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Total testosterone cut-off value indicating androgen-secreting tumor in premenopausal women with hirsutism

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Abstract. – OBJECTIVE: There is insufficient data on which cut-off value must be used to measure the increase in total testosterone (TT) compared to the upper limit of normal (CULN) in the diagnosis of androgen-secreting tumor (ASTM) in female individuals with premenopausal hirsutism (FIPH).

PATIENTS AND METHODS: A total of 413 FIPH over 18 years of age who were admitted to the endocrinology clinic between May 2013 and 30 April 2018 were eligible for the study. Hormone profiles of the participants in the follicular phase and other information were obtained from their files. The androgen suppression ratio (ASR) was analyzed after 48 hours of low-dose dexamethasone suppression test (LDDST) in those whose TT CULN (nmol/L) increased two-fold.

RESULTS: Idiopathic hirsutism was found in 193 participants (46.73%) and polycystic ovary syndrome (PCOS) in 200 (48.43%) and other sources of hirsutism; non-classical congenital adrenal hyperplasia (NCCAH) in 10 patients (2.42%), hyperprolactinemia in 6 patients (1.45%), ASTM of ovarian origin in 2 patients (0.48%), Cushing's disease in 1 patient (0.24%), and adrenal ASTM in 1 patient (0.24%). A cut-off value of two-fold CULN increase for TT sensitivity of 100% and a specificity of 99.5% in indicating an ASTM source, and ASR above 49% in LDDST sensitivity of 80% and a specificity of 100% in excluding an ASTM source, was used.

CONCLUSIONS: At the TT level, a two-fold increase CULN in FIPH indicates an ASTM source. In addition, ASR after LDDST is a useful parameter in the exclusion of ASTM sources in the same patient population.

Key Words:
Total testosterone, Polycystic ovary syndrome, Androgen secreting tumor, Non-classical congenital adrenal hyperplasia, Androgen suppression test with low dose dexamethasone.

Introduction

Hirsutism is defined as the excessive growth of terminal hair on a woman's body in a male-like manner[1]. The most common clinical manifestation of hyperandrogenism is hirsutism, which represents a rather common finding, particularly in females who are in the premenopausal age[2]. However, not all increases in terminal hair are pathological. Ferriman Gallway (FG) scoring was developed to evaluate this[3]. An FG score of > 8 in white Americans and > 10 in Middle Easterners is considered pathological[4]. Although the FG scoring system is widely used, the presence of racial differences and the fact that different etiological causes lead to similar clinical conditions are insufficient points of FG scoring. It is important to distinguish hirsutism from hypertrichosis.

Hypertrichosis occurs mostly in areas outside the hormonal effect areas, such as the upper arm and leg below the knee[5]. Hypertrichosis occurs in individuals with a genetic predisposition towards it or due to the effect of certain drugs (cyclosporine, minoxidil, phenytoin)[5]. Moreover, hyperandrogenemia and oligomenorrhoea are not present in a significant proportion of women with premenopausal hirsutism (PHC); these patients are classified as having idiopathic hirsutism[6]. The majority of patients with premenopausal hyperandrogenemia include patients with polycystic ovarian syndrome (PCOS) and idiopathic hirsutism[5]. In addition, the non-malignant causes of hirsutism include hyperprolactinemia (HP), pituitary or surrenal adenoma-induced Cushing's syndrome (CS), classical and non-classical congenital adrenal hyperplasia (NCCAH), adrenocortical adenoma, and benign ovarian tumors; the

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malignant causes of hirsutism include adrenocortical cancer and malignant ovarian tumours[5].

