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Effects of Isotretinoin Treatment on Levels of Hormones Involved in the Etiopathogenesis of Acne

İzotretinoin Tedavisinin Akne Etiyopatogenezinde Yer Alan Hormon Düzeyleri Üzerindeki Etkileri

Süleyman Emre KOÇYİĞİT, Mustafa ŞAHİN*, Yousef HOUSHYAR**, Fatma Sena DOST GÜNAY***, Demet ÇORAPÇIOĞLU*

Tepecik Training and Research Hospital, Department of Geriatric Medicine, İzmir, TURKEY
*Ankara University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, TURKEY
**Ankara University Faculty of Medicine, Department of Dermatology, Ankara, TURKEY
***Dokuz Eylül University Faculty of Medicine, Department of Geriatric Medicine, Unit for Aging Brain and Dementia, İzmir, TURKEY

Abstract

Objective: This study was performed to measure the effect of isotretinoin treatment on hormonal responses and insulin resistance in acne patients. **Material and Methods:** A total of 30 acne vulgaris patients and 30 control group volunteers were examined between February 2015 and June 2015. Firstly, the basal insulin resistance and endocrine hormone levels were measured in both groups. A daily dose of 120–150 mg/kg oral isotretinoin was administered to the patient group for three months. Following this, insulin resistance and endocrine hormone levels were re-evaluated in both groups. **Results:** Age, waist circumference, and body mass index were similar between the patient and control groups. Liver transaminase, low-density lipoprotein (LDL), adrenocorticotropic hormone, cortisol, 17-hydroxyprogesterone, and total testosterone levels were different in the patient group compared to the control group ($p<0.05$). The levels of dehydroepiandrosterone sulfate (DHEA-S), liver transaminase, LDL, and triglycerides increased after three months of isotretinoin administration ($p<0.05$). The changes in blood triglyceride levels were correlated with the changes in insulin growth factor-1, DHEA-S, total testosterone, progesterone, LDL, and estradiol levels ($p<0.05$). C**onclusion:** Isotretinoin might not affect pituitary gland hormones, adrenal hormones, and insulin resistance significantly. Increased blood triglyceride levels may be expected in patients whose testosterone and progesterone hormone levels are high.

Keywords: Acne vulgaris; isotretinoin; insulin resistance; hormones

Özet

Amaç: Bu çalışma, akne hastalarında izotretinoin tedavisinin hormonal yanıt ve insülin direnci üzerindeki etkisini ölçmek amacıyla planlanmıştır. **Gereç ve Yöntemler:** Şubat 2015-Haziran 2015 tarihleri arasında toplam 30 akne vulgaris hastası ve 30 gönüllü kontrol grubu incelendi. İlk olarak, her iki grupta bazal insülin direnci ve endokrin hormon düzeyleri ölçüldü. Üç ay boyunca hasta grubuna günde 120-150 mg/kg oral izotretinoin uygulandı. Bunu takiben her iki grupta da insülin direnci ve endokrin hormon düzeyleri yeniden değerlendirildi. **Bulgular:** Hasta ve kontrol grubu arasında yaş, bel çevresi ve beden kitle indeksi benzerdi. Hasta grubunda karaciğer transaminazları, "low-density lipoprotein (LDL)", adrenokortikotropik hormon, kortizol, 17-hidroksiprogesteron ve total testosteron düzeyleri kontrol grubuna göre farklıydı ($p<0,05$). Üç aylık izotretinoin uygulamasından sonra dihidroepiandrosteron sülfat (DHEA-S), karaciğer transaminazları, LDL ve trigliserid düzeyleri artmıştı ($p<0,05$). Kan trigliserid düzeylerindeki değişiklik, insülin benzeri büyüme faktörü-1, DHEA-S, total testosteron, progesteron, LDL ve östradiol düzeylerindeki değişikliklerle korele idi ($p<0,05$). **Sonuç:** İzotretinoin hipofiz bezi hormonlarını, adrenal hormonları ve insülin direncini anlamlı bir şekilde etkilemeyebilir. Testosteron ve progesteron hormon seviyeleri yüksek olan hastalarda kan trigliserid düzeylerinde artış beklenebilir.

