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ORIGINAL ARTICLE

Testosterone or dihydrotestosterone: what should be evaluated in hirsutism?

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Abstract

Purpose Dihydrotestosterone is a more potent androgen derived from testosterone and androstenediones, but its measurement has not been routinely recommended in women with hirsutism, and there is limited information in this regard with equivocal findings. This study aimed to evaluate serum dihydrotestosterone level in patients with hirsutism compared to women without hirsutism.

Methods In this case–control study (during 2021–2022), serum levels of total testosterone, free testosterone, and dihydrotestosterone were evaluated in 101 women with hirsutism and 101 healthy women. Hormonal levels were measured with chemiluminescent immunoassay method. Age and hormonal levels in each group, body mass index, menstrual status, complaint of decreased scalp hair density, and ovarian ultrasound findings in hirsutism group were collected and analyzed.

Results There was significant difference in free testosterone and dihydrotestosterone levels ($P<0.001$) and no significant difference in total testosterone level between two groups ($P=0.628$). Dihydrotestosterone level was significantly higher in women with hirsutism with menses irregularity, complaint of decreased scalp hair density, and presence of polycystic ovary on ultrasound ($P<0.05$).

Conclusions Measuring dihydrotestosterone level is not considered in routine evaluation of hirsutism, but we think that this significant difference shows that elevated level of dihydrotestosterone hormone in women with hirsutism is an important factor.

Keywords Dihydrotestosterone · Hirsutism · Testosterone

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Introduction

Growth of terminal hair in some regions such as beard area, upper chest, periumbilicus, and medial upper thighs in women has been named as hirsutism, and it may have a racial pattern. Women with hirsutism often ask about an effective hair removal method and claim that they had no hormonal disturbance in prior evaluation. Therefore, these women are classified as idiopathic hirsutism because they have no elevated levels of circulating androgens with usual hormonal laboratory tests [1–3].

It has been recommended that androgen levels should be evaluated in women with hirsutism regardless of the severity of hirsutism, and free testosterone (T) level is more sensitive than total T level [4].

Almost all women with hirsutism have elevated levels of androgens mainly T level, but this increase may not result in higher than normal limit of total T, as increase in T level is

associated with decrease in sex hormone-binding globulin (SHBG) [1, 2].

Hirsutism score does not associate with the amount of plasma androgens levels, and skin as a paracrine organ could produce or metabolize dihydrotestosterone (DHT) hormone which has a great role in terminal hair growth in different areas of the body. Routine hormonal evaluation in hirsutism includes total and free T level, dehydroepiandrosterone sulfate (DHEAS), and SHBG, and in cases with oligomenorrhea, thyroid hormones and prolactin should be evaluated [1–3]. Evaluation of DHT level is not considered as an essential hormonal measurement in patients with hirsutism, and many patients with normal levels of other androgenic hormones have been classified as idiopathic hirsutism, but they may have no assessment of DHT level. The role of DHT is not well recognized in women, and there is limited information about DHT level status in women with hirsutism [5].

This study was designed to have more information about DHT, T, and free T levels in women with and without hirsutism.

Methods

This study was designed as a case–control study performed during 12 months (2021–2022) in Razi hospital, Rasht, Iran. We included 202 participants, 101 cases with hirsutism and 101 healthy women selected from our patients with the same age group, who visited for esthetic reasons in the outpatient clinic. All non-menopause women aged ≥ 18 years who did not meet our exclusion criteria and had consent for body examination and doing laboratory evaluation were included.

We excluded some cases as follows: age < 18 and > 50 years, previous laser treatment for hair removal in such a way that it was not possible to judge about hirsutism, no consent for doing laboratory evaluation, any condition that can change serum androgens levels such as pregnancy or lactation, history of androgenic tumors, thyroid dysfunction and corticosteroids, and oral contraceptive pill intake during the past 3 months.

