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INVESTIGATIVE REPORT

Isotretinoin Influences Pituitary Hormone Levels in Acne Patients

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Besides suppressing sebum production, the exact mechanism of action of isotretinoin in acne vulgaris is not known. Several hormones have been linked to the pathogenesis of acne. In this study, we investigated the effects of isotretinoin on the pituitary-adrenal axis, whose activity may be increased in acne. Various hormone systems were evaluated before and after 3 months of isotretinoin treatment in 47 acne patients. Free triiodothyronine (T3), thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibody levels decreased significantly during isotretinoin treatment ($p<0.001$, $p<0.02$ and $p<0.02$, respectively), as did those of luteinising hormone, prolactin and total testosterone ($p<0.005$), as well as morning cortisol and adrenocorticotropic hormone ($p<0.005$ and $p<0.05$, respectively). We conclude that isotretinoin causes mild suppression of pituitary hormone levels, which may be beneficial for tackling the pathogenesis of acne.
Key words: acne; hormone; isotretinoin; pituitary.

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Acne vulgaris is primarily a disease of the pilosebaceous unit. Four main pathogenic factors are known to lead to its development: (*i*) follicular epidermal hyperproliferation; (*ii*) excess sebum production; (*iii*) inflammation; and (*iv*) the presence and activity of *Propionibacterium acnes*. With the onset of puberty, androgen-mediated stimulation of the sebaceous gland results in increased sebum production (1). Several hormones implicated in the regulation of sebaceous gland activity have been linked to acne. They include androgens, estrogens, growth hormone, insulin, insulin-like growth factor-1 (IGF-1), corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), melanocortins and glucocorticoids (2). Individuals who are intrinsically insensitive to androgens do not produce sebum and do not develop acne. Conversely, conditions characterised by high androgen activity are often associated with acne formation. Thus, it is commonly believed that hypersensitivity of the sebaceous glands to androgens is the underlying cause of acne (3).

Proopiomelanocortin (POMC) is produced by the anterior pituitary gland in response to CRH released from the hypothalamus. A precursor polypeptide, its cleavage yields melanocortins, ACTH and melanocyte-stimulating hormone (MSH). Human sebocytes express the melanocortin receptors MC-1R and MC-5R through which ACTH and MSH produce various effects on the sebaceous gland (2–4). ACTH also stimulates the production of cortisol in the adrenal gland (5). It is well known that the use of topical or systemic glucocorticoids promotes acneiform eruptions. *In vitro* studies have demonstrated that hydrocortisone stimulates sebocyte proliferation in a dose-dependent manner, and that cortisol is essential for sebocyte differentiation, as well as GH- and IGF-1-induced sebocyte differentiation and IGF-1-mediated proliferation (6). These results suggest that steroids may induce acne by promoting sebocyte proliferation and differentiation (7).

Isotretinoin (ISO), a 13-cis-retinoic acid derivative of vitamin A, is a highly effective therapy for severe nodulocystic acne. Although its mechanism of action is not fully understood, ISO is thought to isomerise to all-*trans*-retinoic acid (ATRA) ISO, which then interacts with retinoid receptors (8).

The mechanism by which decreases sebum production is not well understood. Few published data describe its effects on hormone physiology in acne patients. In this study, we sought to investigate the effect of ISO on various hormone systems in acne patients.

MATERIAL AND METHODS

A total of 47 patients with acne vulgaris (31/16 females/males; mean age 20.8 ± 3.5 years), who were admitted to our outpatient dermatology clinic between October 2009 and March 2010, were included in the study. The study group was selected from a group of male and non-pregnant female patients between the ages of 17 and 34 years with moderate to severe nodulocystic acne. Females at risk of becoming pregnant were advised to use barrier contraception methods (no hormonal contraception was allowed), and produced a negative serum pregnancy test one week before the initiation of ISO therapy. Treatment was commenced on the second or third day of the menstrual cycle in these patients. Patients using vitamin A supplements or satisfying any of the following criteria were excluded from the study: sensitivity or allergy to parabens; previously diagnosed thyroid or pituitary disease; recent history of psychiatric, mood or depressive disorders; and previous therapy with oral retinoids or hormone therapy for any reason in last 3 months.