Anahtar kelimeler: Akne vulgaris; izotretinoin; insülin direnci; hormonlar

Address for Correspondence: Mustafa ŞAHİN, Ankara University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, TURKEY
Phone: +90 312 508 21 00 **E-mail:** drsahinmustafa@yahoo.com

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Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, including hair follicles, associated with the sebaceous glands (1). Although, generally it is known as a disorder of adolescents, it may affect adults (2).

Androgen hormones play an important role in the pathogenesis of acne vulgaris (1). However, several factors, besides androgens, are also involved in the development and differentiation of normal sebaceous glands. Thus, abnormal expression of one or more of these factors leads to acne formation (3). The sebaceous gland activity is also affected by the growth hormone (GH), insulin-like growth factor-1 (IGF-1), insulin, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), melanocortin, and glucocorticoid hormones (1). Insulin enhances acne development in many patients with polycystic ovary syndrome (PCOS) (4).

Isotretinoin, a synthetic retinoid, is the most effective treatment option for acne and is used in moderate or severe acne patients non-responsive to conventional treatments (5). Due to its severe side effects, patients must be monitored regularly by clinicians. However, the mechanism of action of isotretinoin therapy in healing acne vulgaris remains unclear (6). There are limited studies about the effects of isotretinoin on hormones involved in the etiopathogenesis of acne (7,8).

Here, we aimed to understand hormonal disorders in patients with acne vulgaris and to observe changes in hormone and insulin resistance levels after isotretinoin treatment.

Material and Methods

Study Design

A total of 30 female patients between the ages of 18 and 45 were admitted to Ankara University, Faculty of Medicine, Endocrinology and Metabolism Diseases and Dermatology outpatient clinics. These patients clinically diagnosed as acne vulgaris with the severity of 2-4 were included in the study between February 2015 and June 2015. The control group consisted of 30 healthy volunteers. Since hormonal changes are gender-dependent, evaluation of both genders was not possible. Thus, females, with more frequent acne vulgaris, were included in this study. In this group, volunteers were healthy individuals without acne or other inflammatory skin diseases. In this group, the median ages were consistent with the patient group.

Inclusion criteria were:

- Female
- Between 18 and 45 years old
- Having acne vulgaris with clinical severity of 2-4
- Providing written consent to participate in the study

Exclusion criteria were:

- Younger than 18 years old.
- Pregnant
- Having one or more disorders (or diseases) in addition to acne vulgaris
- Having a history of any endocrinopathy (diabetes mellitus, thyroid function disorder, PCOS, adrenal disorder, hypophyseal disorder)
- Dyslipidemia, liver function disorder
- Medications affecting hormone levels and insulin resistance
- Previously received isotretinoin treatment

Clinical Assessment

A form was established in which the anamnesis, physical examination, and laboratory tests were included. According to this form, the age of the patients, age of onset of acne, age of menarche, body height-weight, waist circumference, and smoking history were recorded. The body mass index (BMI) was calculated by dividing body weight in kilograms to height in meters squared. Post-adolescence acne was defined as the acne first seen in the fifth year after menarche. Acne patients were included in this study according to the location of their acne and clinical severity. According to the examination, the following grades were determined:

1. Grade 1: Comedonal acne
2. Grade 2: Mild papulopustular acne
3. Grade 3: Severe papulopustular acne
4. Grade 4: Nodulocystic acne

The modified Ferriman-Galwey (mF-G) scoring system was used for the assessment of hirsutism.

