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Idiopathic hirsutism: Is it really idiopathic or is it misnomer?

Unluhizarci K *et al.* Idiopathic hirsutism

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Abstract

Hirsutism, which is characterized by excessive growth of terminal hair in a male pattern, may result from various causes including polycystic ovary syndrome (PCOS), non-classic congenital adrenal hyperplasia, adrenal or ovarian tumors or it may be idiopathic. Idiopathic hirsutism is currently defined as hirsutism associated with normal ovulatory function, normal serum androgen levels and normal ovarian morphology, however, the pathogenesis of idiopathic hirsutism is not clear. The androgens are the main hormones to stimulate growth of body hair, therefore, there should be any form of increased androgen effect irrespective of normal serum androgen levels in any patient with hirsutism. In accordance to this scientific truth, we have previously shown that, although within normal limits, patients with idiopathic hirsutism have relatively higher serum androgen levels (relative hyperandrogenemia) in comparison to healthy subjects which let us to think that is idiopathic hirsutism really idiopathic? In addition to relative hyperandrogenemia, we have previously shown that, in comparison to healthy subjects, women with idiopathic hirsutism demonstrated higher expression of steroid sulphatase and 17-beta hydroxysteroid dehydrogenase mRNA both in the subumbilical region and arm skin, which contributes to local androgen metabolism. Those results support the idea that, in some patients, although

the adrenals or ovaries do not secrete increased amount of androgens leading to hyperandrogenemia, pilosebaceous unit locally produce increased amount of androgens leading to hirsutism without ovulatory dysfunction. Upon the demonstration of relative hyperandrogenemia and possible increase in local androgen synthesis in patients with idiopathic hirsutism, we think that idiopathic hirsutism is not idiopathic and it may be named as “normoandrogenic hirsutism”. Furthermore, it may not be a different entity but may be an early stage of hyperandrogenic disorders such as PCOS. Clinically, this can be find out by following-up patients with idiopathic hirsutism prospectively.

Key Words: Idiopathic hirsutism; Normoandrogenic hirsutism; Hyperandrogenemia; Androgen excess disorders.

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Core Tip: Idiopathic hirsutism (IH) is defined as hirsutism associated with normal ovulatory function, normal ovarian morphology and normal serum androgen levels, however, its pathogenesis is not clear. We have previously shown that, patients with IH have relatively higher serum androgen levels and demonstrated higher expression of steroid sulphatase and 17-beta hydroxysteroid dehydrogenase mRNA both in the subumbilical region and arm skin, which contributes to local androgen metabolism. Upon the demonstration of relative hyperandrogenemia and possible increase in local androgen synthesis in patients with IH, we think that idiopathic hirsutism is not idiopathic and it may be named as “normoandrogenic hirsutism”.

INTRODUCTION

Hirsutism is a common clinical condition which affects approximately 5%-15% of premenopausal women. It is typically defined as excessive growth of terminal hair in a

male pattern. Hirsutism has a significant negative impact on quality of life and makes a severe psychological distress in women. The occurrence of hirsutism is affected from local androgen concentrations, the interaction between various androgens in serum, and ultimately, sensitivity of the hair follicle to androgens. Hirsutism may be seen as a result of polycystic ovary syndrome (PCOS), non-classic congenital adrenal hyperplasia, ovarian or adrenal tumors or it may be idiopathic^[1-4]. The most common causes of hirsutism among premenopausal women are PCOS and idiopathic hirsutism. While measurable hyperandrogenemia has been detected in 80%-90% of women with hirsutism, the severity of hirsutism and the level of androgen excess are not well-correlated. A well-known example of this condition is idiopathic hirsutism which is characterized by normal serum androgen levels^[5-7]. Apart from idiopathic hirsutism, all the other causes of hirsutism are associated with hyperandrogenemia, thus, the diagnosis of idiopathic hirsutism requires exclusion of other disorders. Although some mechanisms have been proposed, the pathogenesis of idiopathic hirsutism is not well known and in this review we will discuss the potential mechanisms underlying idiopathic hirsutism.

WHAT IS KNOWN ABOUT IDIOPATHIC HIRSUTISM?

