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Effects of Isotretinoin on Free Testosterone and DHEAS and Prolactin in Females with Acne Vulgaris

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ABSTRACT
Background: For mild acne vulgaris that does not respond to conventional therapy modalities and severe nodulocystic acne vulgaris, oral isotretinoin is known to be the most effective treatment. It is the only form of therapy that affects the full etiology of acne.
Objective: This study aimed at investigating how isotretinoin affected the levels of prolactin and androgens in the blood of females with acne vulgaris.
Patients and methods: Fifty adult females with acne vulgaris, between puberty and menopause, who were candidates for isotretinoin treatment, were included in this study. Patients were chosen from the outpatient dermatology clinics.
Results: After receiving isotretinoin treatment, there was a statistically significant drop in prolactin levels; the mean difference was 5.33 and the percentage change was 25.4 percent. Following treatment, there was a statistically significant rise in both DHEAS and free testosterone levels in the cases, with mean differences of 0.58 and -0.22 and percentage changes of 21.5 percent and 27.2 percent respectively.
Conclusion: According to this study, isotretinoin has been successfully used to treat cases of acne vulgaris. It can lower prolactin levels while increasing DHEAS and free testosterone; two key factors that contribute to acne etiology.
Keywords: Acne Vulgaris, Isotretinoin, Serum Androgens, Prolactin.

INTRODUCTION

Acne vulgaris is one of the most prevalent dermatological illnesses in the world. It is a chronic inflammatory disease of the pilosebaceous unit [(1)]. Several factors, including increased sebum production, altered sebum lipid composition, androgen activity, interaction with neuropeptides, manifestation of pro- and anti-inflammatory properties, follicular hyperkeratinization, and Propionibacterium acnes (P. acnes) proliferation, are currently thought to play a role in the pathogenesis of acne [(2)].

Different acne therapies focus on various stages in the etiology of acne, from reducing sebum production and reducing androgens to preventing follicular occlusion, reducing Propionibacterium acnes growth, and reducing inflammation [(3)].

Oral isotretinoin, a vitamin A metabolite product, is the most effective treatment for mild acne that does not respond to conventional therapeutic methods and nodulocystic acne [(4)]. It is the only form of treatment that has consequences for the overall cause of acne, despite the fact that its mode of action is yet unknown. It supports the reduction of P. acnes growth, normalization of the pattern of keratinization within the sebaceous gland follicle, suppression of sebaceous gland activity, and normalization of inflammation. Isotretinoin frequently causes cheilitis, dry skin, photosensitivity, photophobia, paronychia, arthralgia, myalgia, and headaches as adverse effects. It is a pregnancy medication of category X. When using isotretinoin, women of reproductive age should receive appropriate counseling, give their informed consent, and undergo regular pregnancy tests [(5)].

The secret to acne vulgaris development is sebum production. Androgens activate the sebaceous glands, which can change them into more active types. Numerous researchers have explored for connections between the occurrence of acne, serum androgen levels, and sebum secretion rates. Serum dehydroepiandrosterone sulphate (DHEAS) levels are correlated with acne in prepubertal females and sebum production in both sexes. Even while elevated serum androgen levels are associated with severe nodular acne in women, mild to moderate acne frequently has levels that are within the normal range. This raises the question of whether patients with acne vulgaris have a localized increase in androgen production within their sebaceous glands that causes them to secrete more sebum [(6)].

According to this theory, neurohormone prolactin (PRL) may be a sebotrophic hormone and represent a unique therapeutic target in human SG dermatoses like acne. Additionally, (PRL) might have an impact on sebaceous gland (SG) biology [(7)].Although there is evidence that isotretinoin has therapeutic effects that are not mediated by hormones, it is yet unknown how isotretinoin affects human levels of serum androgens, precursor androgens, and prolactin [(8)].

This work aimed for investigation of the effect of oral isotretinoin on serum androgens and prolactin levels in females of reproductive age with acne vulgaris.

PATIENTS AND METHOD

Fifty adult females with acne vulgaris between adolescence and menopause, who were prescribed isotretinoin, were included in this prospective case series investigation. They were recruited from the dermatology outpatient clinic.

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Inclusion criteria: Women of reproductive age with adult acne who met the requirements for isotretinoin treatment. severe nodular acne that can be treated with isotretinoin or moderate acne that didn't respond to other forms of treatment. BMI ranges from 18.5 to 24.9 kg/m^2. Testosterone levels before therapy were typical. Married women who had a negative pregnancy test prior to treatment and used effective non-hormonal contraception throughout the course of treatment. absence of an anomaly in the lab.