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All patients gave their written informed consent, and the study was conducted according to GCP guidelines.

The study was approved by the local ethics committee and was conducted according to the ethical principles of the Declaration of Helsinki.

ISO therapy was initiated at a dose of 0.5–0.75 mg/kg body weight. The drug was administered twice daily with meals. Treatment was continued for at least 5 months. Biochemical parameters were screened immediately prior to initiation (pretreatment) and after 3 months of ISO treatment (posttreatment). These parameters were: free T3 (fT3), free T4 (fT4), thyroid-stimulating hormone (TSH), thyroglobulin, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg), thyroid-stimulating hormone receptor antibody (TRAb), 17-hydroxyprogesterone, progesterone, total and free testosterone, estradiol, luteinising hormone (LH), follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol, adrenocorticotropic hormone (ACTH), haemoglobin, creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C). Fasting blood samples were obtained by venipuncture of the large antecubital veins, without stasis and after 12 hours' fasting. Samples were centrifuged immediately; the plasma was separated and stored at –80°C. In order to limit undesired variation, all samples were studied on the same day and using the same kit. Fasting serum glucose, total cholesterol, triglyceride, LDL-C, HDL-C, ALT and AST concentrations were measured enzymatically using an automatic analyser (Konelab 60i; Thermo Fisher Scientific Inc. MA, USA). Total cholesterol and triglycerides were measured using colorimetric enzymatic tests, and LDL-C and HDL-C using an homogeneous enzymatic colorimetric test (Konelab 60i). Serum glucose levels were measured by the hexokinase method (Konelab 60i). fT3 (normal 2.2–4.2 pg/ml), fT4 (normal 0.65–1.7 ng/dl), TSH (normal 0.3–3.6 mIU/l), thyroglobulin (normal 0.2–70 ng/ml), anti-TPO (normal 1–500 IU/ml) and anti-Tg (normal 5–100 IU/ml), ACTH (normal 4.5–48.8 pg/ml) and DHEAS (normal 80.2–339.5 µg/dl) were measured using chemiluminescence methods (Liason®; Diasorin S.p.A., Saluggia, Vercelli, Italy). TRAb (normal 0–405 U/l) (Zentech S.A., Angleur, Belgium) (catalog no: R-CT-100), 17-hydoxyprogesterone (normal 0.61–3.34 ng/ml) and free testosterone (normal 0.02–3.09 pg/ml) (Diagnostic System Laboratory Inc., Texas, USA) were measured by radioimmunoassay.

Levels of estradiol (reference range 27–433 pg/ml), FSH (reference range 1.79–22.51 mIU/ml), LH (normal 0.2–250 mIU/ml), prolactin (normal 1.2–58.64 ng/ml), progesterone (normal 0.08–18.56 ng/ml), total testosterone (normal 0.1–0.75 ng/ml) and cortisol (normal 6.7–22.6 µg/dl) were measured using chemiluminescence methods (UniCel® DxI 800 Immunoassay System; Beckman Coulter Inc., Clinical Diagnostics Division, Brea, CA, USA), as were SHBG levels (normal 16–110 µmol/l) (Architect i2000sr; Abbott Laboratories, Medical Diagnostics Products, New Jersey, USA).

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences version 15.0; SSPS Inc., Chicago, Il, USA). The normality of data was analysed using the Kolmogorov-Smirnov Test. All numerical variables following a normal distribution were expressed as the mean ± standard deviation (SD), while data that were not normally distributed were expressed as the median (interquartile range (IR)). The paired sample *t*-test was used to compare pretreatment and posttreatment values for hormonal and biochemical data with homogenic variability. The Wilcoxon signed-rank test was used to analyse data with skew distribution.