The grade 2-4 patients were treated with isotretinoin. Fasting blood glucose, fasting insulin, lipid profile, alanine transaminase

(ALT), aspartate transaminase (AST), thyroid-stimulating hormone (TSH), free T3 (fT3), free T4 (fT4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, estradiol, prolactin, morning ACTH, morning cortisol, dehydroepiandrosterone sulfate (DHEA-S), total testosterone, 17-hydroxyprogesterone (17-OHP), GH, and IGF-1 levels were evaluated before starting the drug treatment and at the end of three months (120-150 mg/kg/day oral isotretinoin). Patients with high cortisol levels were given 1 mg dexamethasone suppression test. Insulin resistance was evaluated by the homeostatic model assessment of insulin resistance (HOMA-IR) score. Values of 2.5 and above were accepted as positive for insulin resistance.

Examination of Serum Samples

Serum samples were collected from the venous blood of patients at around 9 AM. Patients were in their early follicular phase (at 2-5 days of menstruation) and fasted for at least 8 h before blood collection.

Fasting blood glucose levels were evaluated by glucose oxidase technique using a spectrophotometer (UniCel DxC SYNCHRON, United States) in the Biochemistry Lab of the Faculty of Medicine at Ankara University. Fasting insulin, GH, 17-OHP, and IGF-1 levels were also determined. The radioimmunoassay (RIA) method was used with ready-made kits (DIAsource, Belgium), and the serum samples were stored at 2-8°C after centrifugation.

Lipid profiles were measured. Samples were prepared for the direct quantitative method (Beckman Coulter, United States) with the storage of serum samples at 2-8°C after centrifugation.

ALT and AST levels were quantified. The samples were prepared for an enzymatic kinetic method and stored at 2-8°C after centrifugation.

FSH, LH, progesterone, estradiol, cortisol, prolactin, total testosterone, TSH, fT3, and fT4 levels were measured. The samples were prepared for the magnetic particle-based chemiluminescence enzyme immunoassay method (Access Immunoassay Systems, Beckman Coulter, United States), and the serum samples were stored at 2-8°C after centrifugation.

The quantity of ACTH was detected. The samples were prepared for an electrochemiluminescence immunoassay (ECLIA) method (Roche Diagnostics GmbH, Mannheim, Germany). Serum samples were centrifuged after collection in EDTA tubes and were stored at -20°C according to the storage conditions of the Biochemistry Laboratory.

Serum DHEA-S levels were specified. The samples were prepared for the ECLIA method (Roche Diagnostics GmbH, Mannheim, Germany) and were stored at 2-8°C after centrifugation.

Statistical Analysis

Descriptive data were demonstrated as mean±standard deviation in the normal distribution, median (min-max) in non-normal distribution. Also, the number of cases and percent of nominal variables were shown.

The significance of the differences between the mean values of groups was determined by the t-test and the Mann-Whitney U test in terms of normally-distributed or not. Categorical variables were assessed by Pearson's chi-squared test or Fisher's exact test.

The relationship between variables was assessed by Pearson's correlation test for normal distribution and Spearman's correlation test for non-normal distribution.

Risk coefficients were determined by performing a multivariate logistic regression analysis. Risk factors independent of the parameters (including hirsutism) affecting the formation of acne were defined.

SPSS 22.0 (SPSS Inc.) was used for all statistical analyses. A value of $p<0.05$ was considered statistically significant.

Ethical Issues

The study was carried out following the Declaration of Helsinki and was approved by the Ethics Committee of the School of Medicine, Ankara University in Ankara, Turkey (Ethics Committee Approval No:02-57-15 and Approval Date:15 February 2015). Informed consent was obtained from each participant.

Results

Demographic Characteristics of the Patients

A total of 30 female patients of acne vulgaris administered 120-150 mg/kg/day of isotretinoin for three months were assessed

as the patient group. Another 30 healthy female volunteers with no inflammatory skin disease were enrolled as the control group. The mean age of the patient group was 23.2±3.7 years, while the mean age of the control group was 23.4±5.2 years. There was no significant difference between the ages of the groups (p=0.592). When both groups were compared, no significant differences were found for menarche age, body height/weight, BMI and waist circumference (Table 1). Also, no significant difference was found in mF-G scoring between the groups. The mF-G score was 8 or above in 30% of the patient group, and 10% of the control group with the scoring system not statistically significant (p=0.053).