Over the last years the diagnostic criteria of idiopathic hirsutism have changed. In early reports, idiopathic hirsutism has been defined as “hirsutism of unknown cause” irrespective of serum androgen levels^[8-10]. However, investigations related to various androgen excess disorders changed the definition of idiopathic hirsutism. Currently, idiopathic hirsutism is diagnosed in hirsute women who have regular ovulatory cycles, normal ovarian morphology and normal serum androgen levels. Since the pathogenesis of idiopathic hirsutism is not well known, in contrast to other androgen excess disorders, no clear molecular or biochemical markers exist in patients with idiopathic hirsutism^[11]. The prevalence of idiopathic hirsutism has been reported between 6-16% in various populations^[3,12,13]. A brief summary regarding the pathogenesis of idiopathic hirsutism is given in Table 1.

Functional hyperandrogenism

Although huge number of studies have been performed for the pathogenesis of PCOS, only limited number of investigations exist regarding the pathogenesis of idiopathic hirsutism. Escobar-Morreale *et al*^[14] investigated the ovarian and adrenal steroidogenic abnormalities in 24 patients with idiopathic hirsutism by using ACTH stimulation test and GnRH analog test. They found that women with idiopathic hirsutism show an increased ovarian 17-hydroxyprogesterone secretion and a minimally increased adrenal 17-20 Lyase activity, suggesting that these patients have mild forms of ovarian and adrenal functional hyperandrogenism^[14]. Rossi *et al*^[15] evaluated the ovarian and adrenal gland functions in 48 women with idiopathic hirsutism by using ACTH stimulation and GnRH analog test. The authors found mild functional ovarian and adrenal hyperandrogenism and suggested as an underlying mechanism of idiopathic hirsutism.

5 α -reductase activity

The androgens found in women include testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEAS). Testosterone is converted to dihydrotestosterone (DHT) via the enzyme 5 α -reductase and DHT has much more affinity to androgen receptor (AR) intracellularly. The most active androgen, DHT, has low serum levels since it is synthesized in androgen target tissues.

Although most literature was old, several studies showed an increased level of 5 α -androstane-3 α , 17 β -diol (3 α -diol) and 3 α -diol glucuronide (3 α -diol-G) which were metabolites of DHT in patients with idiopathic hirsutism^[16-18]. Serum 3 α -diol-G level has been shown a good correlation with the severity of hirsutism in idiopathic hirsute cases, however, those metabolites do not seem to exert androgenic effects, rather they reflect testosterone and DHT production and are considered as a marker of 5 α -reductase activity^[19].

5 α -reductase activity was also evaluated in skin samples of patients with idiopathic hirsutism and PCOS and the authors demonstrated an increased conversion of testosterone to DHT and DHT to 3 α -diol. Those results suggest an increased 5 α -reductase activity in hyper and normoandrogenic phenotypes of hirsutism^[20]. Currently, increased skin 5 α -reductase activity is considered as the main pathophysiologic abnormality of idiopathic hirsutism, leading to increased tissue synthesis of DHT and possibly an alteration in androgen receptor function^[21-23].

Abnormalities in androgen receptor and its function

Androgens exhibit their effect *via* the AR and dysfunctional AR may contribute to variable phenotypes of androgenicity. The AR gene is located on the X-chromosome and this gene contains a polymorphic trinucleotide repeat (CAG). Variances in the AR sequence are mostly identified by tandem repeat polymorphisms (number of CAG repeats) and methylation pattern of AR gene. It has been shown that the ¹transcriptional activity of the AR is inversely correlated with the number of CAG repeats^[24]. The alleles with shorter CAG repeat length are associated with amplified AR activity. We have recently shown that, as in PCOS patients, AR exon 1 CAG repeat length distribution was different in patients with idiopathic hirsutism than control subjects leading to the development of hirsutism *via* increased androgen effect^[25]. On the other hand, Vottero *et al*^[26] did not find any difference in the number of CAG repeats between patients with idiopathic hirsutism and control subjects. Thus, the role of AR abnormalities in the pathogenesis of idiopathic hirsutism require further studies.

Aromatase enzyme (dys)function

²Previously, we have shown that, although the patients with idiopathic hirsutism have normal ³serum androgen levels, these patients have relatively higher serum androgen levels and lower estradiol levels in comparison to healthy subjects^[27]. In other words, those patients were actually hyperandrogenic, however, by using some cut-off values ³derived from the reference values of commercial kits, we diagnose these patients as

idiopathic hirsutism. Moreover, these patients show decreased estradiol/testosterone ratio, which is a product of aromatase activity, leading to relative hyperandrogenemia^[27]. Thus, instead of measuring serum androgen levels alone, when estradiol/testosterone ratio was compared with healthy subjects, patients with idiopathic hirsutism have reduced levels than healthy subjects indicating that these patients are also hyperandrogenic. Mahmoudieh *et al*^[28] investigated the cardio-metabolic risks in 334 women with idiopathic hirsutism and compared the results with 1226 control subjects over a 16-year study period. Similar to our results, they also showed that idiopathic hirsute women had relatively higher serum androgen levels compared to healthy subjects. So, the main question is why we still call those patients as idiopathic?