Exclusion criteria: Refusing to take part. Pregnant women. Usage of hormonal birth control. Medications such corticosteroids, ACTH, phenytoin, testosterone, anabolic steroids, iodides, and bromides that may aggravate or induce acne. Increased androgen symptoms (hirsutism, irregular periods). Comorbidities, an autoinflammatory condition, or an endocrine disorder. Using medicines that affect isotretinoin.

All participants (n=50) were subjected to:

Thorough history-taking: Complete personal, family, and current history, including the onset, course, duration, and previous treatments. Recorded responses to current and previous therapy were included. Married women received advice about contraception. Body mass index (BMI) calculation: Women's weight and height were noted, and the BMI was computed. Exams in dermatology and general medicine.

According to the manufacturer's instructions, all patients had their serum levels of PRL, DHEAs, and free testosterone checked using commercially available (ELISA) kits.

Ethical consent:

The Academic and Ethical Committee at Mansoura University approved the project. Every patient or caregiver of below 18-year patient, signed an informed consent approving their participation in the trial. This research was conducted in accordance with the Declaration of Helsinki, which is the World Medical Association's code of ethics for human subjects' investigations.

Statistical analysis

Version 22.0 of IBM SPSS Statistics for Windows. IBM Corp., Armonk, New York was used to analyze the data that had been gathered. Number and percentage were used to describe qualitative data. After confirming normality with the Kolmogorov-Smirnov test, quantitative data were presented using the median, range, mean, and standard deviation for parametric data. The acquired results significance was assessed at the (0.05) level.

RESULTS

Table (1) shows that mean age of the studied cases was 23.26. 28 cases (56%) had rural residence and the rest had urban residence.

Table (1) Demographic characteristics of the studied cases

	Total number =fifty	
Age/years mean±SD min-max	23.26±4.64 17-35	
Sex Female	**Number**	**Percent**
Residence Urban Rural	Twenty-two Twenty-eight	Forty-four Fifty-six

Table (2) shows that the average prolactin level in the patients significantly decreased after isotretinoin treatment. The mean DHEAS and mean free testosterone levels significantly increased in cases after treatment.

Table (2): Comparison of prolactin, DHEAS and free testosterone levels pre and post treatment

	Pre-isotretino	**Post-isotretino**	**Wilcoxon signed Rank test**	**Mean differen**	**Percent change**
Prolactin (ng/ml)	20.99± 5.12	15.65± 3.79	Z=2.79 P=0.007*	5.33	25.4%
DHEAS (ug/ml)	2.696± 0.64	3.28± 0.71	Z=2.9 P=0.005*	0.58	21.5%
Free testo-sterone (pg/ml)	0.810± 0.19	1.03± 0.23	Z=1.97 P=0.04*	-0.22	-27.2%

*: Significant

Figure 1 shows correlation between free testosterone difference pre- and post-treatment and duration of disease among studied cases.

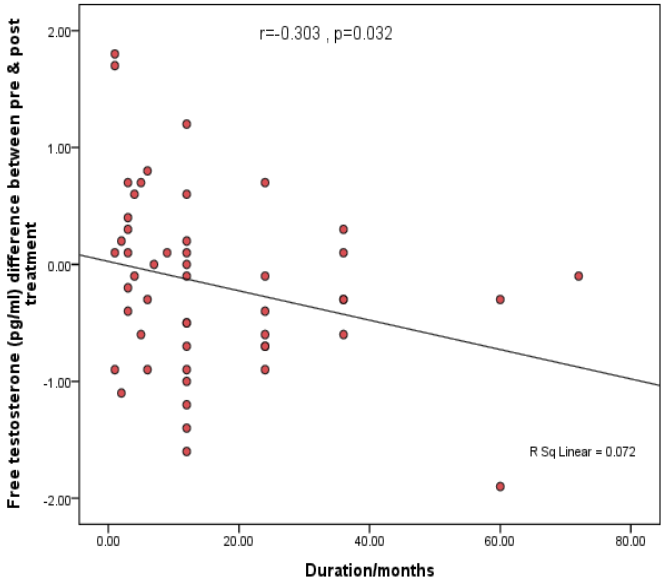

Figure (1): Scatter diagram showing correlation between free testosterone difference pre- and post-treatment and duration of disease among studied cases.

Table (3) illustrates that there was no statistically significant correlation between acne score before treatment and hormonal level.

Table (3): Correlation between acne score and hormonal level pretreatment

		Acne score before
Prolactin (ng/ml) pre-treatment	r	0.069
	p	0.633
Testosterone (pg/ml) pre-treatment	r	-0.203
	p	0.157
DHEAS (ug/ml) pre-treatment	r	0.013
	p	0.929

Table (4): No statistically significant correlation between acne score after treatment and hormonal level was found.

