Can Serum Prostate-Specific Antigen Have an Importance in the Differential Diagnosis of Polycystic Ovary Syndrome and Idiopathic Hirsutismus?

SERUM PROSTAT SPESİFİK ANTİJENİ POLİKİSTİK OVER SENDROMU VE İDİYOPATİK HİRSUTİSMUSUN AYIRICI TANISINDA ÖNEMLİ OLABİLİR Mİ?

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Abstract

Objective: The aim of this study was to determine serum PSA levels between women with and without hirsutismus, and also to compare these values according to more commonly seen type of hirsutismus which are polycystic ovary syndrome (PCOS) and idiopathic hirsutismus (IH).

Material and Methods: The study included 42 women with hirsutismus (25 PCOS and 17 IH) and 20 age matched controls. The age, body mass index, waist-hip ratio and Ferriman-Gallwey scores of all subjects were recorded. Serum total and free PSA levels were measured in all women, and the values were compared between the hirsutic women and control groups, and also were compared according to the type of hirsutismus.

Results: Serum total PSA (0.0409 ± 0.0274 ng/ml) and free PSA levels (0.0143 ± 0.0063 ng/ml) were significantly higher in the hirsute patients than in the control group (total PSA= 0.0112 ± 0.0039 ng/ml and free PSA= 0.0104 ± 0.0020 ng/ml) (p=0.001 and p= 0.001, respectively). Both total and free PSA levels (0.0578 ± 0.023 ng/ml and 0.0162 ± 0.0075 ng/ml) of the women with PCOS were found to be higher than those in the IH patients (0.0160 ± 0.0037 ng/ml and 0.0114 ± 0.0016 ng/ml, respectively) (p for total PSA= 0.001 and p for free PSA= 0.004). Total PSA level was significantly higher in the IH group than in the control group (p= 0.001). But there was no significant difference in serum free PSA level between the IH group and the control group (p= 0.126).

Conclusion: This study indicates that serum PSA level is higher in hirsute patients than in controls. Patients with PCOS have higher total and free PSA levels than women with IH. Therefore, the measurement of serum total and free PSA levels may be beneficial in the differential diagnosis of hirsutic women with hyperandrogenemia from the patients with IH.

Key Words: Polycystic ovary syndrome; prostate-specific antigen

Özet

Amaç: Bu çalışmada hirsutismuslu kadınlarda serum PSA düzeylerinin sağlıklı olgulardan farkının saptanması amaçlandı. Ayrıca en sık karşılaşılan iki hirsutismus tipi olan polikistik over sendromu (PKOS) ve idiyopatik hirsutismusta (İH) PSA düzeyleri karşılaştırıldı.

Gereç ve Yöntemler: Çalışmaya ayrıntılı sistemik ve pelvik muayeneyi takiben hirsutismus tanısı konulan 42 kadın ve 20 sağlıklı olgu dahil edildi. Hirsutismuslu kadınlar, PKOS tanısı konulanlar (n= 25) ve İH saptananlar (n= 17) olmak üzere 2 gruba ayrıldı. Tüm olguların yaş, vücut kitle indeksi, ferriman gallwey skorları kaydedildi ve serum total ve serbest PSA düzeyleri ölçülerek gruplar arasında karşılaştırıldı.

Bulgular: Hirsutismuslu kadınların total PSA (0.0409 ± 0.0274 ng/ml) ve serbest PSA (0.0143 ± 0.0063 ng/ml) düzeylerinin kontrol grubundaki olgulardan (total PSA= 0.0112 ± 0.0039 ng/ml ve serbest PSA= 0.0104 ± 0.0020 ng/ml) anlamlı derecede (p= 0.001 ve p= 0.001) yüksek olduğu görüldü. Ayrıca PKOS'lu olguların total PSA (0.0578 ± 0.023 ng/ml) ve serbest PSA düzeyleri (0.0162 ± 0.0075 ng/ml), İH'lu grup (sırasıyla 0.0160 ± 0.0037 ng/ml ve 0.0114 ± 0.0016 ng/ml) ile karşılaştırıldığında anlamlı derecede yüksek bulundu (p= 0.001 ve p= 0.004). İH grubundaki olguların serum total PSA değeri kontrol grubuna göre anlamlı oranda yüksekken (p= 0.001), serbest PSA düzeyleri ile kontrol grubu arasında anlamlı bir fark saptanmadı (p= 0.126).