The current diagnosis of idiopathic hirsutism relies on normal serum androgen levels which are almost determined by immunoassays. However, the standards and limitations of those assays are matter of debate during the last years^[29]. The Endocrine Society has suggested using liquid chromatography/tandem mass spectrometry (LC-MS/MS) for measuring steroid hormones, particularly testosterone^[30]. In the only study from existing literature evaluating hyperandrogenemia by LC-MS/MS in patients with idiopathic hirsutism, the authors found that cut-off values for testosterone was lowered^[31]. This implies that patients with idiopathic hirsutism may have underestimated serum androgen levels which were not determined by immunoassays.

Local androgen production

Recently, we thought that increased local androgen production may also be the underlying cause of idiopathic hirsutism since skin tissue have all the enzymes required for androgen biosynthesis and catabolism indicating that it behaves as an independent peripheral endocrine organ^[32,33]. Similarly, as seen in acne and androgenetic alopecia, an association between possible local overproduction of active androgens and skin disorders has been suggested^[34].

Previously, it has been shown that ¹steroidogenic acute regulatory protein, cytochrome P450 cholesterol side-chain cleavage (P450scc) and cytochrome P450 17 α hydroxylase (P450c17) have been ¹expressed in the cutaneous tissue suggesting that cholesterol derived in skin tissue ¹could be further used as a substrate for *de novo* steroid hormone synthesis in human epidermis and the sebaceous gland^[34]. In fat cells and hair follicles aromatase play a “detoxifying” role by metabolizing excess androgens locally and disturbances in this metabolism may contribute to hirsutism^[34]. Moreover, in the skin, testosterone, which ²is the potent tissue androgen, results from the conversion of circulating DHEAS, ²through the serial enzymatic activities of steroid sulfatase, 3 β -hydroxysteroid dehydrogenase and 17 β -HSD^[35]. In vitro experiments showed that different skin cells have different duties concerning the presence and activity of androgen metabolism. While keratinocytes degrade androgens, sebocytes are capable of synthesizing ⁹testosterone from adrenal precursors and to inactivate it, thus contributing to maintain androgen homeostasis^[32,35,36]. The enzyme 17 β -HSD type 2 inactivates both testosterone and estradiol to androstenedione and estrone, respectively^[37]. Overall, the skin and its appendages have been equipped with the necessary enzymes for androgen synthesis and metabolism. Physiologic levels of these enzymes found in normal conditions may be upregulated and contribute to peripheral hyperandrogenism in several pathologic conditions.

In patients with idiopathic hirsutism, we have freshly obtained hair follicles and investigated ¹the mRNA expression of enzymes having a role in locally produced androgens and their precursors^[38]. We have shown that, ²women with idiopathic hirsutism exhibited higher expression of *HSD17B2* and steroid sulphatase (STS) mRNA both in the subumbilical region and arm skin when compared to healthy women, suggesting the contribution of these enzymes to local androgen metabolism. In women with idiopathic hirsutism, ¹increased mRNA expression may be considered as a clue for the tendency to local hyperandrogenemia although we did not measure the STS enzyme activity. Moreover, ¹increased mRNA expression of STS was also found in the arm skin without hair. This suggests an overall increased expression of this enzyme in idiopathic

hirsute patients. In the skin biopsies, we have also shown that mRNA expression of *IL6* is significantly lower in patients with idiopathic hirsutism than healthy subjects. This was an important finding since *IL6* affects aromatase expression. Estrogen biosynthesis in human body is highly complex organization and various hormones may activate or inactivate the regulation of aromatase expression in human cells^[39]. **We can speculate that local synthesis of estrogen may be negatively affected by (indirect) effect of aromatase activity**. Unfortunately, there is not adequate data regarding the molecular mechanisms in the pathogenesis of idiopathic hirsutism.