Comparison of Laboratory Data

When the patient (pre-treatment with isotretinoin) and control groups were compared, the values of ALT, AST, and fT4 were higher in the control group than in the patient group. The values of low-density lipoprotein (LDL), TSH, ACTH, cortisol, prolactin, progesterone, 17-OHP, and total testosterone were higher in the patient group than in the control group. There was no statistically meaningful difference between the two groups when we compared other values (Table 2).

Evaluation After Isotretinoin Treatment

Serum levels of ALT, AST, LDL, triglyceride, and DHEA-S were significantly increased, and serum levels of fT4 were significantly decreased in the patient group after three months of isotretinoin treatment. There were no statistically significant differences in the other markers between the two groups (Table 3). There were no statistically significant differences between the BMI and waist circumference values between pre- and post-treatment in the patient group.

Effects of Severity of Acne in Hormonal Parameters

When thirty acne vulgaris patients were evaluated according to the clinical severity of acne, four were at clinical stage 2 (13.3%), nineteen at clinical stage 3 (63.3%), and seven at clinical stage 4 (23.4%). There was no statistically meaningful correlation between the severity of acne and HOMA-IR, fasting insulin, LDL, triglyceride, TSH, cortisol, IGF-1, and testosterone levels.

Correlation Graph and Tables

The correlation analysis of relationships between hormones in acne vulgaris patients before drug administration are summarized in Table 4. There was a strong negative correlation between high-density lipoprotein (HDL) and triglyceride. There were positive correlations of IGF-1 with both DHEA-S and total testosterone. When the correlations between variables were evaluated separately for the patient and control groups, a correlation of prolactin levels with ACTH and cortisol was observed only in the patient group.

Statistically significant changes in markers before and after the treatment were compared with baseline values of these markers. It was observed that the change in LDL was correlated positively with DHEA-S (r=0.458; p=0.012). The change in DHEA-S was not correlated with any of the other parameters. However, the change in triglyceride (ΔTg) was correlated with LDL, ALT, estradiol, progesterone, DHEA-S, and total testosterone (Table 5).

Table 1. Demographic and clinical characteristics according to groups before the drug treatment.

Variables	Patient Group (n=30)	Control Group (n=30)	p
Age	23.2±3.7	23.4±5.2	0.592
Age of menarche	13.3±0.85	13.07±0.98	0.293
Height (cm)	163.03±6.3	164.83±4.7	0.198
Weight (kg)	58.3±8.19	62.2±7.01	0.051
BMI (kg/m^2)	21.9±2.9	22.9±3.1	0.169
Waist circumference (cm)	72.4±10.1	74.1±9.7	0.373

BMI: Body Mass Index.

Table 2. Comparison of laboratory values of patient and control groups at basal level.

Variables	Patient Group n=30	Control Group n=30	p
Fasting blood glucose (mg/dL)	82.6±7.03	86.8±11.7	0.124
Fasting insulin (microIU/mL)	10.1±4.8	10.5±10.8	0.436
HOMA-IR score	2.07±1.06	2.24±2.6	0.412
ALT (U/L)	14.4±3.02	17.07±4.8	0.013
AST (U/L)	18.4±3.3	20.8±5.4	0.048
LDL (mg/dL)	90.8±21.8	75.6±12.4	0.002
Triglyceride (mg/dL)	59.6±26.6	57.3±23.5	0.728
HDL (mg/dL)	55.6±12.2	54.7±13.06	0.662
TSH (microIU/mL)	2.34±1.6	1.37±1.16	0.001
Free T3 (pmol/L)	4.8±0.59	4.71±0.77	0.304
Free T4 (pmol/L)	10.6±1.65	11.8±1.8	0.02
ACTH (pg/mL)	30.1±18.7	12.3±7.4	<0.001
Cortisol (microgram/dL)	22.8±8.6	11.6±4.8	<0.001
Growth hormone (ng/mL)	2.3±2.6	1.3±2.1	0.078
IGF-1 (ng/mL)	322.2±153.5	283.1±106.9	0.264
Prolactin (ng/mL)	18.3±7,3	11.7±4,8	<0.001
LH (mIU/mL)	8.78±6.1	12.1±14.6	0.859
FSH (mIU/mL)	5.38±2.21	6.69±3.5	0.181
Estradiol (pg/mL)	97.43±58.5	93.83±84.9	0.178
Progesterone (ng/mL)	2.9±3.1	0.8±0.9	<0.001
17-OH progesterone (ng/mL)	1.26±0.68	0.92±0.39	0.023
DHEA-S (microgram/dL)	322.2±153.5	283.1±106.9	0.264
Total testosterone (ng/dL)	53.9±15.9	41.06±17.02	0.04