Androgen-secreting tumors (ASTM) are one of the most serious causes of hyperandrogenemia and, therefore, their exclusion is critical. Laboratory tests are mandatory to confirm androgen excess and to determine the source of the secretion. Waggoner et al[7] (1999) determined the sensitivity and specificity as 100% and 98%, respectively, for predicting ASTM for values above 8.67 nmol/L with kits with an upper limit of 3.0 nmol/L[7]. Another method used in the diagnosis of ASTM is based on the suppression of endogenous androgens by exogenous corticosteroids[8]. Khaltsas et al[8] (2003) re-evaluated total testosterone (TT) levels after 48 hours from the low-dose dexamethasone suppression test (LDDST) in patients with high TT levels and found that an androgen suppression rate (ASR) of 40% and below compared to baseline had a sensitivity of 100% and a specificity of 88% in indicating ASTM-induced etiology[8]. Studies in which laboratory parameters should be used in confirmation of the diagnosis of ASTM-induced causes are rather limited, and in existing studies, there is not sufficient data on which cut-off value should be used for the increase of basal TT compared to the upper limit of normal (CULN) in the diagnosis of ASTM-induced causes.

Thus, the aim of this study was to evaluate the reliability of the increase in baseline TT CULN in the diagnosis of ASTM-induced etiology in PHC individuals and to obtain the appropriate cut-off value.

Patients and Methods

Inclusion Criteria

Premenopausal females aged 18 years and older who were referred to the endocrinology clinic for hirsutism between 1 May 2013 and 30 April 2018 were included in the study. Informed consent was obtained from all individual participants included in the study.

Exclusion Criteria

Females who were previously diagnosed and under treatment with hirsutism, pregnant, diagnosed with chronic diseases (chronic liver disease, chronic renal failure, organ transplantation), with previously diagnosed pituitary insufficiency or hypersecretion, and with previously diagnosed adrenal gland disease were excluded.

Study Design and Follow-Up

A modified FG score > 8 was accepted as hirsutism, and hirsutism information was recorded as either present or absent. Those with hirsutism were included in the study and further evaluated according to the current guidelines[4]. Oligomenorrhoea was defined as less than 8 menstrual cycles in 12 months in the last year and recorded as present/absent. In the last year, the increase was recorded as present/absent according to the patient's own evaluation. In addition, the appearance of PCOS on ultrasonography was recorded as present/absent from their medical records. Rotterdam 2004 Criteria[9] were used for the diagnosis of PCOS. Accordingly, the presence of 2 of 3 criteria was considered compatible with the presence of PCOS. The criteria include 1) oligo and/or anovulation, 2) clinical and/or biochemical symptoms of hyperandrogenism, and 3) polycystic ovary appearance on ultrasonography (US)[9]. Follicular phase TT, free testosterone (FT), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), dehydroepiandrosterone sulphate (DHEAS), 17-OH-progesterone (17-OH-P), fasting plasma glucose (FPG), creatinine (Cr), information on thyroid stimulating hormone (TSH), prolactin (PRL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values, height, weight, and age were obtained from the patient files; body mass index (BMI) was calculated in kilogram/m^2.

TT levels measured in ng/dL were converted to nmol/L according to the conversion formula 1 ng/dL = 0.0347 nmol/L. The normal limit for TT levels was calculated as 0.34 nmol/L –1.97 nmol/L and CULN increase levels were calculated as nmol/L.

Further, a Synacthen stimulation test was performed in patients with follicular phase basal 17-OH-P levels above 2.0 ng/mL; those with 17-OH-P levels > 10 ng/mL after stimulation were considered NCCAH[10].

Patients whose morning TT levels were more than two times higher than normal were analyzed again and the ASR was obtained by proportioning to the basal TT level[8]. ASR was controlled with the rate of suppression in cortisol level, and a post-LDDST cortisol level < 1.8 µg/dL was considered compatible with suppression[11]. Patients who did not show suppression were subjected to further evaluation in terms of CS in accordance with the recommendation of the guidelines[11].

Whole abdominal magnetic resonance imaging (MRI) was performed in all patients with TT

levels increased by 1.0-fold or more, according to CULN. In one of the patients whose TT level was two-fold and above no pathology was found in the gynecological examination and in whole abdominal MRI imaging. The patient underwent selective venous sampling to determine the source of androgen hypersecretion. Moreover, patients with TT levels increased 1.0 fold CULN no pathology detected were followed up.