Table (4): Correlation between acne score and hormonal level post-treatment

		Score after
Prolactin (ng/ml) post-treatment	**r**	-0.011
	p	0.939
DHEAS (ug/ml) post-treatment	**r**	-0.114
	p	0.432
Testosterone (pg/ml) post-treatment	**r**	-0.064
	p	0.657

Table (5) illustrates that there was statistically significant decrease of acne score after treatment as compared to pre-treatment value.

Table (5) Comparison of acne score before and after treatment

	Before ttt	**after ttt**	**test of significance**
Acne score	33.40±1.81 33 (31-37)	19.38±4.91 17 (13-30)	t=18.87 p<0.001*
Mild Moderate Severe	0 0 50 (100%)	31 (62.0) 19 (38.0) 0	<0.001*

*: Significant

DISCUSSION

In order to examine the relationship between hormonal changes before and after acne treatment, the current study, a case-series study, was conducted on fifty adult females with acne for whom isotretinoin treatment was recommended. The participants were drawn from the dermatology outpatient clinic at Mansoura University Hospitals. All patients provided written authorization.

The demographics of the current study show that the mean age was 23.26 years, ranging from 17 to 35 years, that all patients were females, and that 28 cases (56%) and 22 cases (44%) respectively were from rural and urban areas. This is consistent with **Khan et al.** [9] investigation on 476 cases of acne vulgaris, aged between 15 and 25, using an Arabic self-administered questionnaire. The majority (86.3%) were single. Nearly all of the respondents (86.3%) were females, and 32.8% of them lived in Dammam. The majority (92.4%) were Saudis. In terms of education, 60.1% possessed only a diploma or less.

Ninety percent of the studied cases had cheilitis, or dry lips, according to the current study. Median disease duration among the cases was 12 months, with a range of 1 to 72 months. Mean weight was 66.68 kg, mean height was 1.69 metres, and mean body mass index was 24.24, with a range of 17.26 to 37.65 kg/m^2.

Borzyszkowska *et al.* [10] revealed in their study, that mean weight was 67.29 kg, mean height was 163.07 and mean BMI was 25.00 kg/m^2. According to **Alshammrie *et al.*** [11]**,** 36% of their female acne vulgaris patients had (BMI) of less than 24.9, 26% had a BMI between 25 and 29.9 kg/m^2, and 38% had a BMI greater than 30 kg/m^2, which was consistent with our findings. Thus, a high body mass index is linked to acne occurrence. Of a total of 400 patients, **Balighi *et al.*** [12] discovered that 134 (34 percent) of them first presented with signs of cheilitis. (63 percent) of them were females. The lower lip received 55% of the cheilitis, the two lips received 30%, and the top lip received 16 percent. Compared to just 8% of patients who showed no indications of cheilitis, over a quarter (27 percent) of cheilitis patients developed acne excoriee. Even prior to isotretinoin therapy, cheilitis is fairly common among those with acne vulgaris.

Regarding the mean prolactin level among cases before isotretinoin treatment, it was 20.99 ng/ml that decreased to 15.65 post treatment, Mean DHEAS level before isotretinoin treatment was 2.696 Ug/ml, which increased to 3.28 ug/ml post treatment, while mean free testosterone level before isotretinoin treatment was 0.810 pg/ml that increased to 1.03 pg/ml post treatment with statistically significant difference.

Feily *et al.* [8] studied a total of thirty-six women, aged eighteen to thirty years, who had moderate-to-severe acne and were given daily doses of 20 mg isotretinoin for three months. They discovered that the blood prolactin levels were 27.29 ±11.55 before treatment and dropped to 17.86 ±7.92 after. While mean DHEAS level before isotretinoin treatment was 1.88 ± 0.91 Ug/ml, which increased to 2.73 ±1.29 Ug/ml post treatment with statistically significant difference, which is in agreement with our results, mean free testosterone level before isotretinoin treatment was 2.6 ±3.11 pg/ml, which increased to 3.08 ±2.36 pg/ml after treatment.

Our findings are generally in line with those of **Karadag *et al.*** [13]**,** who discovered that isotretinoin elevated free testosterone and decreased DHT. According to **Karadag *et al.*** [14]**,** isotretinoin medication boosted DHEA levels while decreasing prolactin and total testosterone levels. In a different clinical experiment, patients using isotretinoin had significantly

lower levels of total testosterone and prolactin, but not of free testosterone or DHEA.According to these results, isotretinoin therapy raises free testosterone and DHEA while lowering total testosterone, prolactin, and DHT. We speculate that isotretinoin stimulates the dissociation of testosterone from sex hormone-binding globulin, boosting free testosterone levels and preventing the conversion of testosterone to DHT, despite the fact that the mechanism behind these changes is not well understood [(8)].

In a study performed by **Melnik** [(10)], who looked at how isotretinoin medication affected hair follicles, they found that after just the second day of treatment, shaft elongation was greatly reduced, and on the sixth day of treatment, 80 percent of these follicles entered the catagen state.

