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RESEARCH ARTICLE

EVALUATION OF DIHYDROTESTOSTERONE (DHT) LEVELS IN WOMEN WITH IDIOPATHIC HIRSUTISM: A CASE CONTROL STUDY REGARDING HOW IT RESPONDS TO HAIR-REMOVAL LASER

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ABSTRACT

Background: Hirsutism is a common disorder in women of reproductive ages, occurs about 5-10%, which could have great impact on women's quality of life. There are many hirsute women with not any other clinical or laboratory clues of hyper-androgenism, called idiopathic hirsutism, and among them there are many cases of laser-resistance, that necessities further evaluation and combination therapies.

Methods and Materials: This case-control study conducted on 130 patients with laser-resistant idiopathic hirsutism. Patients who needed to 6 or more laser sessions, for acceptable therapeutic response, considered as the case group and the responsive patients who needed to 5 or less sessions of laser, as the controls. Serum Prolactin, Testosterone (T) and Dihydrotestosterone (DHT) levels were measured.

Results: Mean age, height, weight, hirsutism score, prolactin also testosterone and dihydrotestosterone levels in case and control groups were statistically significant different. Relative androgen levels were higher in the case group.

Conclusion: Patients with laser-resistant idiopathic hirsutism substantially had higher levels of androgens, although in normal ranges, which could result in being benefited from anti-androgens in combination with hair-removal lasers, also amount of androgens levels especially DHT at the beginning of laser therapy could be to somewhat predictor of patient's prognosis regarding to final therapeutic response.

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INTRODUCTION

Hirsutism is a common disorder of women in reproductive ages and known as androgen-induced terminal hair growth in a male-pattern distribution, which occurs about 5-10%. Hirsutism could have great impact on women's quality of life and brings decreased self-steam. (Mofid *et al*., 2008; Azziz *et al*., 2000; Himelein and Thatcher, 2006) Hirsutism results from hyper-androgenism or genetically higher sensitization to androgens that finally converts vellus hairs to terminals which are darker and have higher caliber. (Messenger, 1993; Rosenfield, 2005) About half of the Testosterone (T) formation in women relates to adrenal and ovary and the other half to peripheral production of weak androgens. (Deplewski and Rosenfield, 2000; The evaluation and treatment of androgen excess, 2006) Idiopathic hirsutism includes about 20% of total hirsutism cases, recognize by higher sensitivity to normal androgen levels also increased peripheral activity of 5-alfa reductase and subsequent higher levels of more potent androgen generation from testosterone in skin and hairs which means Dihydrotestosterone (DHT). (Azziz *et al*., 2000; Harrison *et al*., 2010; lindsey ann brodll ms and marygail mercurio mD hirsutistim diagnose and mangment gender medicine, 2010)

Significant differences of hair**s** in different body parts have been demonstrated regarding androgens sensitivity and ability to metabolize 5-alpha reductase. This enzyme has 2 types each encoded by a separate gene and this makes different distribution pattern and biochemical properties. Type 1 exists

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in proximal end of sebaceous glands and type 2 in distal part. Type 2 is also in testis, prostate and hair follicles of scalp. Type 2 presence since birth in the skin, whereas type 1 appears during puberty. (Azziz *et al*., 2000; Deplewski and Rosenfield, 2000; The evaluation and treatment of androgen excess, 2006; lindsey ann brodll ms and marygail mercurio mD hirsutistim diagnose and mangment gender medicine, 2010)

In moderate or severe hirsutism and those with rapidly progressive hirsutism or in the presence of other clinical symptoms highly suggestive of malignancy or PCOS which are associated with hyper-androgenism**,** hormonal evaluation like measuring morning testosterone levels should be considered. Pathogenesis of mild and idiopathic hirsutism consists of hyper-androgenism in the setting of normal lab data tests (undiagnosed abnormality); enhance activity of 5-alpha reductase or androgen receptor dysfunction**.** Measuring androgens level**s** in isolated mild hirsutism is not useful and does not change the therapeutic management. (Azziz *et al*., 2000; Harrison *et al*., 2010)