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) statistics 20 (IBM Corp., Armonk, NY, USA) was used to compare the data. After the normal distribution was determined, an independent samples *t*-test was applied to the data with a normal distribution. Moreover, the Mann-Whitney U test was applied to compare data that did not have a normal distribution. Pearson's Chi-squared test was used to compare ratios. Further, receiver operating characteristic (ROC) analysis was used to determine the best value associated with the disease. A *p*-value lower than 0.05 was considered statistically significant.

Results

General Characteristics of the Study Group

A total of 413 patients with hirsutism were included in the study. Of the 413 patients, 193 (46.73%) had idiopathic hirsutism and 200 (48.43%) had PCOS. The following were the other etiological causes: Cushing's disease was found in 1 patient (0.24%), testosterone-producing adrenal adenoma in 1 patient (0.24%), NCCAH in 10 patients (2.42%), HP in 6 patients (1.45%), and Sertoli-Leydig cell malignant tumor of ovarian origin in 2 patients (0.48%). In addition, in 1 patient with NCCAH, an ovarian tumor was detected in the imaging performed because TT was high and did not show suppression in LDDST (the patient's operation and pathology information could not be obtained in the hospital's database). The general characteristics of the patients are summarized in Table I.

Clinical Findings

The frequency of those who reported an increase in hirsutism in the last year was higher in the PCOS group than in the idiopathic group (61.0%, 39.0%, $p = 0.008$, respectively). In all three patients with elevated TT due to ASTM, there was an increase in hirsutism in the last year. When one patient with no pathological data was included, all four patients experienced an increase in hirsutism in the last year. Furthermore, an increase in hirsutism in the last year was found in 4 (40%) of 10 patients with NCCAH. On the other hand, no increase in hirsutism was observed in the last year in any of the patients with HP and CS. When evaluated together, the association of oligomenorrhoea along with an increase in hirsutism for the past year was seen in two of three (66.7%) of the patients with ASTM, and it was found in three of four patients (75%) when a patient with no pathological data included. On the other hand, both clinical findings were present in 153 of 200 (76.5%) of PCOS patients.

Laboratory Findings

According to the etiological causes, the increase in TT and increase in CULN are depicted in Figure 1, and DHEAS and 17-OH-P levels are depicted in Figure 2.

There were seven patients with a two-fold or more increase in TT level CULN and four patients who had TT suppression rates below 40% after LDDST (Table II).

In patients with a two-fold increase in TT level CULN, the sensitivity and specificity of ASR above 49% in excluding the ASTM source were found to be 80% and 100%, respectively.

Patients with a 1.0-fold–2.0-fold increase in TT CULN and no pathological findings on imaging were followed up. The mean follow-up period was 10.6 months (range: 2-13.5). During the follow-up period, no patient with an increase in TT value and ASTM was identified.

PCOS

PCOS was diagnosed with oligomenorrhoea and clinical and/or laboratory findings of hyperandrogenemia in 171 (85.5%) of 200 patients and with clinical and/or laboratory findings of hyperandrogenemia and PCOS appearance on ultrasonography in the remaining 29 (14.5%) patients. In all but one patient among the PCOS participants, TT increased less than two-fold CULN. In a patient in whom an increase was detected, the level of increase CULN was 2.25, ASR was 80% after LDDST in the mentioned patient, and no pathology related to ASTM was detected on imaging.

NCCAH

In 3 of 10 patients with NCCAH, TT level increased more than two times CULN (2.13-, 2.04-, and 5.80-fold, respectively), and suppression over 40%

Table I. Laboratory and clinical characteristics of the study group.