Androgens, on the other hand, exhibit side effects via reversing fT or dihydrotestosterone [(15-16)]. According to **Acmaz *et al.*** [(17)]**,** the side effects of isotretinoin treatment included a substantial decrease in (mFG) and acne scores. The nonclassical pathway of androgen formation was studied by **Karlsson *et al.*** [(18)], who came to the conclusion that 11-cis retinol dehydrogenase can decrease the androgenic response in peripheral tissues by boosting (PSA) gene production by a factor of five to six. With 60 female volunteers, **Gokalp *et al.*** [(19)] looked at how isotretinoin medication affected the levels of fT, fT4, fT3, TSH, FSH, LH, and E2. Treatment with isotretinoin dramatically decreased fT levels. However, contrary to our findings, the levels of fT4, fT3, TSH, FSH, LH, and E2 were not significantly altered.

According to a study by **Cetinözman *et al.*** [(20)], oral isotretinoin reduced acne lesions without altering testosterone levels. Although fT levels were significantly lower in a study by **Acmaz *et al.*** [(17)]**,** there was no statistically significant difference in FSH, LH, DHEAS, sex hormone-binding globulin (SHBG), and tT levels six months after isotretinoin treatment. This contradicted our findings and may have been caused by the different inclusion criteria used in the two studies.

In a study by **Akpolat** [(21)] they examined how isotretinoin treatment affected hirsutism, the menstrual cycle, and hormonal responses in young people with acne vulgaris. Menstrual irregularity and hirsutism rates varied at the first, third, and sixth months of treatment, as was discovered. The levels of fT, tT, and DHEAS were greater at the third and sixth months of treatment than they were at the beginning, while the level of SHBG at the sixth month was found to be lower than it was at the first and third months.

The current study found a substantial negative link between pre-treatment free testosterone levels and disease duration in analysed instances as well as a negative correlation between pre- and post-treatment free testosterone levels and disease duration in studied cases.

According to **Zhang *et al.*** [(22)] the severity of acne in both men and women was positively connected with testosterone and the androgen-to-estrogen ratio, and negatively correlated with estradiol expression. The severity of female acne was positively associated with follicle-stimulating hormone and adversely associated with age and progesterone.

Free testosterone levels, prolactin levels, DHEAS levels, clinical data, and age of the analyzed cases were not found to be significantly correlated in the current investigation.

While serum levels of FSH, estradiol, progesterone, testosterone, and the ratio of androgen to estrogen were statistically significant in female acne patients, FSH, LH, progesterone, and PRL were not different between acne grades, according to **Zhang *et al.***[(22)] data.

According to the current study, eight percent of the investigated cases had abnormal ALT, 6% had abnormal AST, and twelve percent had abnormal TGS in terms of liver enzymes. Which is in keeping with **Alajaji *et al.*** [(23)] findings that 12.7 percent of patients had increased (ALT) and 5.4 percent had elevated aminotransferase (AST) at baseline. In comparison to 6.5 percent of patients at baseline, 12.7 percent of patients had increased triglyceride levels during their most recent visit.

The current investigation found no evidence of a significant relationship between hormone level and acne score before or after therapy. In contrast to before therapy, the acne score was much lower after treatment, dropping from 33.4 to 19.38.

On 2nd month of receiving isotretinoin medication, **Secrest *et al.*** [(24)] discovered improvements in the overall and emotional domain scores of greater than 50 percent (e.g., overall scores reduced from 39.4 to 17.5 by month two; a decrease of 22). In terms of quality of life, Skindex-16 scores peaked between months 3 and 5. At month 4, however, overall Skindex-16 scores had improved by 4.4-fold (from 39.4 at baseline to 8.9) and Emotional domain scores had improved by 4.8-fold (from 57.7 at baseline to 11.9); as a result, patients receiving isotretinoin treatment had improved their quality of life by more than 50 percent by month 2 and could anticipate four-to-five-fold improvements from baseline with isotretinoin full coarse.

The present study sample size was limited, and it was cross-sectional in nature. Case control studies should be undertaken to corroborate our findings, and we did not gather data on the prevalence of acne in our patient group. Future clinical research would undoubtedly find this to be important. The fact that our study did not particularly search for any higher androgen levels and clinical response rates associations, is another potential issue. But in our clinical experience, we've seen that high androgenic levels are linked to worse clinical response rates. When anti-androgenic medications are used, the clinical outcome in this population of people with high levels of androgens is dramatically improved.

CONCLUSIONS

Depending on current study results, isotretinoin has demonstrated to be a significant pharmacological advance in acne vulgaris treatment. It can lower prolactin levels while increasing DHEAS and free testosterone, two key factors that contribute to acne etiology.

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Competing interests: Nil.

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