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TSH: Thyroid-Stimulating Hormone; ACTH: Adrenocorticotropic Hormone; IGF-1: Insulin-like Growth Factor 1; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; 17-OH progesterone: 17-hydroxyprogesterone; DHEA-S: Dehydroepiandrosterone Sulfate.

When linear regression analysis was used to evaluate the factors affecting the change in triglyceride levels, one-unit increase in testosterone and progesterone levels was observed to cause triglyceride increase of 1.48% and 8.47-fold, respectively (p=0.05 and p=0.048, respectively).

Discussion

In the present study, ALT, AST, LDL, and DHEA-S levels changed with isotretinoin treatment at the end of the third month of treatment in adult women. DHEA-S and testosterone were possibly associated with IGF-1 in acne etiopathogenesis. DHEA-S, testosterone, and progesterone were correlated with changes in triglyceride levels after isotretinoin treatment.

Acne is generally known as a disease of the adolescent period. However, recent epidemiological studies have shown that the development of acne in the post-adolescent period has increased and lasts until the mid-forties and is seen more often among women (2,9). In our study, the mean age of the patients was 23.23±3.7 years, and all participants had post-adolescent acne. Acne is frequently seen between the ages of 20-29 (10). When the site of acne was evaluated, we detected acne on the face of all patients and the torso in 33%. Dreno et al. identified acne on the face in 89.8% of patients and on the torso in 48.4% (11). Furthermore, the age of individuals with post-adolescent acne, age of onset, and site of acne show similarity with the literature.

Androgens play a key role in the etiology of acne by causing sebum production and follicular hyperkeratinization (12). Therefore, acne and hirsutism are common clinical

Table 3. Comparison of laboratory findings between basal evaluation and three months after isotretinoin treatment in the patient group.

Variables	Before isotretinoin Mean±SD	After isotretinoin Mean±SD	p
BMI (kg/m^2)	21.9±2.9	21.6±2.7	0.679
Waist circumference (cm)	72.4±10.1	72.1±9.8	0.907
mF-G score (>8) (%)	30.0	27.3	0.818
HOMA-IR score	2.07±1.06	2.22±0.88	0.206
ALT (U/L)	14.4±3.02	17.8±8.4	0.017
AST (U/L)	18.4±3.33	22.17±5.8	<0.001
LDL (mg/dL)	90.8±21.8	108.4±23.9	<0.001
Triglyceride (mg/dL)	59.6±26.6	89.2±41.3	<0.001
TSH (microIU/mL)	2.34±1.66	2.12±1.11	0.405
Free T4 (pmol/L)	10.6±1.6	10.1±1.3	0.04
ACTH (pg/mL)	30.1±18.7	30.06±21.9	0.478
Cortisol (microgram/dL)	22.8±8.6	24.8±10.5	0.417
IGF-1 (ng/mL)	326.7±146	264.1±73.6	0.184
Prolactin (ng/mL)	18.3±7.3	16.9±9.8	0.289
LH (mIU/mL)	8.7±6.1	10.5±7.04	0.153
FSH (mIU/mL)	5.38±2.21	6.33±2.4	0.128
Estradiol (pg/mL)	97.4±58.5	90.4±52.7	0.614
Progesterone (ng/mL)	2.98±3.12	1.7±1.3	0.120
17-OH progesterone (ng/mL)	1.26±0.68	1.09±0.45	0.344
DHEA-S (microgram/dL)	322.2±153.5	341.9±106.1	0.002
Total testosterone (ng/dL)	53.9±15.9	57.6±15.8	0.088

