Original Investigation
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Facial hypertrichosis after isotretinoin therapy: Is it a side effect or coincidence?

İzotretinoin tedavisi sonrası yüzde hipertrikoz: Yan etki mi tesadüf mü?

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Abstract

Background and Design: Excessive hair growth after isotretinoin treatment for acne vulgaris is not common, but may be one of the most undesirable side effects of the drug. The aim of this study is to investigate the relationship between systemic isotretinoin use and facial hypertrichosis.

Materials and Methods: Female acne patients in premenopausal age were included in this prospective study. Laboratory tests [beta-human chorionic gonadotropin, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, aspartate aminotransferase, alanine aminotransferase] were evaluated initially and monthly during the study period. Hormone levels [luteinizing hormone, follicle stimulating hormone, total testosterone, free testosterone, dehydroepiandrosterone-sulfate (DHEAS), prolactin, 17-hydroxyprogesterone, glucose, and insulin] and abdominopelvic/transvaginal ultrasonography were also evaluated when there was a complaint or clinical findings of excessive hair growth. Body mass index (BMI) was calculated at the beginning of the study. Severity of the acne was assessed with Global Evaluation Acne Scale (GEAS). Hirsutism scores were calculated with Modified Ferriman-Gallwey score (m-FGS). Baseline and monthly taken digital dermoscopic photographs from the chin and cheeks were transferred to the ImageJ program to count the hair. Hair increases of >5% at the end of the treatment according to the basal hair count was accepted as hypertrichosis.

Results: Thirty patients aged between 18-34 (median: 21.5) participated in the study. Mean duration of the therapy was 6.2±0.6 months. Facial hair growth was detected in three (10%) patients. One patient had an elevated DHEAS level with normal abdominal ultrasonography findings. Without the cessation of isotretinoin therapy, DHEAS level decreased to normal limits after two months. There was no statistically significant difference found between the mean GEAS (p=0.52), basal m-FGS (p=0.42), and BMI (p=0.71) of three patients with facial hypertrichosis, and in the remaining 27 patients. Facial hypertrichosis disappeared spontaneously 2 months (1-3 month) after the treatment courses were completed.

Conclusion: The patho-mechanism of isotretinoin induced facial hair growth is not fully clarified. Since the facial hypertrichosis disappeared spontaneously when the treatment was ended, we think that this may be due to a temporary drug induced hormonal imbalance in susceptible individuals.

Keywords: Acne vulgaris, hirsutism, hypertrichosis, isotretinoin

Öz

Amaç: İzotretinoin tedavisi sonrası görülen kıl artışı sık olmamasına rağmen ilacın en rahatsız edici yan etkilerinden biri olabilir. Bu çalışmanın amacı, sistemik izotretinoin kullanımı ile yüzde gelişen hipertrikoz arasındaki ilişkinin araştırılmasıdır.

Gereç ve Yöntem: Bu prospektif çalışmaya premenapozal dönemdeki kadın akne vulgaris hastaları dahil edildi. Laboratuvar testleri (beta-insan koryonik gonadotropin, total kolesterol, trigliserid, düşük yoğunluklu lipoprotein, yüksek yoğunluklu lipoprotein, aspartat aminotransferaz, alanin aminotransferaz) tedavi başında ve çalışma boyunca aylık olarak değerlendirildi. Çalışmanın başında vücut kitle indeksi (VKİ) hesaplandı. Hastaların kıl artışı şikayeti olduğunda veya artış hekim tarafından gözlendiğinde ek olarak hormon [lüteinleştirici hormon, folikül uyarıcı hormon, total testosteron, serbest-testosteron, dehidroepiandrosteron-sülfat (DHEAS), prolaktin, 17-hidroksiprogesteron, glikoz, insülin] seviyeleri ve abdominopelvik/transvajinal ultrasonografi değerlendirildi. Akne şiddeti Global Akne Değerlendirme Ölçeği (GADÖ) ile, hirsutizm skoru