Sonuç: Bu çalışmada hirsutismuslu olgularda serum PSA düzeyinin sağlıklı kadınlardan daha yüksek olduğu saptandı. Böylece, serum PSA düzeyinin ölçümü hiperandrojenik hirsutismuslu olguların ayırıcı tanısında faydalı olabilir.

Anahtar Kelimeler: Polikistik over sendromu; prostat spesifik antijen

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Prostate-specific antigen (PSA) is a serine protease with chymotripsine-like enzymatic activity, and is a well established tumor marker of prostate cancer.[1] Steroid hormones regulate the gen expression and protein production of

PSA in nonprostatic tissues. Androgens, glucocorticoids, and progestins up-regulate PSA production, while estrogen seems to have no effect on PSA regulation.[2]

Diamandis et al[3] recently demonstrated detectable levels of PSA in women by using ultrasensitive assay, and subsequent studies revealed that this has been found to be present in several female tissues and fluids such as breast, ovaries, periurethral glands, milk and amniotic fluid.[4,5]

Polycystic ovary syndrome (PCOS) and idiopathic hirsutismus (IH) are the most common cause of the hirsutismus. Melegos et al[6] showed that mean serum PSA levels in hirsute women are higher than in nonhirsute healthy controls, suggesting this idea with some recent studies.[7,8] However, in the literature, there are few data about serum PSA levels in patients with idiopathic hirsutismus.

The aim of this study was to determine serum PSA levels between women with and without hirsutismus, and also to compare these values according to more commonly seen type of hirsutismus which are polycystic ovary syndrome and idiopathic hirsutismus.

Material and Methods

Sixty two women attending to our clinic (25 patients with PCOS, 17 patients with IH and 20 healthy controls) were included to the study. An informed consent was taken from all women at beginning.. The patients and controls were interviewed, and history and then physical examinations were conducted.

The body mass index (BMI: weight (kg)/height $(m^2)^2$), and the waist to hip ratio (WHR) were determined. Waist to hip ratio was calculated from the circumferences measured in duplicate in the supine position (waist, midway between the lower rib margin and iliac crest; hip, widest circumference over the great thoracanters).

Hirsutismus was defined by Ferriman-Gallwey score (FGS), and a score of 8 or more was considered as clinical hirsutismus. Twenty age –matched, nonhirsute women with regular menstrual cycles served as controls. The control subjects had a score of FGS less than 8.

The diagnosis of PCOS was based on at least two of the three following abnormalities: oligoovulation or anovulation, clinical and/or biochemical hyperandrogenism, and/or polycystic ovaries detected by ultrasound.[9,10]

Diagnosis of IH was made if the patient had no signs or symptoms of hyperandrogenemia other than hirsutismus, absence of oligo-amenorrhea with proven ovulation, and normal testosterone levels.

Patients who had taken any hormonal medication for the 6 months were excluded from the study. None of the patients had evidence of late-onset congenital adrenal hyperplasia, ovarian or adrenal secreting tumor, Cushing's syndrome, acromegaly, hyperprolactinemia, or thyroid disorders. Patients who had multivitamin medication were excluded because biotin administration has an interfering effect on the PSA assay.

All the venous blood samples were collected at the same time of day (8-10 AM in the morning) in the early follicular phase (A_3 day) of the menstrual cycle for serum total PSA, and free PSA and a standard hormonal profile determination including serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), 17-OH progesterone, thyroid stimulating hormone (TSH), T3, T4, total testosterone, dehydroepiandrostenedione-sulphate (DHEAS). Samples which had haemolysed and lipemia were excluded.