Over the past two decades, laser therapy has had a considerable improvement in treatment of hirsutism. The main goal of hair-removal laser therapy is to perform selective thermal damage of hairs without any injure to surrounding tissues, for this purpose, the target of laser will be the melanin of hairs follicles, which absorbs light at a wavelength of 600 to 1100 nanometer. (Sanchez *et al*., 2002; Haedersdal *et al*., 2006; Martin *et al*., 2008) It is recommended that any therapy that has been used for hirsutism continue for at least 6 months (average life cycle of the hair follicle) to be able to determining the therapeutic effects and if encountered inadequate response to treatment, combination therapy may used. (Martin *et al*., 2008) Hair-removal lasers like Alexandrite and Diode, lead to hair reduction of 50% during the 6-months treatment, however, hair re-growth remaining to happen in women with hyper-androgenism and characterized by conversion of vellus hairs into terminals. (Rosenfield, 2005)

In this case-control study we decided to evaluate hormonal profile of laser-refractory cases of idiopathic hirsutism, especially DHT which dose not check as a routine test, since probable undiagnosed or mild hyper-androgenism also increased activity of the 5-alpha reductase enzyme and resultant overproduction of DHT, all known as hirsutism stabilizer**,** has been proposed previously but needed to be perform more well-designed studies for better judgment and management. (Jenkins and Ash, 1973) Despite the testosterone, there are few articles focusing on DHT levels and response to the laser. If any increased DHT androgen levels have been found in women with laser-resistant hirsutism**,** drugs with inhibitory affect on peripheral conversion of T to DHT (like Finasteride) may be a beneficial therapeutic method and also DHT levels may be used for estimation the response prognosis of laser therapy.

METHODS AND MATERIALS

This case-control study on 130 patients, investigated serum Prolactin, Testosterone (T) and Dihydrotestosterone (DHT) levels in a group of women with hair-removal laser resistant idiopathic facial hirsutism after at least 6 session of therapy, that considered as the case group and the similar women but acceptable response to hair-removal laser as the controls, in 2013-2014. Patients selected from 18-40 years old women referred to Laser Clinic of Razi Hospital affiliated to Tehran University of Medical Sciences (TUMS), with hirsutism score of at least 6 based on Ferriman-Gallwey system in upper-lip and chin and not any clinically and laboratory evidence of pathologic hyper-androgenism like elevated testosterone more than 1 ng ml and etc. Existence of thyroid disease, cushing's syndrome, cancerous or pre-cancerous lesions, or usage of certain hormones, anti-androgens or drugs with affect on hormone production and metabolism, also being in the last 6 weeks of pregnancy and lactation, excluded the patients. Eligible patients after filling the informed consent form enrolled the study and their demographic data like age, height, weight and the degree of hirsutism based on Ferriman-Gallwey system, were recorded. If five or lesser sessions of laser therapy resulted in more than 2 degrees reduction of hirsutism, patients considered as responsive control group and if at least 6 sessions of laser had not acceptable outcome which means that less than or equal to 2 degree decrease of hirsutism score, patients considered as case group. Thereafter in both groups' blood levels of Prolactin, T and DHT were measured.

According to the study of doctor Steiner *et al*. (2008), the normal levels of testosterone is in the range of 0.05- 0.8 ng/mL and the normal levels of dihydrotestosterone and prolactin considered as 24-368 pico gram/per ml and 30-302 ng/mL, respectively. Mean normal levels of DHT in hirsute and normal patients based on ng/mL is about 0.55±0.21 and 0.29±0.19, respectively.

Sample size calculated regarding the values extracted from Steiner *et al*. (2008) study. Considering standard deviation equal to the sum of the standard deviations of DTH levels in hirsute and normal patients (0.40 ng) also a = 5%, b = 80%, Z1-a / 2 = 1.96, Z1-b = 1.28, $\Omega = 0.40$, E = 0.55, we estimated at least 50 patients in each study group, which finally 65 patients enrolled in case and 65 in control group.