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modifiye Ferriman-Gallwey (m-FGS) skoru ile hesaplandı. Çene ve yanakların bazal ve aylık çekilen dijital dermoskopik fotoğrafları kıl sayımı için ImageJ programına aktarıldı. Bazal kıl sayısına göre tedavi sonunda %5'ten fazla kıl artışı hipertrikoz olarak kabul edildi.
Bulgular: Çalışmaya 18-34 (ortanca: 21,5) yaş arasındaki 30 hasta katıldı. Ortalama tedavi süresi 6,2±0,6 aydı. Yüzde kıl artışı 3 (%10) hastada tespit edildi. Bir hastada DHEAS seviyesi yüksek olup bu hastanın abdominal ultrasonografisi normaldi. İzotretinoin tedavisi kesilmeden DHEAS seviyesi 2 ay sonra normale döndü. Yüzde kıllanma artışı olan 3 hasta ile diğer 27 hastanın ortalama GADÖ (p=0,52), bazal m-FGS (p=0,42) ve VKİ (p=0,71) değerleri karşılaştırıldığında istatiksel olarak anlamlı fark bulunmadı. Tedavi kürleri tamamlandıktan ortalama 2 (1-3) ay sonra hipertrikozun spontan olarak kaybolduğu gözlendi.
Sonuç: İzotretinoinle indüklenen yüzde kıl artışının patomekanizması tam olarak aydınlatılamamıştır. Tedavi tamamlandıktan sonra kıllanmanın spontan olarak düzelmesi, bu durumun duyarlı kişilerde ilaca bağlı geçici bir hormonal dengesizlik sonucu oluşabileceğini düşündürmektedir.
Anahtar Kelimeler: Akne vulgaris, hirsutiz, hipertrikoz, izotretinoin

Introduction

Isotretinoin has been widely used from the early 1980s, when it was approved as a standard treatment for acne vulgaris. The mechanism of action of isotretinoin is reducing the size of the sebaceous gland, reducing sebum secretion and follicular keratinization, as well as preventing the growth of *Propionibacterium acnes* and the inflammation[1].

Although the use of isotretinoin is a milestone for acne treatment and successful results have been obtained, patients should be evaluated for their suitability for the treatment, and all possible side effects should be monitored throughout the treatment. It is known that systemic isotretinoin-related adverse events may be observed in various systems, and they result in mucocutaneous, ocular, systemic, and laboratory side effects. The most reported side effects involving the skin are: xerosis, cheilitis, flare of acne, dermatitis, photosensitivity, skin fragility, erythema, flushing, and pruritus[2]. Even though the isotretinoin induced excessive hair growth, hypertrichosis, and hirsutism are rarely reported, they may be the most worrisome side effects experienced by the patients.

Hirsutism is defined as a male-pattern hair growth in the androgen sensitive areas because of the androgen overproduction or increased end-organ sensitivity in women. Excessive hair growth in hypertrichosis is an androgen independent condition that can be localized or generalized and may appear on any part of the body[3]. The exact mechanism of systemic isotretinoin induced hair growth is unclear. Only a limited amount of information about this topic is available, and only few cases have been reported[4-7]. This study aims to investigate the relationship between the systemic isotretinoin use and localized excessive facial hair growth.

Materials and Methods

This prospective observational clinical study included 30 female acne patients. The study protocol was approved by İstanbul Medipol University Local Ethics Committee (approval number 330, date: 15.09.2017), and written informed consent was obtained from all the participants. Exclusion criteria of the study were; taking any systemic medication, having systemic diseases including metabolic syndrome, thyroid dysfunction, asthma, inflammatory bowel disease, hepatitis, neurologic, psychiatric, rheumatologic or endocrinologic diseases, menstrual cycle abnormality, and malignancy. Patients' severity of acne and body mass index (BMI) were calculated. Laboratory tests including beta-human chorionic gonadotropin (β-HCG), total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, aspartate transaminase and alanine transaminase were evaluated initially and monthly during the study. Hormone levels including luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), dehydroepiandrosterone-sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), prolactin, glucose and insulin, and abdominopelvic/transvaginal ultrasonography were also evaluated if there was a complaint or clinical finding of excessive hair growth. Modified Ferriman-Gallwey score (m-FGS) was used to examine the total body hair density. This scoring method evaluates the nine-androgen sensitive body areas and grades them from 0 (no hair) to 4 (frankly virile) according to density of hair[8]. Eight and above scores were defined as hirsutism, and these patients were not involved in the study. The severity of acne was assessed with Global Evaluation Acne Scale (GEAS) which is interpreted on a six-point scale[9]. BMI was calculated at the beginning of the study. Oral isotretinoin treatment was initiated 0.4-0.8 mg/kg/day and continued until a cumulative dose of 120-150 mg/kg was achieved. All side effects were recorded on patients' follow up charts.

During the treatment, a possible facial hypertrichosis was inspected by the digital dermoscopy (FotoFinder®). Chin and cheeks were the target areas for the dermoscopic photographing. Gonion points of the mandible and inferior edge of the chin were superposed with a lower end of the dermoscopic lens (Figure 1) to picture the same area in every assessment. Baseline and monthly taken dermoscopic photographs were transferred to the ImageJ program which is a Java based software commonly used to analyze and count the cells[10]. Dermoscopic lens allows to examine approximately 1 cm^2 of the skin area. Counting was started from the left upper part of the dermoscopic photo and continued to the right side followed by below, like reading the area line by line. An example of marking and counting the hair shaft with the ImageJ is featured in the Figure 2. Hair increase rate was calculated by comparing the number of hair at the end of the treatment to the basal number of hair. An increase of >5% was accepted as hypertrichosis.