	Idiopathic	PCOS	NCCAH	ASTM
Age (year)	34.6 (IQR: 15.0)*	30.8 (IQR: 9.0)*	31.9 (IQR: 8.0)*	39.5 (IQR: 5.0)*
BMI (kg/m^2)	31.2 (IQR: 10.0)*	31.3 (IQR: 8.9)*	30.3 (IQR: 9.6)*	30.3 (IQR: 9.6)*
TT (nmol/L)	1.27 ± 0.75	1.74 ± 0.68	1.90 ± 1.36	12.59 ± 10.81
DHEAS (µg/dL)	246.83 ± 108.1	273.5 ± 121.4	323.0 ± 234.6	129.0
FSH (mIU/mL)	5.62 ± 1.5	4.84 ± 1.4	7.1 ± 3.6	6.2 ± 2.1
LH (mIU/mL)	3.87 ± 1.9	5.95 ± 4.4	7.4 ± 8.1	4.2 ± 1.2
E2 (pg/mL)	37.4 ± 16.2	40.8 ± 20.9	35.7 ± 20.7	34.0
PRL (ng/mL)	16.7 ± 10.3	17.6 ± 10.6	22.1 ± 18.9	7.2 ± 0.3
17-OH-P (ng/mL)	1.26 ± 0.94	1.41 ± 0.97	13.3 ± 12.3	0.95
FPG (mg/dL)	90.6 ± 17.4	95.0 ± 24.7	84.6 ± 9.6	84.0
Cr (mg/dL)	0.70 ± 0.12	0.70 ± 0.11	0.76 ± 0.15	0.86
TSH (mIU/L)	2.15 ± 1.95	2.34 ± 1.40	2.10 ± 0.83	0.80 ± 1.4
AST (IU/L)	19.6 ± 6.3	21.4 ± 7.4	17.8 ± 5.3	24.0

PCOS: polycystic ovarian syndrome, NCCAH: non-classical congenital adrenal hyperplasia, ASTM: androgen-secreting tumor, BMI: body mass index, TT: Total testosterone, DHEAS: dehydroepiandrosterone sulfate, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, PRL: prolactine, 17-OH-P: 17-oh-progesterone, FPG: fasting plasma glucose, Cr: creatine, TSH: thyroid stimulating hormone, AST: aspartate transferase; *since it does not show a normal distribution, median and an interquartile range (IQR) of 25-75 percentiles are given.

was detected in the first two patients after LDDST (72.6%, 84.0%, respectively). On the other hand, no suppression was detected (3.6%) in the third patient of 10 (sixth patient in Table II), and abdominal MRI imaging revealed a 34 × 23 mm solid lesion in the right ovary; no adenoma was detected in the surrenal glands, and then later on, no further operative and pathological information was available.

ASTM

In patients with ASTM-induced hirsutism, the increased fold in TT with CULN was significantly higher compared to other sources (Figure 1) ($p < 0.001$). In premenopausal women, the sensitivity and specificity of TT for predicting an ASTM-induced etiology were 100% and 100%, respectively, when the cut-off value was 2.4-fold for the increase in TT with CULN, whereas the sensitivity and specificity were 100% and 99.5%, respectively, when the cut-off value was 2.0-fold for the increase in TT with CULN. The ROC curve showing that TT is a highly reliable test in predicting the etiology of ASTM is depicted in Figure 3. In contrast, no ASTM

