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Original Research

The effect of low-dose isotretinoin therapy on serum androgen levels in women with acne vulgaris ☆

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ABSTRACT

Background: Acne vulgaris is a common dermatologic disease that causes significant social and psychological morbidity. Isotretinoin, as a vitamin A derivative, is the most effective agent in the treatment of acne. Evidence suggests that isotretinoin's therapeutic function is independent of hormonal mediation; however, the effect of isotretinoin on serum androgens and precursor androgen levels in humans remains unclear.

Objective: Herein, we aim to investigate the effect of low-dose isotretinoin on androgen levels in women and postulate the role of concomitant anti-androgen therapy (e.g., spironolactone).

Methods: A total of 36 women, age 18 to 30 years, with moderate-to-severe nodulocystic acne were treated with 20 mg isotretinoin (Roaccutane) daily for 3 months. A hormone panel was obtained at baseline and after completion of the treatment course. The panel included dehydroepiandrosterone (DHEA), 17-hydroxyprogestrone, testosterone, free testosterone, dihydrotestosterone (DHT), luteinizing hormone, follicle stimulating hormone, and prolactin.

Results: Serum levels of testosterone ($p = .015$), prolactin ($p = .001$), and DHT ($p = .001$) were significantly decreased, while serum levels of DHEA ($p = .001$) significantly increased after isotretinoin treatment. No significant change was found in the other hormones evaluated.

Limitations: The distribution of acne was not assessed in our patient population. We did not directly evaluate for associations between elevated DHEA levels and clinical response rates.

Conclusion: Isotretinoin alone can decrease androgen levels, but increase an important driver of acne pathogenesis (i.e., DHEA). The co-administration of an anti-androgenic agent (e.g., spironolactone) may optimize the therapeutic efficacy of isotretinoin by limiting iatrogenic increases in DHEA and perhaps allow for more widespread use of low-dose isotretinoin.

Introduction

Acne vulgaris is a common dermatologic pathology that causes significant social and psychological morbidity. Acne is primarily a disease of the pilosebaceous unit (Rassai et al., 2013, 2014). There are four main pathogenic factors that influence acne development: follicular epidermal hyper-proliferation, sebum production, inflammation, and the presence of *Propionibacterium acnes*. Acne pathogenesis is exacerbated with the onset of puberty, when androgen-mediated stimulation of the sebaceous gland causes increased sebum production. The upregulated androgen axis is the main cause for the age distribution in this disease (Karadag et al., 2011; Pazyar et al., 2012; Rassai et al., 2013, 2014).

Isotretinoin has a profound inhibitory effect on the size and function of sebaceous glands, resulting in reduction of acne lesions.

☆ Human subjects were included. The manuscript reports on clinical research. No animals were used in this study.

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Evidence suggests that isotretinoin's therapeutic function is independent of hormonal mediation (Farrell et al., 1980); however, the effect of isotretinoin on serum androgens and precursor androgen levels in humans remains unclear (Feily and Namazi, 2011; Gomez and Moskowitz, 1980; Lookingbill et al., 1988; Marynick et al., 1983). Herein, we investigate the effect of low-dose isotretinoin on androgen levels in women and postulate the role of concomitant anti-androgen therapy.

Methods

A total of 36 women, age 18 to 30 years, with moderate-to-severe nodulocystic acne were enrolled in the study. All patients provided written informed consent prior to enrollment, and the study was approved by the university ethics committee.

Pregnancy, hypersensitivity to parabens, polycystic ovarian disease, recent mood or depressive disorders, thyroid disease, pituitary disease, and use of finasteride, retinoids, or hormonal contraception within 3 months of enrollment were exclusionary criteria.

A baseline hormone panel was obtained from each patient on day 2 to 3 of their menstrual cycle. The panel included dehydroepiandrosterone (DHEA), 17-hydroxyprogestrone, testosterone, free testosterone, dihydrotestosterone (DHT), luteinizing hormone, follicle stimulating hormone, and prolactin. Patients were then treated with 20 mg isotretinoin (Roaccutane) daily for 3 months. The hormone panel was repeated after completion of the treatment course.

Statistical analysis was performed using paired Student's *t* tests if variables were normally distributed. For DHT, which did not show a normal distribution, a Wilcoxon test was used. SPSS (version 21) was used for the data analysis.

Results

Serum hormone levels before and after isotretinoin therapy are summarized in Table 1. Serum levels of testosterone ($p = .015$), prolactin ($p = .001$), and DHT ($p = .001$) were significantly decreased after isotretinoin treatment. In contrast, serum levels of DHEA ($p = .001$) significantly increased after isotretinoin treatment. Luteinizing hormone, follicle stimulating hormone, free testosterone, and 17-hydroxyprogesterone showed no significant change after treatment ($p > .05$ for all).