SD: Standard Deviation; BMI: Body mass index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDL: Low-Density Lipoprotein; TSH: Thyroid-Stimulating Hormone; ACTH: Adrenocorticotropic Hormone; IGF-1: Insulin-like Growth Factor 1; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; 17-OH progesterone: 17-hydroxyprogesterone; DHEA-S: Dehydroepiandrosterone Sulfate.

Table 4. Correlation analysis of basal hormone levels of the patient group before drug treatment.

Correlation Coefficient (r)	ALT	ACTH	Cortisol	HDL	IGF-1	DHEA-S	Free T3
Triglyceride	n/s	0.259*	n/s	-0.472**	n/s	n/s	n/s
AST	0.631**	-0.301*	n/s	n/s	n/s	n/s	n/s
Prolactin	n/s	0.480**	0.465**	n/s	n/s	n/s	n/s
Progesterone	-0.260*	0.374**	0.409**	n/s	0.283*	n/s	n/s
DHEA-S	n/s	n/s	n/s	n/s	0.415**	-	0.343**
Testosterone	n/s	n/s	0.370**	n/s	0.512**	0.689**	0.399**
Free T3	n/s	n/s	n/s	n/s	0.406**	0.343**	-
Cortisol	n/s	0.709**	-	n/s	0.316*	n/s	n/s

ALT: Alanine Aminotransferase; ACTH: Adrenocorticotropic Hormone; HDL: High-Density Lipoprotein; IGF-1: Insulin-like Growth Factor 1; DHEA-S: Dehydroepiandrosterone Sulfate; AST: Aspartate Aminotransferase; n/s: not significance.
*p <0.05 **p<0.011.

Table 5. Correlation analysis of the change in triglyceride level with the hormonal parameters.

Correlation Coefficient (r)	LDL	ALT	DHEA-S	Total testosterone	Progesterone	Estradiol	IGF-1
(ΔTg)	-0.592**	-0.36*	0.423*	0.445**	0.495**	0.425*	0.365*

LDL: Low Density Lipoprotein; ALT: Alanine Aminotransferase; DHEA-S: Dehydroepiandrosterone Sulfate; IGF-1: Insulin-like Growth Factor 1.
*p<0.05 **p<0.01.

symptoms of hyperandrogenism among women. When hirsutism was evaluated with modified Ferriman-Gallwey scoring, there were nine individuals in the patient group (30%), and three subjects in the control group (9%) who had an mF-G score over 8 in our study. However, there was no relationship between acne severity and mF-G score and between HOMA-IR and BMI. The hirsutism rate was high in the group with acne, although it was not statistically meaningful (p=0.052). A study by Borgia et al., including 129 women with acne reported a hirsutism rate of 19.38%, unrelated to acne severity (13). Also, the mF-G score was not different pre- and post-treatment in this study.

We highlighted that neither acne severity nor isotretinoin treatment had effects on insulin and glucose levels. In another study, when pre- and post- isotretinoin treatment levels were evaluated in women diagnosed with severe post-adolescent acne, basic parameters were similar in the control and patient groups; likewise, both androgenic hormones and insulin resistance were unchanged post-treatment in the patient group (14). Retinoic acid (RA) was subcutaneously given to non-obese rats, and there was no change in insulin and glucose levels after injection in an experimental study. Although there were some changes in white adipose tissue after RA administration, the brown adipose tissue distribution was unchanged (15). A decrease in brown adipose tissue is associated with type 2 diabetes mellitus and obesity.