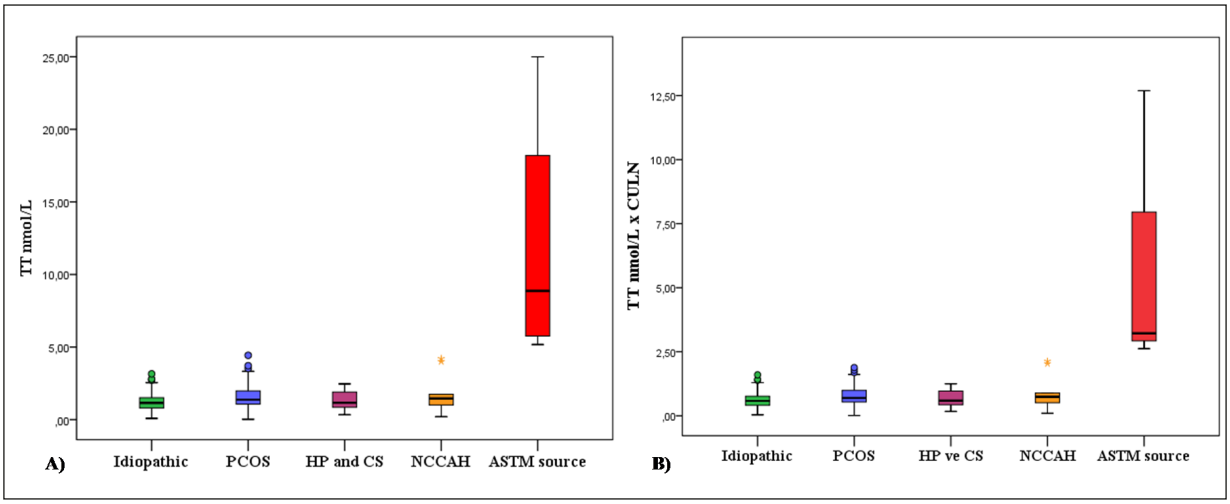

Figure 1. TT levels (**A**) and increase (**B**) compared to the upper limit of normal (CULN) according to aetiological sources. *Refers to a person at the extreme of the normal distribution. PCOS: polycystic ovarian syndrome, HP: hyperprolactinemia, CS: Cushing's syndrome, NCCAH: non-classical congenital adrenal hyperplasia, ASTM: androgen-secreting tumor, TT: total testosterone.

Table II. Characteristics of patients with a two-fold increase CULN in TT.

Patient	Age	Level of increase CULN in TT	ASR with LDDST	Radiological imaging	Etiological source
1	37	2.67	7.7%	Solid lesion 50×42 mm was detected in the right ovary	Sertoli Leydig cell malignant ASTM
2	31	2.13	72.6%	No pathology was detected	NCCAH
3	26	2.04	84.0%	No pathology was detected	NCCAH
4	42	3.22	NA	Solid lesion 40×36 mm in the left adrenal gland, consistent with adrenal adenoma	Benign adrenal ASTM
5	42	12.7	-8.0%	No pathology was detected	Sertoli Leydig cell malignant ASTM in the left ovary*
6	25	5.8	3.6%	Solid lesion 34×23 mm in the right ovary	NCCAH + pathological information could not be obtained
7	21	2.25	80%	No pathology was detected	PCOS

CULN: compared to the upper limit of normal, TT: total testosterone, ASR: androgen suppression ratio, LDDST: low-dose dexamethasone suppression test, ASTM: androgen-secreting tumor, NCCAH: non-classical congenital adrenal hyperplasia, NA: not available, PCOS: polycystic ovarian syndrome, *no pathology was detected in imaging and gynecological examination; pathological androgen production in the left ovary was detected by venous sampling.

was detected with DHEAS. The MR image of the patient with Sertoli Leydig cell malignant ASTM in the right ovary is shown in Figure 4.

Discussion

In our study, it was observed that the level of increase in TT CULN in FIPH was a rather reliable parameter in the identification of patients who required further investigation. In addition, ASR after LDDST had an important place in the exclusion rather than the diagnosis of ASTM-derived etiologies in the patient group that required further investigation.

In our study, patients with idiopathic hirsutism and PCOS constituted 95.2% of all admissions due to hirsutism. Bozdag et al[2] found the prevalence of hirsutism to be 13% (8-20%) and the prevalence of PCOS to be 6% (5-8%) according to NIH[12] diagnostic criteria, 10% (8-13%) according to the Rotterdam[9] diagnostic criteria, and 10% (7-13%) according to the AE-PCOS Society[13] criteria in a selected population[2,9,12,13]. In the same