RESULTS

Comparisons of blood lipid and hepatic parameters before and after ISO treatment are summarised in Table I. We found that levels of total cholesterol, LDL-C, triglycerides ($p < 0.0001$, 0.0001 and 0.005, respectively), AST ($p < 0.005$) and ALT ($p < 0.001$) increased following treatment, while HDL-C levels ($p < 0.0001$) decreased, in accordance with previous findings (9, 10). There was no significant change in fasting blood glucose levels ($p > 0.05$). Comparisons of pre- and posttreatment hormonal parameters are summarised in Tables II and III. We found that levels of fT3, TSH and TRAb decreased significantly following ISO treatment ($p < 0.001$, 0.02 and 0.02, respectively). There were no significant changes in the levels of thyroglobulin, anti-Tg or anti-TPO after ISO treatment (Table II). With regard to estradiol, prolactin, progesterone, 17-hydroxyprogesterone, FSH and LH, we found that posttreatment LH and prolactin levels were significantly lower than pretreatment values (Table III), while there were no significant changes in the other hormonal parameters. Moreover, while there were no changes in free testosterone, DHEAS or SHBG levels, posttreatment total testosterone levels were also significantly lower than initial values ($p < 0.005$). Morning cortisol and ACTH levels were also significantly reduced following ISO treatment ($p < 0.005$ and 0.05, respectively).

When we analyzed men and women seperately, posttreatment total testosterone levels were still significant ($p = 0.003$), however cortisol and LH levels lost their significance in women. In men, however, posttreatment levels of cortisol ($p = 0.044$), but not total testosterone ($p = 0.063$) or LH ($p = 0.07$), were lower than pretreatment values. These disparities may be related to the decrease in statistical power caused by dividing the study group into two subgroups.

Table I. *Pre- and posttreatment values for biochemical parameters (*n = *47)*

	Pretreatment Mean ± SD or Median (IR)	Posttreatment Mean ± SD or Median (IR)	*p*-value
Fasting blood glucose (mg/dl)	84.2 ± 8.4	87.0 ± 7.0	>0.05
Total-C (mg/dl)	149.4 ± 37.5	162.4 ± 40.7	<0.0001
LDL-C (mg/dl)	73.5 ± 23.0	93.0 ± 32.6	<0.0001
HDL-C (mg/dl)	50.2 ± 14.2	46.7 ± 13.4	<0.05
Triglyceride (mg/dl)	78.4 ± 31.7	191.9 ± 66.7	<0.005
AST (mg/dl)	18.2 ± 4.9	24.6 ± 6.4	<0.0001
ALT (mg/dl)	14.0 (10.0)	18.0 (14.0)	<0.001

SD: standard deviation; Total-C: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table II. *Thyroid function tests and related antibodies (*n = *47)*

	Pretreatment Mean ± SD or Median (IR)	Posttreatment Mean ± SD or Median (IR)	*p*-value
fT3 (pg/ml)	3.3 ± 0.5	2.9 ± 0.4	<0.001
fT4 (ng/dl)	1.0 ± 0.2	1.0 ± 0.2	0.086
TSH (mIU/l)	2.0 ± 0.8	1.7 ± 0.9	<0.02
TRAb (U/l)	8.5 ± 1.3	8.1 ± 1.3	<0.02
Thyroglobulin (ng/ml)	7.2 ± 4.6	7.5 ± 5.5	0.526
Anti-Tg (IU/ml)	5.4 (2.3)	5.0 (1.02)	0.108
Anti-TPO (IU/ml)	2.5 (3.3)	2.5 (2.4)	0.292

SD: standard deviation; fT3: free T3; fT4: free T4; TSH: thyroid-stimulating hormone; TRAb: thyroid-stimulating hormone receptor antibody; Anti-Tg: anti-thyroglobulin; Anti-TPO: anti-thyroid peroxidase.