Statistical Analysis

The statistical analyses were performed by using IBM SPSS Statistics Version 26.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). Normality of the distribution was verified with Shapiro-Wilk test. Normally distributed samples were not evaluated with the Mann-Whitney U test, and the t-test was performed for normally distributed samples for comparing the scores. Throughout the analyses, p-values <0.05 were considered as statistically significant.

Results

Thirty female patients aged between 18-34 (median: 21.5) enrolled in this study. Mean duration of the therapy was 6.2±0.6 months. The severity of acne was mild for 4 (13.3%), moderate for 18 (60%), and severe for 8 (26.7%) patients according to GEAS. Mean scores for

modified-FGS and BMI were 4.8±1.5 and 20.7±1.6, respectively. The reported side effects of the therapy were myalgia which was observed in 2 (6.7%) patients, arthralgia in 7 (23.3%), gastrointestinal complaints in 4 (13.3%), xerophthalmia in 4 (13.3%), menstrual irregularity in 5 (16.7%), and mood disturbances in 6 (20%) of the patients. A clinically noticeable excessive facial hair growth was detected in 3 (10%) patients. Facial hair were counted by both the researchers. The mean numbers of the counted hair before the treatment and at the end of the treatment are shown in the Table 1. Hypertrichosis disappeared spontaneously within an average of 2 (minimum: 1, maximum: 3) months after the treatment cycles were completed. There was no statistically significant difference between the mean GEAS (p=0.52), basal m-FGS (p=0.42), and BMI (p=0.71) of 3 patients with facial hypertrichosis and the remaining 27 patients.

In addition to regular laboratory follow up tests for systemic isotretinoin treatment, hormone levels (LH, FSH, TT, FT, DHEAS, 17-OHP, prolactin), glucose, insulin, and abdominopelvic/transvaginal ultrasonography were also evaluated in these three patients. One patient had an elevated DHEAS level, 4250 ng/mL, with normal abdominal ultrasonography findings. Without cessation of the isotretinoin therapy, DHEAS level decreased to normal limits after 2 months.

Discussion

Nearly half of women experience unwanted facial hair problems throughout their lifetime[11]. Hyperandrogenic abnormalities, including polycystic ovary syndrome, adrenal hyperplasia, and androgen-secreting tumors, as well as the androgenic drug use, are the causes of excessive hair growth in women[12]. Regardless of circulating androgen levels, enzyme overactivity and receptor sensitivity also may cause hypertrichosis[13]. Unlike complex endocrinologic interactions, which are considerably well-known, the patho-mechanism of isotretinoin-related excessive facial hair growth is relatively unknown due to the lack of data.

It is known that retinol and retinoids have essential roles on hair follicle homeostasis and hair cycle starting from the process of embryogenesis[14]. Hair follicle and sebaceous gland are originated from a pilosebaceous unit. Retinoids have inhibitory effects on sebaceous glands, but their effect on the piliary component is unclear. Hair cycle is regulated by the signaling between epithelial and mesenchymal cells in the hair bulb regions, containing stem cells and transiently proliferating cells. Hair follicles could convert retinol into retinoic acid through the action of an activating enzyme, retinal dehydrogenase, at different phases of the hair cycle[15]. The effect of retinoids on hair follicles can be determined according to the specific receptor with which it interacts. Retinoid receptors are known as nuclear retinoid acid receptor (RAR) and nuclear retinoid-X-receptor (RXR)[16]. *In vitro* studies have shown that inserting the nuclear RAR agonist all-trans-retinoic acid into human hair culture inhibited the survival of hair follicles, whereas nuclear RXR agonists stimulated the growth of hair follicles[17]. Topical application of all-trans-retinoic acid has been shown to prolong the anagen phase, shorten the telogen phase of hair follicles in mice, and stimulate hair growth in human androgenetic alopecia[18,19]. In another in vitro study investigating the relationship between isotretinoin and hair growth, it was reported that 13-cis retinoic acid induces the growth of equine hair follicleslesles[20].