Hirsutism was clinically diagnosed by an individual dermatologist based on hirsutism definition in previous reports [1–3]. The collected data were age of participants, total T, free T, and total DHT levels in both groups, and complaint of decreased scalp hair density, presence of polycystic ovary (PCO) on ultrasound, menses irregularity, and body mass index (BMI) in hirsutism group. Some androgenic presentations such as acne and seborrheic dermatitis were not considered in this study and complaint of scalp hair loss was evaluated as a subjective symptom for patients with hirsutism.

It was not possible to measure free DHT for our participants in this study. Hormonal levels were assessed in fasting venous blood samples during follicular phase of menstrual cycle (days 3–5 of period) in an individual laboratory by chemiluminescent immunoassay technique (LIAISON Instrument, Germany). Evaluation of androgenic hormones other than DHT level should be considered during follicular phase of menstrual cycle, but there is no fluctuation in DHT level during menstrual cycle [3–5]. Normal serum levels for total T, free T, and DHT were defined as 0.35–3.47 ng/ml, up to 2.8 pg/ml, and 24–368 pg/ml, respectively.

Quantitative variables were described using mean ± SD or median (quartile1–quartile3). Qualitative data were reported by number and percentage. Quantitative variables with normal distribution in subgroups were evaluated using kurtosis, skewness, Q–Q plot, box plots, and Shapiro–Wilk test. For the comparison of variables in subgroups with abnormal distribution, Mann–Whitney

Table 1 Age of participants and comparison of testosterone, free testosterone, and dihydrotestosterone levels in both groups

Variables		Groups ($N=202$)		P value
		Without hirsutism ($N=101$)	With hirsutism ($N=101$)	
Age (years)	Median (Q1–Q3)	31 (23–38.5)	30 (23–38)	0.805*
Age groups (years)	18–27	45 (44.6%)	45 (44.6%)	>0.999**
	28–37	29 (28.7%)	29 (28.7%)	
	38–47	27 (26.7%)	27 (26.7%)	
Total testosterone level (ng/ml)	Mean ± SD	1.78 ± 0.92	1.63 ± 0.78	0.628*
	Median (Q1–Q3)	1.57 (1.23–2.11)	1.60 (1.00–2.20)	
Free testosterone level (pg/ml)	Mean ± SD	1.03 ± 0.53	2.11 ± 1.08	<0.001*
	Median (Q1–Q3)	0.89 (0.69–1.28)	2.00 (1.40–2.60)	
Dihydrotestosterone level (pg/ml)	Mean ± SD	274 ± 104.85	352.26 ± 149.60	<0.001*
	Median (Q1–Q3)	294.8 (191.5–366)	336 (255.5–427.5)	
Total testosterone/dihydrotestosterone ratio (ng/pg)	Mean ± SD	0.0075 ± 0.0055	0.0053 ± 0.0033	<0.001*
	Median (Q1–Q3)	0.0062 (0.0046–0.0082)	0.0051 (0.0034–0.0064)	

*Mann–Whitney test, **chi-square test

Table 2 Comparison of hormonal status in both groups

Hormonal status		Groups ($N=202$)		P value
		Without hirsutism ($N=101$)	With hirsutism ($N=101$)	
Total testosterone	Increased level (>3.47 ng/ml)	5 (5.0%)	4 (4.0%)	>0.999*
	Normal	96 (95%)	97 (96%)	
Free testosterone	Increased level (>2.8 pg/ml)	1 (1.0%)	21 (20.8%)	<0.001**
	Normal	100 (99%)	80 (79.2%)	
Dihydrotestosterone	Increased level (>368 pg/ml)	23 (22.8%)	45 (44.6%)	<0.001**
	Normal	78 (77.2%)	56 (55.4%)	

*Fisher's exact test, **chi-square test

test and Kruskal–Wallis test were applied. For comparison of qualitative variables, the chi-square and Fisher's exact test were used. All statistical tests were performed in SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). All P values were two sided; significance level was set at $P<0.05$.