Based on Haak *et al*. (2010) study, patients who had normal testosterone levels during 6-months of treatment with the IPL laser (Intense pulsed Light) and LPDL laser (Long pulsed diode laser) had median percent of hair reduction in months 1, 3 and 6, about 77%, 53% and 40% with ILP and about 68%, 60% and 34% with LDPL respectively, that shows hirsute women with normal or near-normal testosterone levels are alike and well respond to treatment with IPL or LPDL laser, so in our study the type of laser was not important.

Hair removal lasers of Razi hospital were Alex, ND Yag1064, Diod, IPL and Starlux were used in different therapeutic sessions, based on different skin types and hair diameters. The data of patients analyzed with SPSS ver. 19. The results reported as mean blood levels of T, DHT and prolactin and compared between the two groups. The significance level was 0.05. Response to the hair-removal laser as responder or failure assessed and recorded by one single dermatologist.

Ethics

Patients informed about the aim of study and then filled the consent form also data of patients recorded and analyzed regarding the confidentially rules.

RESULTS

In this study, 130 female patients with idiopathic hirsutism (65 patients in case group and 65 in controls) who were treated with hair removal laser, evaluated. We found that the mean age, height, weight, hirsutism score, prolactin level also testosterone and dihydrotestosterone levels in case (6 or more sessions of laser) and control (5 or less sessions of laser) groups were statistically significant diffrent, which has been demonstrated in Table 1. ($p<0.05$) Figure 1, 2 and 3 respectively demonstrates prolactine, testosterone and dihydrotestosterone levels in the case and control group.

Table 1. Comparison between case and control group regarding demographic data and hormonal profile

	5 or less sessions of hair-removal laser (Control group)	6 or more sessions of hair-removal laser (Case group)	P value
Age	29.4±5.3	27.4±5.1	0.02
Height	163.9±5.8	161.8±4.5	0.02
Weight	64.5±8.4	60.4±7.1	0.003
Hirsutism score*	6.1±0.39	6.4±0.95	0.03
Prolactin	13.6±4.9	19.6 ±15.6	0.004
Testosterone	0.22±0.18	0.57±0.27	<0.001
Dihydrotestosterone	209.4±115.2	620.3±397.1	<0.001

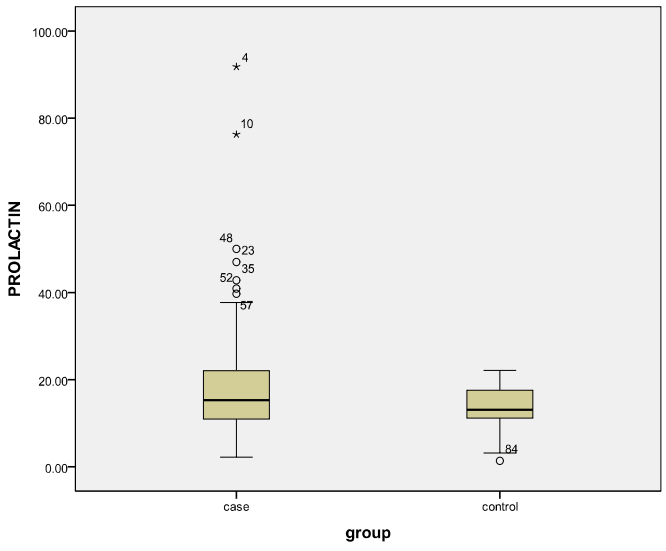

Figure 1. Serum prolactin levels in the case group (6 or more sessions of hair-removal laser) and the controls (5 or less sessions of hair-removal laser)

Alongside, lack of any clinical presentaton of hyper-androgenism other than hirsutism and normal ranges of androgen levels, patients with more severe hirsutism were more likely being resistant to laser therapy and to have higher levels of circulating androgens. ($p<0.05$)