Assays:

Total PSA, free PSA, FSH, LH, TSH, 17-OH progesterone and DHEAS assays are based on the quantitative "sandwich immunoassay" principle using biotinylated monoclonal specific antibody, and a monoclonal specific antibody labelled with a ruthenium complex react to form a sandwich complex in sera. All the samples were run in the same assay. The lower detection limits were 0.003 ng/ml for total PSA, and 0.001 ng/ml for free PSA.

E2, T3, T4, testosterone assays are based on the quantitative "competitive immunoassay" principle using a polyclonal specifically directed

against parameters in sera. Endogenous molecules in the sample competes with added molecules derivate labelled with a ruthenium complex for the binding sites on the biotinylated antibody.

All samples were measured by commercial Electrochemiluminescence immunoassay kits (Modular Analytics E170, Roche Diagnostic, Mannheim, Germany) according to the manufacturer's instructions.

Statistical Analysis

Statistical analyses were performed using "one way Anova test" to compare all values among the 3 groups and "Tukey Post Hoc test" to compare the values between two groups, "independent t test" to compare the values between the patients with hirsutismus and control subjects. All values were given as mean ± S.D. (standard deviation). P values of < 0.05 were considered as significant.

Results

Table 1 shows demographic characteristics, basal serum hormonal levels, and serum total and free PSA levels of the patients with hirsutismus and control subjects. There were no significant differences in the mean age (p= 0.485), BMI (p= 0.597) and WHR (p= 0.379) between the two groups, and the mean FGS was 13.47±2.14 in the women with hirsutismus and 6.61±1.12 in the control group, revealing highly significant difference (p= 0.001). There was no significant difference in the mean estradiol (p= 0.858) and FSH level (p= 0.144) between the two groups, while serum LH, 17-OH-progesterone, DHEAS and total testoster-

Table 1. Demographic, clinical characteristics, hormonal levels and total and free PSA levels of the patients with hirsutism and control subjects (mean±SD and range in parenthesis). BMI: Body mass index, WHR: Waist to hip ratio, FGS: Ferriman-Gallwey score.

	Hirsutismus (n= 42)	**Control (n= 20)**	**P value**
Age (year)	23.00 ± 4.00 (16-30)	23.80 ± 4.57 (12-32)	0.485
BMI (kg/m^2)	22.85 ± 3.74 (18-28)	22.25 ± 5.05 (16-30)	0.597
WHR	0.756 ± 0.048 (0.68-0.85)	0.745 ± 0.038 (0.7-0.81)	0.379
FGS	13.47 ± 2.14 (10-18)	6.61 ± 1.12 (5-7)	0.001
Estradiol (pg/ml)	35.21 ± 13.99 (12-60)	34.55 ± 12.71 (15-55)	0.858
FSH (mIU/ml)	5.65 ± 1.05 (4.2-7.5)	6.06 ± 0.88 (4.9-7.3)	0.144
LH (mIU/ml)	7.43 ± 3.19 (2.3-12)	4.10 ± 1.52 (2.2-6.2)	0.001
DHEAS (µg/dl)	267.35 ± 53.67 (190-369)	192.65 ± 28.80 (156-225)	0.001
17-OH-Progesterone (ng/ml)	2.79 ± 1.66 (1-6)	1.01 ± 0.46 (0.51-1.8)	0.001
Total testosterone (ng/dl)	84.95 ± 30.53 (33-150)	65.50 ± 18.44 (36-95)	0.003
Total PSA (ng/ml)	0.0409 ± 0.0274 (0.01-0.095)	0.0112 ± 0.0039 (0.005-0.0160)	0.001
Free PSA (ng/ml)	0.0143 ± 0.0063 (0.006-0.03)	0.0104 ± 0.0020 (0.008-0.0130)	0.001

one levels were significantly higher in the hirsute patients than in the control group (p= 0.001, p= 0.001, p= 0.001 and p= 0.003, respectively). Serum total PSA (0.0409 ± 0.0274 ng/ml) and free PSA levels (0.0143 ± 0.0063 ng/ml) were significantly higher in the hirsute patients than in the controls (total PSA= 0.0112 ± 0.0039 ng/ml and free PSA= 0.0104 ± 0.0020 ng/ml), revealing highly significant difference (p= 0.001 and p= 0.001, respectively).