Results

A total of 101 women with hirsutism and 101 healthy women without hirsutism aged 18 to 47 years (mean age 30.13 ± 8.02 years, median 30 years) were enrolled in this study. Mean age and age group distribution of the participants were not significantly different in two groups and were matched, because DHT level decreases with aging [6] (Table 1).

Comparison of mean total T level and frequency of hyper total T level (> 3.47 ng/ml) in two groups showed no significant difference ($P=0.628$ and $P>0.999$, respectively) (Tables 1 and 2). There was significant difference in free T, total DHT levels, frequency of hyper DHT (> 368 pg/ml), and hyper free T (> 2.8 pg/ml) level between two groups ($P<0.001$) (Tables 1 and 2). Forty-five cases (44.6%) of women with hirsutism and 23 cases (22.8%) of healthy women showed hyper DHT level. Increased levels of total T and free T were only observed in 4 (5.9%) and 11 (16.2%) of cases with hyper DHT level (68 cases) of both groups.

DHT level was significantly higher in women with hirsutism with menses irregularity, complaint of decreased hair density of scalp, and presence of PCO on ultrasound. But DHT level was not significantly associated with BMI in hirsutism group (Table 3). Also T/DHT level ratio in women with hirsutism did not have a significant association with BMI ($P=0.623$).

Discussion

Androgenic hormones such as T and DHT bind to sex hormone-binding globulin (SHBG), but active form of these hormones is non-bound or free androgen. In women with hirsutism especially in persons with polycystic ovary syndrome (PCOS), SHBG level decreases due to hyperinsulinemia. Therefore, total T level will be in normal range due to decreased SHBG level, but free T level increases with decreasing SHBG [7, 8]. Non-significant increase in total T and significant increase in free T level in our patients could be explained by this concept. But, Munzker

Table 3 Association of dihydrotestosterone level with complaint of decreased scalp hair density, presence of polycystic ovary on ultrasound, menses irregularity, and body mass index in hirsutism group

Variables in hirsutism group ($N=101$)			Dihydrotestosterone level (mean ± SD)	P value
Complaint of decreased scalp hair density	Yes	$N=59$	380.54 ± 158.05	0.020*
	No	$N=42$	312.52 ± 128.37	
Polycystic ovary (in ultrasound)	Yes	$N=37$	387.40 ± 130.96	0.028*
	No	$N=64$	331.94 ± 156.78	
Menses irregularity	Yes	$N=42$	398.86 ± 153.2	0.005*
	No	$N=59$	319.08 ± 138.94	
Body mass index	<18.5	$N=2$	405 ± 14.14	0.425**
	18.5–24.9	$N=51$	341.53 ± 172.52	
	≥25	$N=48$	361.46 ± 124.99	

*Mann–Whitney test, **Kruskal–Wallis test

et al. reported that total T, free T, and free DHT level were significantly higher in PCOS cases and total DHT level was not significantly different compared to healthy subjects [9], and Azizz et al. believed that intracellular concentration of DHT is more important than serum level of DHT [10].

We found that 44.6% of women with hirsutism had increased level of DHT. Similarly, 40% of cases with idiopathic hirsutism and 35% of PCOS patients have had increased level of DHT in previous report [11]. In men, 70% of DHT is produced by peripheral conversion of T, but in women, DHT is mainly originated from androstenedione. In PCOS patients, androgenic precursors such as androstenedione which are derived from adrenal glands could be transformed to T and DHT in the ovaries and peripheral tissues [7]. PCOS patients have higher DHT and androstenedione levels due to hyperactivity of 5-alpha reductase in the ovary, skin, and adipocytes, and obesity could aggravate hyperandrogenemia in these cases [7, 11]. Therefore, non-significant difference in total T level but significant difference in total DHT between the two groups could be explained by increased 5-alpha reductase activity that transforms T to DHT hormone. Low frequency of hyper T (5.9%) and hyper free T (16.2%) in cases with hyper DHT level reflects the more important role of higher 5-alpha reductase activity in these people and less significant role of overproduction of total T and free T.