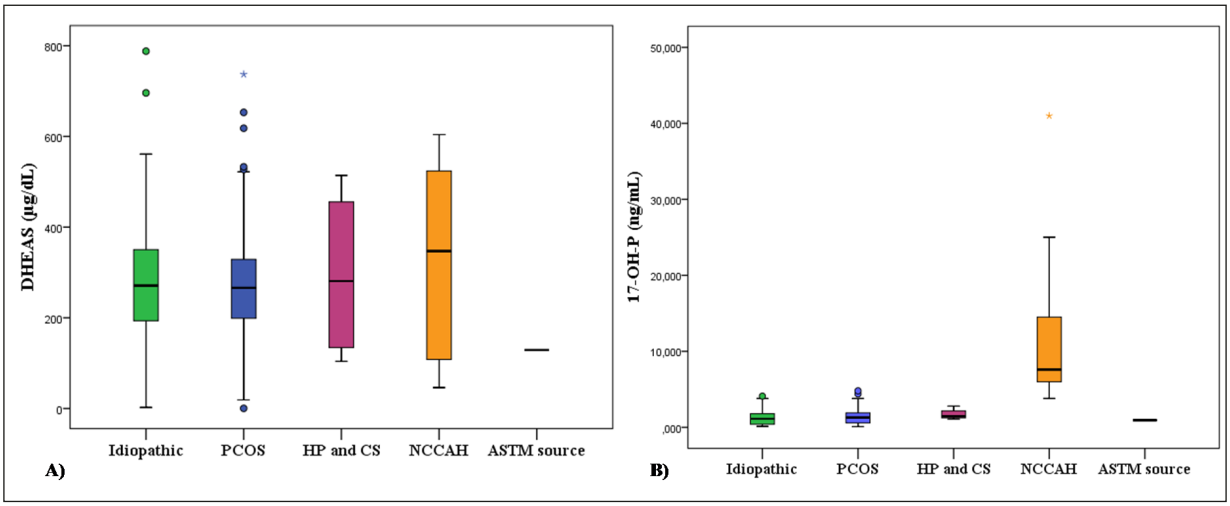

Figure 2. DHEAS (**A**) and 17-OH-P (**B**) levels according to etiological sources. *Refers to a person at the extreme of the normal distribution. PCOS: polycystic ovarian syndrome, HP: hyperprolactinemia, CS: Cushing's syndrome, NCCAH: non-classical congenital adrenal hyperplasia, ASTM: androgen-secreting tumor, DHEAS: dehydroepiandrosterone sulfate, 17-OH-P: 17-OH-progesterone.

study, the prevalence of PCOS was found to be 6% (5-8%) according to NIH diagnostic criteria, 9% (7-12%) according to the Rotterdam diagnostic criteria, and 10% (7-14%) according to the AE-PCOS Society criteria[2].

Although it is one of the most common clinical conditions, the diagnostic process faces certain difficulties due to reasons such as diversity of etiological causes and being affected by geographical and ethnic factors. According to Bozdag et al[2], unselected population-based studies have indicated that the prevalence of PCOS was found to be 6% (5-8%) according to NIH diagnostic criteria, 9% (7-12%) according to the Rotterdam diagnostic criteria, and 10% (7-14%) according to the AE-PCOS Society criteria[2]. Hirsutism is one of the most common causes of presentation in daily practice for PCOS. Clinical findings may be insufficient in the diagnostic process. In light of the findings of our study, oligomenorrhoea and an increase in hirsutism in the past year were present together in 76.5% of PCOS patients and 75% of ASTM patients. Although oligomenorrhoea and an increase in hirsutism in the last six months or one year is a rather important and alarming finding, it is not sufficient to make a diagnosis. Reliable laboratory values are required for differential diagnosis in patients with clinical findings that suggest ASTM.

The current guidelines[5,14] recommend that the FG score should be examined in patients presenting with hirsutism, and further evaluation should be conducted if it is higher than expected according to the current ethnicity[5,14]; moreover, TT, FT, and DHEAS should be measured in laboratory tests for further evaluation[5,14]. However, there is insufficient data in the literature on the cut-off value for TT CULN in patients who undergo further evaluation and in whom ASTM is considered. In our study, we found that levels of at least a two-fold increase in TT CULN correlated very well with ASTM. Waggoner et al[7], conducted a study on 478 patients who presented with hirsutism within a 10-year period and found an increase in TT levels in 11 patients[7]. They found ASTM (ovarian hilar cell tumor) in 1 of 11 patients with increased TT levels[7]. In the study of Waggoner et al's[7], when the increase in