Table 2 shows the comparison of the basal serum hormone levels, and serum total and free PSA levels of the PCOS, IH and control groups. The mean FGS of the patients with PCOS and IH was similar and higher than in the control group (p= 0.001). There were no significant differences in the mean estradiol (p= 0.917) and FSH levels (p= 0.176) among the three groups. But serum LH, 17-OH-progesterone, DHEAS and total testosterone levels were significantly higher in the PCOS group than in the IH group and control group, as expected (p= 0.001 for each parameter). Both total and free PSA levels of the women with PCOS (0.0578 ± 0.023 ng/ml and 0.0162 ± 0.0075 ng/ml) were found to be higher than those in the IH (0.0160 ± 0.0037 ng/ml and 0.0114 ± 0.0016 ng/ml, respectively) (p value for total PSA= 0.001 and p value for free PSA= 0.004). Total PSA level was significantly higher in the IH group than in the control group (p= 0.001). But there was no significant difference in serum free PSA level between the IH group and the control group (p= 0.126).

Table 2. Comparison of the the basal serum hormonal levels, and serum total and free PSA levels of the groups (mean±SD and range in parenthesis). BMI: Body mass index, WHR: Waist to hip ratio, FGS: Ferriman-Gallwey score.

	PCOS (n= 25)	IH (n=17)	Control (n=20)	P value
Age (year)	22.52 ± 4.35 (16-30)	23.70 ± 3.44 (20-30)	23.80 ± 4.57 (12-32)	0.526
BMI (kg/m^2)	23.36 ± 3.56 (19-28)	22.11 ± 3.98 (18-27)	22.25 ± 5.05 (16-30)	0.562
WHR	0.760 ± 0.04 (0.69-0.85)	0.744 ± 0.046 (0.68-0.82)	0.745 ± 0.038 (0.70-0.81)	0.263
FGS	13.84 ± 1.86 (11-16)	12.94 ± 2.46 (10-18)	6.61 ± 1.12 (5-7)	0.001
Estradiol (pg/ml)	34.56 ± 13.1 (15-55)	36.17 ± 15.56 (12-60)	34.55 ± 12.71 (15-55)	0.917
FSH (mIU/ml)	5.50 ± 0.97 (4.2-6.8)	5.87 ± 1.15 (4.3-7.5)	6.06 ± 0.88 (4.9-7.3)	0.176
LH (mIU/ml)	9.60 ± 1.86 (7.2-12)	4.24 ± 1.69 (2.3-6.3)	4.10 ± 1.52 (2.2-6.2)	0.001
DHEAS (µg/dl)	288.40 ± 54.30 (201-369)	236.41 ± 35.30 (190-273)	192.65 ± 28.83 (156-225)	0.001
17-OH-Progesterone (ng/ml)	3.53 ± 1.70 (1.1-6)	1.70 ± 0.78 (1-3.1)	1.01 ± 0.46 (0.51-1.8)	0.001
Total testosterone (ng/dl)	97.17 ± 29.52 (48.7-150)	66.98 ± 22.45 (33-105)	65.50 ± 18.44 (36-95)	0.001
Total PSA (ng/ml)	0.0578 ± 0.023 (0.027-0.095)	0.0160 ± 0.0037 (0.01-0.02)	0.0112 ± 0.0039 (0.005-0.016)	0.001
Free PSA (ng/ml)	0.0162 ± 0.0075 (0.006-0.03)	0.0114 ± 0.0016 (0.009-0.014)	0.0104 ± 0.0020 (0.008-0.013)	0.001

