmogorov-Smirnov test. The means of parametric data, which showed normal distribution, were compared using Student's T test. The Mann-Whitney U test was used to compare the parametric data which were determined not to be normally distributed. Categorical data was compared using Chi-square or Fisher's exact test as appropriate. A ROC curve was drawn to measure the significant cut-off value for AMH level and its the sensitivity and specificity in distinguishing the two groups. P value below 0.05 were considered statistically significant.

RESULTS

The patients were divided into two groups as Phenotype A (n=47) and Phenotype D (n=55) and compared in terms of BMI, AMH and other hormones (Table-1). There were no significant differences in AMH values between these two groups (p=0.565). In addition, no significant difference was found between the two groups in terms of age, BMI, basal hormones, 75gr OGTT and HOMA-IR (Table-1).

Table 1. Comparison of patients, phenotope A and D

	Phenotype A (n= 47)	Phenotype D (n=55)	P value
Age	22.5± 2.9	23.1± 2.4	0.419*
BMI	27.5± 6.1	28.7± 6.5	0.254*
Basal FSH	6.4±1.8	5.9±1.9	0.187**
Basal LH	10.7±9.9	9.2±7.2	0.146*
Basal E2	58.7±33.2	55.9±38.0	0.269*
TSH	2.2±1.0	2.2±1.1	0.557*
Prolactin	14.5±10.0	12.1±5.6	0.460*
FAI (Free androjen index)	1.9±1.1	1.0±0.8	<0.001*
AMH	7.0±2.0	6.7±2.2	0.565*
75GR Fasting Glucose	88.7±11.0	87.5±9.4	0.798*
75GR 2nd Hour Glucose	109.7±20.0	112.5±20.7	0.470*
HOMA-IR	3.6±3.3	4.3±4.2	0.702*
Fasting Insulin	15.3±11.7	18.9±17.9	0.655*
Androstenedion	12.5±5.8	9.6±4.6	0.006**
DHEA-S	279.1±102.6	231.5±103.4	0.011*
Free Testosterone	3.26±1.0	1.6±0.4	<0.001*
Total Testoterone	0.5±0.1	0.3±0.1	<0.001**
SHBG	34.1±19.5	55.3±46.0	0.015*
HbA1c	5.6±0.5	5.5±0.4	0.734*

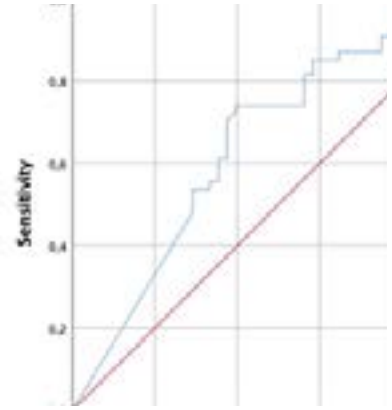
Patients were divided into two groups; PCOS with and without insulin resistance (IR). 20 patients (42.6%) in the Phenotype A group and 28 patients (50.9%) in the Phenotype D group were insulin resistant (Table-2). BMI was found to be significantly higher in the PCOS with IR group compared to the group without IR. In addition, basal LH was lower in the PCOS with IR group ($p<0.05$). TSH was found to be significantly higher in the PCOS with IR group. FAI was higher in the PCOS with IR group, while SHBG was higher in the group without IR. AMH was found to be significantly lower in the PCOS with insulin resistance group ($p=0.006$) (Table-2).

Table 2. Comparison of patients with and without insulin resistance (IR)

	PCOS without IR (n:54)	PCOS with IR (n:48)	P value
Age	22.7±2.5	23.1±2.7	0.321*
BMI	26.1±5.1	30.5±6.8	0.002*
Basal FSH	6.3±1.9	6.0±1.8	0.350**
Basal LH	11.9±10.5	7.7±5.0	0.020*
Basal E2	60.8±39.0	53.1±31.5	0.383*
TSH	1.9±0.9	2.5±1.1	0.012*
Prolactin	13.7±9.6	12.6±5.9	0.856*
FAI	1.2±0.8	1.7±1.2	0.021*
AMH	7.4±1.9	6.2±2.2	0.006*
75GR Fasting Glucose	83.4±6.2	93.2±11.1	<0.001*
75GR 2nd Hour Glucose	98.1±11.2	126.0±18.0	<0.001*
HOMA-IR	1.6±0.5	6.6±4.1	<0.001*
Fasting Insülin	7.6±2.4	28.0±16.7	<0.001*
Androstenedion	10.4±4.9	11.6±5.9	0.241**
DHEA-S	253.1±102.8	253.8±109.1	0.877*
Free Testosterone	2.4±1.0	2.3±1.2	0.382*
Total Testosterone	0.4±0.2	0.4±0.1	0.069**
SHBG	53.3±38.6	36.9±34.9	<0.001*
HbA1c	5.4±0.3	5.7±0.5	0.009*