We found that T/DHT ratio was significantly lower in women with hirsutism that could be explained by significantly higher DHT level in patients with hirsutism. Munzker et al. reported that T/DHT ratio was a biomarker of undesirable metabolic phenotype in PCOS patients, and this ratio was significantly higher in PCOS women [9]. We did not find any association between DHT and T/DHT level ratio with BMI in cases with hirsutism. Wu et al. reported that 5-alpha reductase activity in PCOS patients has been associated with insulin resistance and abdominal obesity [8], while we evaluated BMI not abdominal circumference that may explain our result. Also, we included all women with hirsutism not only PCOS patients.

5-Alpha reductase hyperactivity is a hereditary trait which was found even in daughters of patients with hirsutism, and obesity does not necessarily determine the level of 5-alpha reductase activity [10].

We found that DHT level was significantly higher in women with hirsutism with menses irregularity and presences of PCO on ultrasound.

DHT causes facial hair growth and decrease of scalp hair growth (16); therefore, higher DHT level in cases with hirsutism and complaint of decreased scalp hair density in our findings could be explained. However, it has been reported that increased serum DHT level is not correlated with the severity of androgenetic alopecia in women, and sensitivity of the follicles to DHT is more important [11].

Osuka et al. reported that prescription of DHT hormone in baby mouse model could induce PCO. On the other hand, PCO by itself could result in higher production of DHT which actually creates a vicious cycle. Therefore, control of DHT level may decrease the chance of PCO development and help for better clinical management of this condition [12].

Zhao et al. observed variation in androgen levels in PCOS with different races and recommended that DHT level and androstenedione levels should be evaluated in these patients [13]. Also Pankajakshan et al. emphasized on the role of DHT in hirsutism. They reported PCOS women with hirsutism had significantly higher level of DHT and DHEAS than PCOS cases without hirsutism [14]. Minooie et al. described that 5-alpha reductase activity increases in women with hirsutism, and there is significant variation of its activity on different areas of the body. They suggested DHT level measurement to know more about the role of androgens on the hair follicles [15]. De Kroon et al. explained that theoretically DHT is a more important factor for hirsutism than T. However, it is rapidly transformed into its metabolites and circulates in blood in very low concentrations, which makes some errors in accurate measurement of DHT level. This may have caused different results in serum DHT level in idiopathic hirsutism in previous reports. DHT-reduced metabolite, 5α-androstane-3α,17β-diol glucuronide, is markedly elevated in idiopathic hirsutism with no significant androgenicity and reflects an increased 5α–reductase activity in these patients [16].

We think that investigations about other biochemical markers may help to unravel the causes of hirsutism. There were some limitations in our study as follows; this research was a small sample-sized cross-sectional study with specific genetic characteristics of our region. Also score of hirsutism, classification of hirsutism, and levels of SHBG, DHT metabolites, free DHT, and 5-alpha reductase activity were not assessed in our participants.

Despite our convincing results, we cannot conclude about the necessity of DHT level measurement in patients with hirsutism, and further large-scale studies in other parts of the world with different genetic characteristics are needed to be done. Control of DHT level might be considered for patients with hirsutism and hyper DHT level, especially in recalcitrant patients that are more resistant to hair removal lasers. Finasteride as an inhibitor of 5-alpha reductase has been recommended for better control of hirsutism as a distressing event especially in women with hyper DHT level to improve their quality of life [16–18].

However, the management of abnormal laboratory findings in hirsutism may not necessarily be associated with clinical improvement [19].

More information and future clinical and laboratory researches about the role of DHT may be helpful for better management of hirsutism.

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Data Availability The raw data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethical approval This research project was approved by the ethics committee of Guilan University of Medical Sciences (code: IR.GUMS.REC.1400.114) and supported by the Vice Chancellor of Research and Technology, Guilan University of Medical Sciences. This study was conducted in accordance with the principles for human experimentation as defined in the Declaration of Helsinki.

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

Conflict of interest The authors declare no competing interests.

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