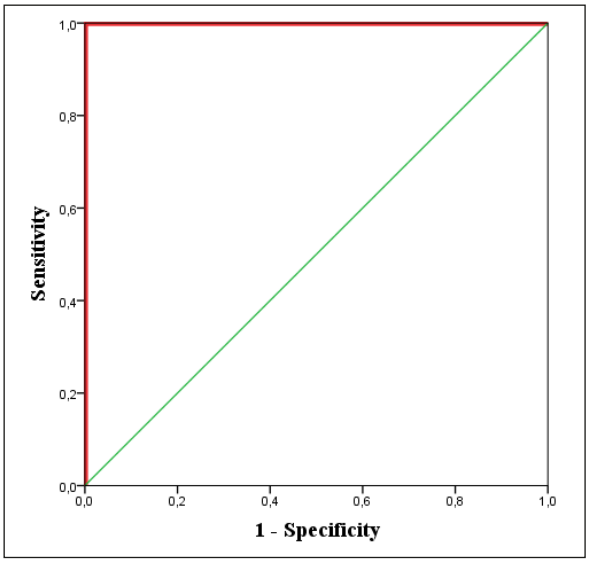

Figure 3. ROC curve indicating the reliability of increasing levels of total testosterone compared to the upper limit of normal in the diagnosis of androgen-secreting tumor.

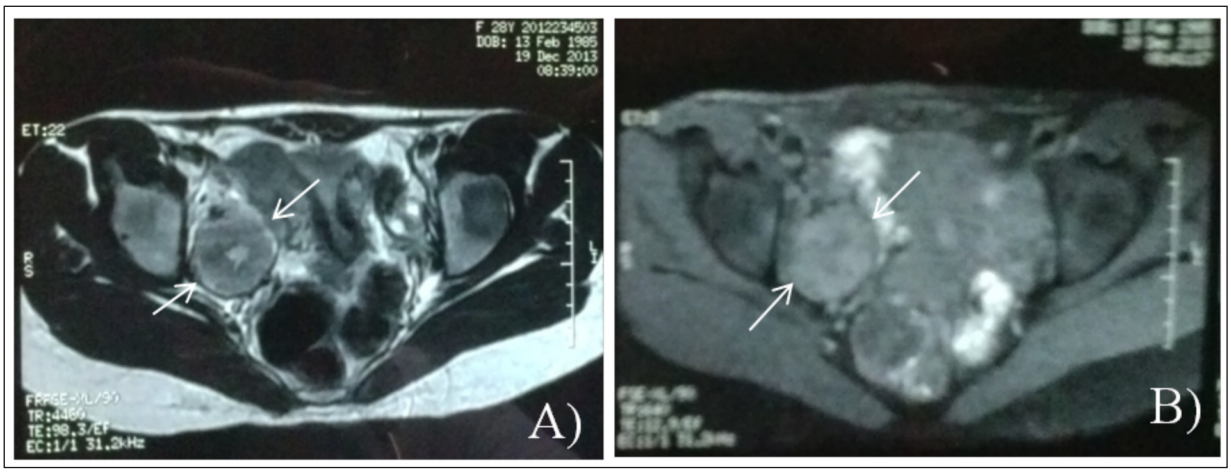

Figure 4. Magnetic resonance imaging image of a 50x42 mm Sertoli Leydig cell malign androgen-secreting tumor, regular bordered lesion in the right adnexal lobe with hypo in T1-weighted sequences (**A**) and slightly hyperintense signal change in T2-weighted sequences (**B**).

the levels of TT CULN was calculated, this level was found to be 2.3-fold. In our study, we found the sensitivity and specificity of TT kits with an upper limit of 1.97 nmol/L and a cut-off value of 4.73 nmol/L (2.4-fold) to be 100% in identifying the source of ASTM origin. On the one hand, our study is similar to Waggoner et al's[7] study, because it included population-based patients, and the rate of increase of TT CULN that indicated ASTM source was rather close to each other[7]. On the other hand, although kits measuring TT with nmol/L were used in both studies, the CULN levels yielded different values. As can be clearly observed, there will be confusion in evaluation when there are different normal limits, even in kits using the same units of TT measurement. Furthermore, when we consider those kits using different units, which are also widely used, this is a significantly more important problem than the previous one to establish a common threshold value. The threshold value obtained from our study is based on nmol/L and any other application without conversion of the relevant units into nmol/L may yield incorrect results. Therefore, other units should be converted to nmol/L, and then the level of increase of the kit should be determined in nmol/L. In this respect, our choice of unit in our study supports the previous studies[7] using nmol/L, and we believe that will contribute to a more precise determination of the cut-off value for the level of increase of TT CULN by using nmol/L.