All those results support the idea that, in some patients, although the adrenals or ovaries do not secrete increased amount of androgens leading to hyperandrogenemia, pilosebaceous unit locally produce increased amount of androgens leading to hirsutism without ovulatory dysfunction. Thus, patients with idiopathic hirsutism may have an increased androgen synthesis within the skin tissue so, calling those patients as “idiopathic” is misnomer. In that scenario, patients with idiopathic hirsutism may be a very early stages of PCOS and this can be answered only long term follow-up of those patients whether they will represent hyperandrogenemia in the future or not. If so, another question is what may be the factor determining transition of idiopathic hirsutism to PCOS phenotype?

Insulin resistance and idiopathic hirsutism

Insulin resistance and associated hyperinsulinemia seem one of the most important factor in androgen excess disorders^[40]. Unlühizarci *et al*^[27] and some others^[41,42] showed that patients with idiopathic hirsutism may also have insulin resistance and it is more prominent in overweight or obese patients. Amiri *et al*^[43] made a meta-analysis to investigate the relationship between insulin resistance and idiopathic hirsutism. In addition to demonstrating altered metabolic parameters and insulin resistance in patients with idiopathic hirsutism, the authors suggest **that increased peripheral androgen activity in women with idiopathic hirsutism is associated with insulin metabolism**. We have previously shown that 18.7% of the patients with idiopathic

hirsutism had impaired glucose tolerance (IGT) and more importantly, we found that after excluding the patients with IGT, the patients were still demonstrating insulin resistance^[27]. It is well known that in the presence of insulin resistance and hyperinsulinemia patients with hirsutism exhibit more advanced metabolic and reproductive symptoms. Moreover, weight loss and decreased insulin resistance resumes menses and improves hyperandrogenemia in patients with PCOS. Thus, if our hypothesis is correct, insulin resistance may be the triggering factor in the transition of patients with idiopathic hirsutism to PCOS phenotype.

Androgens produced by alternative pathways

On the other hand, 11-oxygenated C19 steroids are important androgens and have been shown to have a role in patients with PCOS or congenital adrenal hyperplasia^[44]. These steroids have been shown to stimulate androgen receptors similar or greater than testosterone or DHT. It may be possible that these 11-oxygenated C19 steroids may have a role in patients with idiopathic hirsutism, however, their serum levels are not routinely measured by commercial assays^[31,44]. We think that this is an interesting candidate area of scientific research for exploring the pathogenesis of idiopathic hirsutism.

IDIOPATHIC HIRSUTISM: IS IT A MISNOMER?

Currently, idiopathic hirsutism is defined as hirsutism associated with normal serum androgen levels, normal ovarian morphology and ovulatory functions^[5]. It is well known that ⁴dermal papilla plays a fundamental role in the regulation of hair growth, and cells of dermal papilla seem to have the primary role of androgen regulation of hair growth^[6,7]. There should be any form of increased androgen level or effect even in patients with idiopathic hirsutism since androgens are the main hormones to stimulate growth of body hair. Even though those patients have normal serum androgen levels, they suffer from a hyperandrogenic sign, namely hirsutism and we think that idiopathic hirsutism is not idiopathic and it may be named as “normoandrogenic hirsutism”,

furthermore, it may not be a different entity but may be an early stage of hyperandrogenic disorders such as PCOS.

In various endocrine disorders, even serum levels of hormones are within normal limits, locally produced hormones may be higher and clinically important. By analogy, patients with subclinical hyperthyroidism have normal serum thyroid hormone levels (in addition to suppressed serum TSH level) but an increased tissue response exist leading to thyrotoxic manifestations such as tachycardia. We speculate that the same situation exist in patients with idiopathic hirsutism and by the time, those patients may show increased serum androgen levels similar to overt hyperthyroid patients. We suggest that normal serum androgen levels do not always mean to expose normal androgen effect on skin.

CONCLUSION

By definition, although idiopathic hirsutism is characterized by normal serum androgen levels, those patients exhibit hirsutism and in the presence of scientific data/evidences on relative hyperandrogenemia, increased local androgen production, insulin resistance (although not universal), AR polymorphism and increased DHT production we think that idiopathic hirsutism is misnomer and it is not actually idiopathic. As discussed above, it has more complex pathogenesis than any other androgen excess disorder such as congenital adrenal hyperplasia which is characterized by steroidogenic enzyme deficiencies. Thus, instead of idiopathic, we suggest “normoandrogenic hirsutism” until a more appropriate name is found. Furthermore, it may not be a different entity but may be an early stage of hyperandrogenic disorders such as PCOS. Clinically, this can be find out by following-up patients with idiopathic hirsutism prospectively. Additionally, by establishing the pathogenesis/underlying mechanisms of idiopathic hirsutism, new therapeutic strategies may be offered.

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