Discussion

PSA is expressed in several female tissues and its serum levels can be measured in women using ultrasensitive assays. Steroid hormones regulate the gene expression and protein production of PSA in nonprostatic tissues. Androgens, glucocorticoids and progestins seemed to have a stimulatory effect. Most detectable PSA in serum (65% to 90%) is bound to antiprotease alpha1-antichymotrypsin, whereas 10% to 35% of detectable PSA is unbound or free. Clearance of free PSA may be through the kidneys by glomerular filtration or through formation of new complexes with antiproteases.[11] Because PSA production in women is stimulated by androgens serum total and free PSA concentrations might be a serum marker of androgen excess in hirsute patients.[6-8]

Hirsutism, which is characterized by excessive growth of terminal hair in a male pattern, is a common clinical condition in women. It may result from various causes including polycystic ovary syndrome, nonclassic adrenal hyperplasia, adrenal or ovarian tumors, or it may be idiopathic. Idiopathic hirsutism (IH) is considered to be one of the most common forms of hirsutism. The real mechanism for hirsutism in IH seems to be hypersensitivity of skin's hair apparatus to normal levels of androgens probably due to increased 5 α reductase activity.[12]

There is only one study in the literature comparing the serum total and free PSA levels between patients with PCOS and IH and healthy controls. In their study, Emral et al reported that total and free PSA levels in PCOS patients were higher than IH and control groups consistency with our study.[13] They found that total PSA level in IH patients was significantly higher than the control group, and they also found that free PSA level in IH group was not significantly different than control patients suggesting the similar results with the present study. In our study, serum total and free PSA levels were significantly higher in the hirsute patients than in the controls. In addition, both total and free PSA levels of the women with PCOS were significantly higher than those in the IH group, suggesting that the ultrasensitive assay of serum PSA level may be beneficial in the differential diagnosis of hirsutic women with hyperandrogenemia from the patients with idiopathic hirsutismus.

Serum PSA level in male decreases with the use of 5 α reductase inhibitors in patients with benign prostatic hyperplasia (BPH) and prostatic carcinoma via blockade of conversion testosterone into dehydrotestosterone.[14,15] However, this might be due to the reduce in the prostate gland volume, and might not reflect the relationship between the PSA and 5-α reductase activity.

In contrast to the present study, Galadari et al[16] reported that total PSA levels in IH patients was not significantly different than in the control group. They did not find any association between the level of PSA and presence of hirsutismus. Several factors might have influenced their results, explaining the differences with the findings of the present study. In their study, the number of control patients was limited, and in addition, there was significant difference in the BMI between the patients. PSA assay used in their study may not be sensitive enough to detect small changes in serum PSA levels.

Negri et al[7] have shown that the increased serum PSA concentrations in hirsute patients decrease during treatment with antiandrogen drugs, regardless of which antiandrogen drugs were used, finally reaching levels comparable with those of normal women. Although the source of serum PSA in women is still unknown, this result may reflect the role of androgen action on PSA production in one or more androgen sensitive tissues.

Escobar-Morreale et al[17] showed that there was no decrease in elevated serum PSA level in hirsute patients after the 3-6 cycles of treatment with oral contraceptive pills. Antiandrogen drugs are probably more effective than oral contraceptives in blocking androgen action at the tissue level, or progestins in the contraceptive pills may stimulate the PSA production in tissues.

PSA level in women may vary with many factors including age and menstrual cycle day.[18] However, in our study, there was no significant difference in these parameters between the groups.

Hyperandrogenemia as in patients with PCOS might stimulate the production of PSA in androgen sensitive tissues. PSA level in IH patients did not increase as seen in PCOS patients. Increased 5 α reductase activity in IH patients might stimulate the PSA production in extragonadal sites, although they have normoandrogenemia. However, further studies are needed to elucidate this hypothesis.

In conclusion, the results of this study indicate that serum PSA level is higher in hirsute patients than in controls. Patients with PCOS have higher total and free PSA levels than women with IH. Therefore, the ultrasensitive assay of serum PSA level may be beneficial in the differential diagnosis of hirsutic women with hyperandrogenemia from the patients with idiopathic hirsutismus.

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