Another result obtained from our study is that ASR after LDDST is a reliable tool in excluding ASTM etiology in patients with a two-fold or more increase in TT CULN. The desire and effort to suppress androgens with corticosteroids has a long history[15-21]. Studies[15-21] on the treatment of oligomenorrhoea or infertility with corticosteroids date back to the 1950s. Rodriguez-Rigau et al's[22] study, conducted in 1979 on 106 premenopausal female patients with clinical and laboratory hyperandrogenemia, found significant suppression in androgen levels and improvement in ovulation in patients treated with 7.5 mg-10 mg prednisone for 1 to 17 months (mean 4.5 months)[22]. The basic idea or mechanism here is to suppress non-autonomous androgen production with external corticosteroids, as in NCCAH. While the attempt to suppress androgens with steroids was initially used for therapeutic purposes, its usability for diagnostic purposes was subsequently investigated. Kaltsas et al[8], who conducted important studies on this subject, found that observation of ASR suppression after LDDST reliably indicated ASTM-induced etiology and indicated that it could also be used for diagnostic purposes. In the same study[8], the sensitivity and specificity of 40% or lower suppression in androgens after LDDST compared to baseline was found to be 100% and 88%, respectively, in signaling an ASTM etiology of adrenal or surrenal origin[8]. In individuals presenting with hirsutism, increases in TT level by two-fold or more CULN should be taken seriously. While it can be said that autonomic androgen secretion is excluded in almost all patients who show sufficient suppression after LDDST, it is not possible to say that all patients who do not show sufficient ASR are ASTM. In patients with a one-to-two-fold increase in TT CULN, the etiological cause is rather likely to be due to PCOS; thus, TT production in these patients may not suppressed below 40% after LDDST and may not yield reliable results. In this respect, our study differs from the study of Kaltsas et al[8] because we argue that ASTM signaling is appropriate in all patients with a high TT of ASR by LDDST. In our study, we believe that ASR with LDDST will be more efficient in excluding the ASTM source in the group of patients with a two-fold or more increase in TT CULN. However, this needs to be supported by additional research.

Limitations

Our study has a few weaknesses. The first weakness is that some data could not be accessed due to its retrospective nature, and virilism findings were not recorded. Secondly, the fact that our study consisted of patients referred to the second-level endocrine clinic, may have caused a low number of ASTMs to be identified.

Conclusions

In premenopausal women presenting with hirsutism, a two-fold increase in TT levels CULN is strongly associated with ASTM. In addition, the demonstration of adequate ASR after LDDST in individuals with a two-fold increase in TT levels CULN is a reliable tool for the exclusion of ASTM-induced hyperandrogenemia.

Funding

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Ethics Approval
The present study was approved by the Ethics Committee of the Health Sciences University, Bursa Yüksek Ihtisas Training and Research Hospital, "2011-KAEK-25 2022/09-12". In light of the retrospective nature of the study, all procedures were performed as part of routine care. The researchers affirm that they adhered to the Declaration of Helsinki.

Authors' Contributions
Mutlu Güneş: Conceptualization, supervision, methodology, software, validation, writing- reviewing and editing. Elif Güneş: Conceptualization, supervision, methodology, data curation, writing-original draft preparation, visualization, investigation, writing- reviewing and editing. Ferdiz Öztürk: Data curation, methodology, validation, writing, reviewing and editing.

Conflict of Interest
The authors declare that they have no conflicts.

Data Availability
The data used for this manuscript will be made available upon reasonable request to the corresponding author.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

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