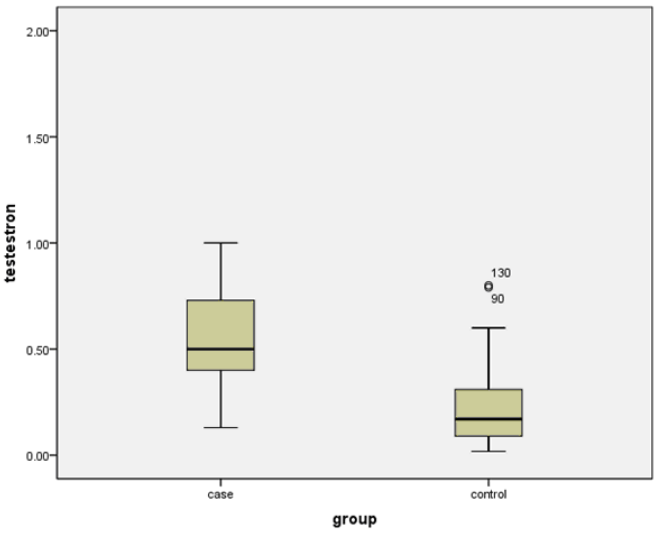

Figure 2. Serum testosterone levels in the case group (6 or more sessions of hair-removal laser) and the controls (5 or less sessions of hair-removal laser)

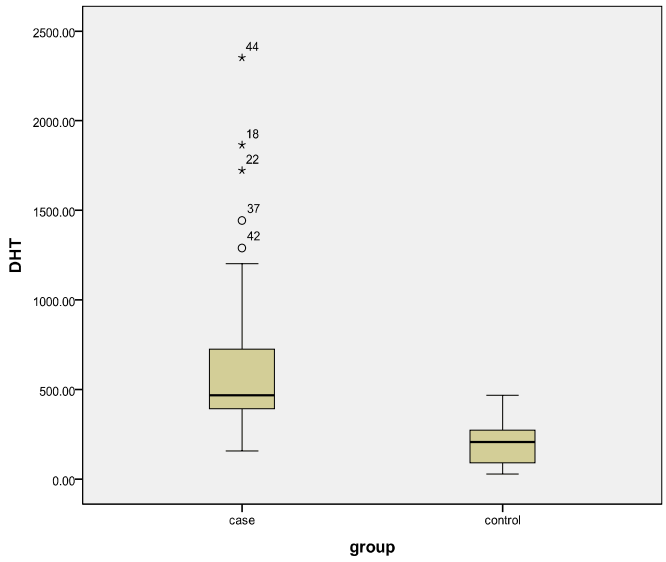

Figure 3. Serum dihydrotestosterone (DHT) levels in the case group (6 or more sessions of hair-removal laser) and the controls (5 or less sessions of hair-removal laser)

The correlation coefficient of hirsutism score with prolactin level was -0.06 (P=0.4), with testosterone level was 0.16 (p = 0.05) and with dihydroergotamine was 0.28 (p=0.001). The results showed that the mean testosterone and dihydrotestosterone and prolactin levels in patients with further need to laser sessions were significantly higher than those responsive to fewer sessions of laser.

DISCUSSION

About 5-10% of women of childbearing age suffer from hirsutism which brings about a lot of unpleasant emotional and psychiatric effects. Therefore it seems using of hair reduction methods (preferably permanent ways), like laser therapy, are really necessary. Hair-removal lasers destruct the hairs by photothermolysis. (Mofid *et al*., 2008; Azziz *et al*., 2000;

Himelein and Thatcher, 2006; Martin *et al*., 2008; Rosenfield *et al*., 2005) Women with hirsutism may have androgen imbalance so their response to laser would be difficult, unpredictable and usually about 49-27%. (Haak *et al*., 2010) In a study of Xu *et al*. (2010), protective effect of DHT on apoptosis of hair cells has been demonstrated, it causes lower levels of Caspase 3 and 9 which are resulting in chemical stress-induced death prevention. In this study we tried to evaluate the serum levels of routine (testosterone and prolactin) and non-routine (DHT) hormonal profile of women with idiopathic hirsutism in a case –control study, based on their response to laser therapy.

In our study, a blood level of DHT was significantly higher in patients with laser-resistant idiopathic hirsutism, which represents an increase of 5 alpha reductase-induced peripheral conversion of testosterone to DHT also we found higher levels of testosterone and prolactin. It could be concluded that blood levels of this hormones in patients with idiopathic hirsutism with planning for use of hair removal- lasers, could be a predictive method of relative therapeutic response; means that, even in normal androgen levels, higher levels may be associated with poorer response. Therefore in refractory idiopathic hirsutism cases, androgen-lowering therapies could be a helpful option.