The number of clinical studies investigating the systemic isotretinoin induced excessive hair growth in women is less. In the study of Tükenmez Demirci et al.[4], 20% of the female acne patients taking isotretinoin had excessive hair growth, and 45% of these patients had menstrual

Figure 1. (a) Screening facial hair with dermoscopy, (b) Targeting chin, (c) Targeting gonion points of mandible

Table 1. Hair count and increase rate

Patient number	Hair count* Basal-Final			Hair increase rate (%)		
	Right cheek	Left cheek	Chin	Right cheek	Left cheek	Chin
1.	42-59	54-78	24-42	40%	44%	75%
2.	95-158	50-65	73-80	66%	40%	9%
3.	100-105	77-130	58-73	5%	68%	25%

*Mean number of the researchers' counts

Figure 2. An example of counting hair with ImageJ program

irregularities. Ramot et al.[5] reported two cases, papulopustular rosacea and acne vulgaris, who had excessive hair growth on face after isotretinoin treatment. Hypertrichosis was reported in 2 of the 150 patients in a study by Karadag et al.[6], evaluating the side effects of systemic isotretinoin. In the previous study, hypertrichosis disappeared after the treatment was discontinued, as in our patients. In a recent prospective study evaluating the effect of isotretinoin on hormones, 33% of the patients had menstrual irregularity and the hirsutism scores of 17% of the patients increased three months after the initiation of the therapy. Nevertheless, isotretinoin treatment was not found to have a significant effect on the insulin resistance, pituitary and adrenal hormones[7]. On the contrary, there are studies showing the use of isotretinoin which decreases ovarian volumes, and mFG score and reduces testosterone levels in patients with polycystic ovarian syndrome[6,21,22]. Unfortunately, the complex effect of isotretinoin on hair cycle physiology has not been elucidated yet in the mentioned studies.

One of the hypotheses seeking an answer to the problem of excessive hair growth during treatment is that isotretinoin may indirectly cause hypertrichosis by triggering insulin resistance. Because insulin can interact with many hormones and be affected by various metabolic events, the results of the studies show differences[23]. As in many studies in the literature[24-26], insulin resistance was not detected in our patients. Besides making minor emotional changes, isotretinoin is known to trigger or worsen mental illnesses[27]. In this study, three patients with increased hair growth stated that they lived a stressful life and also experienced mood disorders such as feeling unhappy, lonely, and feeling depressed. It can be thought that the excessive growth of facial hair may be related to the increase in cortisol caused by stress. On the other hand, systemic isotretinoin treatment protocols may take a long time to reach the target dose. For excessive facial hair, hormonal imbalance during this long treatment period, regardless of isotretinoin, may be considered, rather than the possible hypertrichotic effect of isotretinoin.

It is not unpredictable that the effect of isotretinoin on scalp hair and facial vellus hair is not identical due to the different life cycle and responses to hormonal stimuli. To the best of our knowledge there are only two prospective studies investigating the relationship between systemic isotretinoin and scalp hair density among humans. In these studies, a fixed localization determined on the scalp was photographed with a computerized digital dermoscopy and evaluated in a special trichoscopic software program (Trichoscan) before and after treatment. Kmiec et al.[28] showed that isotretinoin had a statistically significant decreasing effect on the total hair count, density, and anagen hair on the scalp, whereas İslamoğlu and Altınyazar[29] found no significant changes after the measurements.

Study Limitations

There were some limitations in this study. Firstly, the sample size was small and there was no control group involved. Secondly, instead of evaluating the hormone profile before starting the treatment, we checked the hormone levels only when excess hair was noticed. Basal and monthly measurement of hormone levels and ovarian ultrasound for each participant could be optimal for this study. On the other hand, there is no similar study counting facial hair in the literature. Although ImageJ program is not the optimal way to count hairs, it can be an alternative in the absence of trichoscopic software programs. The advantage of counting facial hair with ImageJ is that shaving is not obligatory before the assessment.

Conclusion

Facial hypertrichosis remains one of the unexplained effects of isotretinoin. Different results of studies investigating the effect of isotretinoin on hair growth physiology reveal that there is a gap in this regard and more research is needed. Evaluation of patients at regular intervals, preferably with devices compatible with trichoscopic count, will certainly help determine the frequency of this undesirable effect. Although facial hair growth was observed in 10% of the patients included in this study, the spontaneous disappearance of hair after treatment ends suggests that this effect may be due to a temporary drug-induced hormonal imbalance in susceptible individuals rather than accidental. Further studies involving large numbers of patients are needed to understand the complex hormonal interactions. To elucidate this ambiguous effect, endocrinological and psychological evaluation of each patient before and during isotretinoin therapy, regardless of any medical history or symptoms, may be recommended.

Ethics

Ethics Committee Approval: The study protocol was approved by İstanbul Medipol University Local Ethics Committee (approval number 330, date: 15.09.2017).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S., A.Ü., Concept: E.S., Design: E.S., Data Collection or Processing: E.S., A.Ü., Analysis or Interpretation: E.S., Literature Search: E.S., Writing: E.S.

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