The increase of sebum excretion in acne vulgaris, changes in lipid composition, and differences in oxidant/antioxidant levels of lipids on the surface of the skin lead to acne growth (16). Our study showed higher LDL levels in the patient group than in the control group. Triglyceride and HDL levels were not different between the control and patient groups. A previous study indicated higher total cholesterol and LDL levels than the control group, while the HDL levels were lower in non-obese female patients with acne vulgaris who did not have hirsutism (17). Another study, with 184 acne patients and 82 healthy people, showed no difference in LDL and triglyceride levels between the groups; however, HDL levels were lower in the acne patient group (18). Generally, there is no consensus in the literature regarding acne vulgaris and the lipid profile. Additionally, isotretinoin treatment leads to increased ALT and AST levels. In light of this information, the lipid profile and liver enzymes should be checked in acne patients. Our study highlights that isotretinoin treatment causes significantly increased triglyceride and LDL levels. In a previous study, it was demonstrated that triglyceride levels increased after short-term isotretinoin application, not related to insulin resistance (19). In our study, we also found out that hypertriglyceridemia and insulin resistance were not relevant. We found out that triglyceride and androgens had a strong correlation with IGF-1 levels. There might be other effective factors beyond isotretinoin. IGF-1 sebocytes play an important role in increasing lipid synthesis (20). For SEB-1 sebocytes, IGF-1 increases lipogenesis by increasing sterol response element-binding protein-1 (SREBP-1) levels via the PI3 k/Akt and MAPK/ERK signal transduction pathways (21). SERBP-1 expression regulates fatty acid synthesis genes and is increased by androgens (22). Molecular-lev1el relationships between these markers are supported by our study. In our study, changes in triglyceride levels were related to basic DHEA-S, total testosterone, oestradiol, and progesterone levels. There might be different unknown factors playing a role in hypertriglyceridemia.

For acne vulgaris etiology, IGF-1 affects the stage of sebum production. The maximum sebum production starts at puberty, and this state correlates with peak values of IGF-1 and GH levels in the intermediate phase of puberty (23). Thus, increased GH and IGF-1 levels play an important role in acne progression. As the oscillation of GH is rapid and distant, evaluating serum levels is not accurate. However, evaluating IGF-1 in serum tests is more convenient because the oscillation of IGF-1 is stable and reflects the cumulative effect of GH. In a previous study, 82 female patients between the ages of 20-25 years with post-adolescent acne had higher IGF-1 levels than the control group (24). Parallel to the levels of GH and IGF-1, DHEA-S levels progressively increase at puberty. DHEA-S and other adrenal androgens may be an important factor for sebum se-

cretion in the prepubertal period and during the pubertal period (25). As an increase in both IGF-1 and DHEA-S corresponds to the same period, a relationship between these hormones may exist. Aizawa et al. showed an increase in DHEA-S and IGF-1 levels in post-adolescent women with acne, but there was no correlation between them (24). However, another study found a relationship between IGF-1 level and dihydrotestosterone (DHT) in 8 women with acne, while IGF-1 was related to DHEA-S and androstenedione in 8 men with acne and IGF-1 levels were not different from the control group (26). IGF-1 and other factors lead to acne growth in women, although it can occur in women with normal IGF-1 levels (26). Serum DHEA-S and total testosterone levels are related to the presence of acne in the prepubertal period, and adolescent girls aged 14-17 years (27). Many studies have pointed out a complex relationship between IGF-1 and androgens. In a previous study, the relationship between serum androgens and IGF-1 was shown through an increase in IGF-1 after applying oral DHEA-S in postmenopausal women (28). Similarly, another study monitored oophorectomized women administered with testosterone and showed a linear increase in IGF-1 levels (29). IGF-1 and androgen might play a role in acne pathogenesis. Forkhead box O1 (FOXO1) regulation of androgen receptor activity on the genetic level may explain the relationship between IGF-1, androgens, and androgen receptors. These play important roles in sebum production, sebocyte growth, and keratinocyte proliferation (30). IGF-1 levels were decreased in a study after isotretinoin treatment, due to declining gene expression related to the androgen receptor and an increasing FOXO1 nuclear concentration (31). In our study, IGF-1 levels were similar between the patient and control groups. After isotretinoin treatment, there was no statistical change in IGF-1 levels. However, in the correlation analysis, IGF-1 levels were strongly related to both DHEA-S and testosterone levels.