Discussion

To date, few studies have explored the effect of isotretinoin on androgen levels, and the results of published studies are inconclusive and at times conflicting. We identified that 3 months of therapy with low-dose isotretinoin resulted in significant decreases in levels of serum total testosterone, prolactin, and DHT but increased DHEA levels. The remaining fold changes in serum hormone levels were not significant.

Our results are relatively concordant with those of Lookingbill et al. (1988) and Karadag et al. (2015). Lookingbill et al. (1988) found that isotretinoin caused elevation of free testosterone and depression of DHT. Karadag et al. (2011) found that isotretinoin therapy resulted in decreased prolactin and total testosterone levels but increased DHEA levels. In another clinical trial, total testosterone and prolactin levels were significantly decreased in patients treated with isotretinoin, with no change in free testosterone and DHEA levels (Karadag et al., 2011).

Together, these reports suggest that isotretinoin therapy decreases total testosterone, prolactin, and DHT, while increasing free testosterone and DHEA. Although the mechanism of these changes is not well understood, we hypothesize that isotretinoin induces the separation of testosterone from sex hormone-binding globulin, thereby increasing free testosterone levels and inhibiting the transformation of testosterone to DHT.

Isotretinoin alone can decrease androgen levels, but in prior reports (including our own), isotretinoin increased DHEA levels. DHEA is an important driver in the acne pathogenesis of hyperandrogenic patients; 72% of acneic women have been found to have clinical and/or biochemical hyperandrogenemia (Lookingbill et al., 1988). Hence, it is important to address androgen-derived pathogenesis during acne treatment. At our institution, we find that co-administration of isotretinoin with spironolactone achieves superior therapeutic efficacy. We postulate that sprinolactone decreases the level of DHEA and other androgens that are further increased by isotretinoin, thereby improving and optimizing the therapeutic efficacy of isotretinoin. Perhaps this therapeutic optimization with the addition of spironolactione may allow for more widespread use of low-dose isotretinoin.

Taken together, our data indicate that isotretinoin has an effect on certain serum androgen levels (Feily and Namazi, 2011). Given the conflicting results in current studies, a randomized, controlled, and adequately powered study is needed to elucidate the effects of isotretinoin on serum hormone levels and the clinical benefit of treating acne with oral isotretinoin alone versus oral isotretinoin with spironolactone. An investigation of the effects of a weight-based dosage (e.g., 0.5 mg/kg/day orally over 15–20 weeks) on serum androgen levels would also be of interest. Such clarification would facilitate clinical understanding of isotretinoin therapy, validate the need for concomitant antiandrogen treatment, and advance therapy.

Limitations

One possible limitation of our study is that we did not collect information on the distribution of acne in our patient population. This would certainly be of importance in future clinical studies.

Table 1
Effect of isotretinoin treatment on serum hormone levels (n = 36).

Hormone	Pretreatment (Mean ± SD)	Posttreatment (Mean ± SD)	Effect size	*p*-value	Fold change[b]
Prolactin	27.29 ± 11.55	17.86 ± 7.92	0.92	.001[a]	−0.65
Testosterone	1.06 ± 0.44	0.79 ± 0.48	0.58	.015[a]	−0.75
DHT	754.57 ± 140.13	307.58 ± 225.12	2.27	.001[a]	−0.41
Free testosterone	2.6 ± 3.11	3.08 ± 2.36	0.17	0.46	+1.18
DHEA	1.88 ± 0.91	2.73 ± 1.29	0.74	.001[a]	+1.45
17-hydroxyprogestrone progesterone	1.69 ± 1.43	1.22 ± 0.61	0.38	0.07	−0.72
LH	6.77 ± 4.60	8.50 ± 6.76	0.29	0.21	+1.26
FSH	6.6 ± 2.54	6.78 ± 1.87	0.07	0.73	+1.03

DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; FSH, follicle stimulating hormone; LH, luteinizing hormone; SD, standard deviation
[a] Significant.
[b] Mean of posttreatment/mean of pretreatment.

In addition, we administered lower doses of isotretinoin because we plan to evaluate the efficacy of low-dose isotretinoin plus spironolactone to high-dose isotretinoin alone in our current ongoing investigations. Our aim is to determine whether we are able to decrease the required therapeutic dose of isotretinoin prescribed to our patients.

Another possible limitation is that we did not directly evaluate for any direct associations between increased androgen levels and clinical response rates. However, in our practice, we have seen that high androgenic levels lead to worse rates of clinical response. The addition of anti-androgenic agents significantly improves the clinical response in this group of patients with high androgenic levels.

Conflict of Interest

None

Funding

None.

Study Approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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