According to ROC curve analysis (Figure 1), AMH level was a differential parameter for insulin resistance in patients with PCOS. The cut-off value for AMH was 6.26 ng/ml, with a sensitivity of 70.4% and a specificity of 62.5% (Table-3).

Figure 1. ROC Curve of Serum AMH Levels in Predicting Insulin Resistance in Patients with PCOS



.Tables 3: ROC curve analysis for various parameters that can be used to predict miscarriage hospital admission between groups.

	AUC	p	Cut-off value	Sensivity (%)	Specifity (%)
AMH level (ng/ml)	0.654 (0.546-0.761)	0.008	6.26	70.4	62.5

AUC: Area under curve

p<0.05 was considered statistically significant

DISCUSSION

In our study, we aimed to compare phenotype D group (OA+P-CO) without hyperandrogenism and phenotype A group (OA+P-CO+HA) to better understand the relationship between hyperandrogenism and AMH. Because the only difference between the 2 groups was the presence of hyperandrogenism. Considering that AMH levels in PCOS are associated with hyperandrogenism (10), it can be expected that AMH levels should be lower in the phenotype D group. However, studies have shown that AMH levels can help to differentiate between different PCOS phenotypes (3), and many studies have suggested that AMH levels are significantly higher in women with PCOS with phenotype A (4, 5). In a study, Phenotype A was identified as the most severe form of PCOS and it was emphasized that AMH values were higher than in all other phenotypes (16). As hyperandrogenism is a component of phenotypes A, B, and C, the conclusion of this study appears to be contradictory.

On the other hand, Carmina et al. reported in their study in 2016 that AMH did not seem to be useful in differentiating PCOS phenotypes (17). However, in another study they conducted in 2022, they compared different phenotypes in thin and obese PCOS patients separately and found that AMH values were higher in the phenotype A group, which was made up of individuals who were both thin and obese (18). On another thought, considering that AMH is a marker secreted by the ovaries and is associated with hyperandrogenism by affecting FSH (19), it can be expected to be higher in phenotypes A and C where hyperandrogenism and polycystic ovaries are together. However, these studies report high AMH levels especially in phenotype A and cannot clearly reveal the relationship between hyperandrogenism and AMH.

There is also a study stating that there is no correlation between PCOS phenotypes and serum AMH levels (20). Similarly, we did not find a significant difference between phenotypes A and D in terms of AMH in our study. We think that the relationship between AMH and hyperandrogenism is not clear and that increased AMH values in patients with PCOS are mostly associated with polycystic ovaries.

The second aim of our study is in order to reveal the relationship between insulin resistance and AMH. All patients were reclassified as insulin resistant and non-resistant. There was no significant difference in insulin resistance between phenotypes A and D. This finding was correlated with the study of Gupta et al (21). In their study, it was reported that there was no significant difference between all phenotypes in terms of insulin resistance. We compared the insulin-resistant and non-insulin-resistant PCOS groups and showed that AMH and LH is significantly lower in insulin-resistant PCOS. On the other hand, in a study, AMH and HOMA-IR were compared among the four PCOS phenotypes, and it was shown that phenotype A had the highest AMH and HOMA-IR levels (19). Li et al. suggested that HOMA-IR and AMH were positively correlated and HOMA-IR levels were higher in women with high AMH level PCOS (13). In yet another similarly conducted study, AMH was found to be significantly higher in women with PCOS with insulin resistance than in women without insulin resistance (22). Zhao et al. reported that AMH levels were positively correlated with HOMA-IR levels (23). By the way there are also studies showing that there is no significant relationship between serum AMH levels and insulin resistance (12, 24).

However, similar to what is shown in our study, there are also studies show that a negative correlation between AMH and insulin resistance (25). In our study, we found that AMH was above 6.26 in patients with PCOS in the presence of insulin resistance. We demonstrated a negative correlation between AMH and insulin resistance. Jun et al. investigated the relationship between AMH and HOMA-IR in women with PCOS.

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