Hyperandrogenism is related to sebum production and severe acne growth (32). A previous study showed that total testosterone, DHT, androstenedione, sex hormone-binding globulin (SHBG), free testosterone, and free DHT are increased in patients with acne (33). In the literature, it has been found that total testosterone and DHEA-S levels are decreased after three months of isotretinoin treatment (8). However, in another study, it was stated that there was no change in androgen levels after six months of isotretinoin treatment, and there was no relationship between acne severity and androgens (20). While we observed a higher total testosterone level in the acne group than in the control group, an increase in the DHEA-S level was identified three months after isotretinoin treatment. A total of three patients complained about hirsutism in the third month of treatment. As isotretinoin may increase DHEA-S levels, these data emphasize the evaluation of patients in this respect. Also, our study confirmed a strong positive correlation between basic free T3, DHEA-S, and total testosterone. Thyroxin-binding globulin, along with SHBG, plays an important role in acne vulgaris etiology, and further studies are suggested from this point of view.

In the present study, when we assessed correlations between other hormones, cortisol level was found to be significantly correlated with prolactin, progesterone, and IGF-1 levels. The role of progesterone in acne pathogenesis remains unclear. However, it is known that glucocorticoid, progesterone, and IGF-1 levels can increase in acne vulgaris (34). We also observed a significant increase in progesterone in the acne group compared to the control group. The influence of progesterone on acne is more complicated, and the fluctuation of sebum production in women during the menstrual cycle is attributed to progesterone effect (1). Progestins may cause an increase in pro-inflammatory cytokine production, such as IL-6 (1). Therefore, the correlation between progesterone, cortisol, and acne vulgaris could be dedicated to the pro-inflammatory process. CRH genes are intensely involved in the skin, and CRH is known to trigger lipogenesis (35). Acne flares have been seen during a period of stress, associated with the strong effect of CRH on the sebaceous glands (36). Additionally, CRH increases the level of prolactin during stress periods in animal models (37). IGF-1 plays a role in acne pathogen-

esis by increasing the pro-inflammatory cytokine release via the NF-κB pathway through its receptor in sebocytes (38). It can be hypothesized that the positive correlation of IGF-1 and cortisol is due to this pro-inflammatory effect of IGF-1 in the study.

This study has some limitations. First, the sample size was small; second, this study was single-centered. Third, patients with acne vulgaris were not of the same clinical severity. Fourth, isotretinoin treatment did not reach a cumulative dose. Fifth, it was not asked whether all participants had menstrual disorders. Concurrently, this study has several strengths. First, only women in the reproductive period were included. Second, the assessments were made in comparison to a control group. Third, in this study, a broader hormone profile was evaluated compared to previous studies.

Conclusion

In conclusion, interactions between hormones and interactions at the molecular level play essential roles in the etiopathogenesis of acne vulgaris. Isotretinoin had no conspicuous effect on hypophyseal function, adrenal hormones, or insulin resistance. For a deeper understanding of acne vulgaris etiopathogenesis and the effects of isotretinoin, further studies are necessary. Thus, we aim to contribute to the literature with our findings to enlighten future studies in this respect.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mustafa Şahin, Süleyman Emre Koçyiğit; Design: Süleyman Emre Koçyiğit; Control/Supervision: Mustafa Şahin, Demet Çorapçıoğlu; Data Collection and/or Processing: Süleyman Emre Koçyiğit, atma Sena Dost Günay, Yousef Houshyar; Analysis and/or Interpretation: Mustafa Şahin, Süleyman Emre Koçyiğit; Literature Review: Mustafa Şahin; Writing the Article: Süleyman Emre Koçyiğit; Critical Review: Süleyman Emre Koçyiğit, Fatma Sena Dost Günay; References and Fundings: Süleyman Emre Koçyiğit, Yousef Houshyar; Materials: Süleyman Emre Koçyiğit, Mustafa Şahin.

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