Horton *et al*. (1982) study, evaluated total and free testosterone levels, DHT and 3 alpha-diol glucuronide (indicative of peripheral activity of androgens), in patients with idiopathic hirsutism, and found all of them significantly elevated, except from total testosterone. In the study of Straner *et al*. (1982), T and DHT levels in genitalial skin of women with hirsutism and normal controls, were compared, that found DHT levels and T in patients about 1.9 and 1.84 times more than the normal respectively, since genitalial skin of hirsute women significantly fewer metabolize and converts DHT to 3 alpha-diol.

In study of Dewis *et al*. (1984), comparing the levels of DHT and T in normal women, hirsute women with normal menses, hirsute women with oligomenorrhea and non-hirsute women with oligomenorrhea, were measured. Study showed that T levels in women with hirsutism and oligomenorrhea were higher than the normal but DHT levels were not significantly different among 4 groups. In a case-control study of Chhabra *et al*. (2012), age-matched women with hirsutism or not, mean level of free testosterone, total testosterone, DHEAS and 17OHP, LH, FSH, prolactin and SHBG were found significantly more in patients than the controls. As well as a significant association between free testosterone levels and hirsutism was demonstrated.

In studies of Adams *et al*. (1986) and Jahanfar *et al*. (1993), stastistically significant diffrence between free and total testosterone levels was shown in hirsute and the normal group. In the study of Runtiainen *et al*. (1985), highly significant positive correlation between hirsutism severity and the level of free testosterone was found, in the contrary of the results extracted from Souter *et al*. (2004) study, that did not find any correlation. Our study results were compatible with the results of all mentioned studies, just inconcordant with the results about DTH of Dewis *et al*. (1984) study also the results about free testosterone of Souter *et al*. (2004) study.

Karn *et al*. (2014), in a randomized clinical trial compared the hirsute patients with probable diagnosis of PCO (higher androgen levels: total T and DHEAs) and the idiopathic hirsute patients, all patients received Long pulse Nd- YAG laser with the goal of 50% reduction of hairs. Mean number of sessions required for laser therapy was 8.1 in the first and 5.7 in the second group ($p<0.05$). Patients with high androgen levels and elevated LH: FSH ratio required more treatment sessions for hair removal laser.

Our study results to somehow confirmed the results of Karn *et al*. (2014) study, since despite different design an goal, we also found higher levels of androgens even in normal ranges, could causes need to more laser sessions to respond.

Limitations

One of the limitations was the high cost of the hormonal kits and the other important one was the not using a fixed type of hair removal laser. Patient may be treated with different types of laser and also a same patient with different types in consecutive sessions. But since the pattern of laser usage probably was equally distributed in case and control group, it may not be considered as a major confounder. It should be notified that because of study design and purpose, sampling performed among clinically idiopathic hirsute patients who were under therapy with hair-removal laser, all of these patients did not have a basic hormonal profile so if in the study they founded to have an abnormal testosterone level were excluded and be substituted by another eligible patient to reach the goal sample size, which imposed a further financial burden to the study.

Recommendations

For better and more exact conclusion and management we needed to design mo well-deign studies like controlled clinical trials.

Conclusion

This study showed that patients with laser-resistant idiopathic hirsutism and normal ranges of androgens substantially had higher levels of androgens rather than the responsive control group that logically benefited them from anti-androgens in combination with hair-removal lasers, particularly inhibitors of testosterone to DHT conversion such as Finasteride. Also amount of blood androgens levels especially DHT at the beginning of treatment could be to somewhat predictor of patient's prognosis regarding therapeutic response, in patients with idiopathic hirsutism who are candidate for laser therapy.

What does this study add?

* Patients with laser-resistant idiopathic hirsutism substantially may have higher levels of androgens, although in normal laboratory levels.

* This patients may benefit from anti-androgens in combination with hair-removal lasers.
* Amount of androgens levels especially dihydrotestosterone (DHT) at the beginning of laser therapy could be a predictor of patient's prognosis regarding to final response.

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