DISCUSSION

In this study, we found that ISO treatment induced several changes in the hormonal status of acne patients: TSH, fT3, cortisol, ACTH, LH, total testosterone and prolactin levels declined significantly after 3 months of treatment (see Table III).

Very few clinical studies have investigated the effects of retinoids on pituitary hormone levels. Angioni et al. (11) studied the effects of the aromatic retinoid acitretin on pituitary hormone levels in eleven adult male psoriasis patients. They found significant decreases in TSH, fT3 and prolactin levels after treatment, consistent with our results. They did not, however, detect changes in cortisol, testosterone, LH or FSH levels, which may reflect the use of another retinoid and the smaller patient group in this study compared to our study.

To our knowledge, this is the first study investigating the effects of ISO on thyroid hormone levels. Decreases in TSH and fT3 levels may be caused by central hypothyroidism due to RXR-mediated suppression of TSHβ gene expression, as previously shown for bexarotene (12). However, it is unclear whether treatment of acne with ISO generates enough 9-cis-isomers to account for any RXR-mediated effect. Although the decrease in TRAb levels after ISO treatment was statistically significant, the size of the change (average 4%) may not be clinically important in individuals without thyroid disease.

Table III. *Pre- and posttreatment evaluation of pituitary-adrenal axis and sex hormones (*n = *47)*

	Pretreatment Mean ± SD or Median (IR)	Posttreatment Mean ± SD or Median (IR)	*p*-value
Estradiol (pg/ml)	84.0 (75.0)	67.0 (95.5)	0.615
FSH (mIU/ml)	6.0 ± 3.6	5.9 ± 2.5	0.874
LH (mIU/ml)	8.1 (11.6)	6.7 (6.0)	< 0.02
Prolactin (ng/ml)	13.3 ± 5.7	11.6 ± 4.4	< 0.02
Progesterone (ng/ml)	1.9 (3.8)	1.5 (2.6)	0.791
17-hydroxyprogesterone (ng/ml)	2.3 (2.1)	2.3 (2.2)	0.191
Total testosterone (ng/ml)	0.7 (0.4)	0.5 (0.4)	< 0.005
DHEAS (μg/dl)	217.6 ± 104.9	205.6 ± 80.0	0.354
Free testosterone (pg/ml)	2.9 (2.0)	2.5 (1.1)	0.338
SHBG (μmol/l)	40.6 ± 19.8	51.7 ± 34.1	0.055
Cortisol (μg/dl)	13.1 ± 5.2	11.0 ± 5.8	< 0.005
ACTH (pg/ml)	28.9 ± 17.0	24.9 ± 13.6	< 0.05

SD: standard deviation; FSH: follicle-stimulating hormone; LH: luteinising hormone; DHEAS: dehydroepiandrosterone sulfate; SHBG: sex hormone-binding globulin; ACTH: adrenocorticotropic hormone.

It has been demonstrated that retinoids are able to induce the transcription of the dopamine receptor type 2 (D2R) gene in cultured pituitary cells, this effect being due to the presence of a functional retinoic acid response element (RARE) in the D2R promoter (13). The decrease in the levels of prolactin following ISO treatment may be related to an increase in central dopaminergic tonus. In a previous study, we showed that IGF-1 and IGFBP-3 levels also decrease following ISO treatment (14), responses that may also have stemmed from an increase in dopaminergic tonus.

Retinoic acid has been shown to inhibit proliferation and induce differentiation and apoptosis in different cell types (15). Some of these effects result from reduced binding of the transcription factors AP-1 and Nur77 to their cognate DNA sites (16, 17). These factors are also essential in the control of the *POMC* gene, which is the precursor for both ACTH and α-MSH (18–20). Páez-Pereda et al. (21) have shown that ATRA inhibits ACTH secretion both *in vitro* and *in vivo* through an effect on *POMC* transcription, and also inhibits ACTH-secreting tumour cell development and proliferation. They found that retinoic acid inhibits the transcriptional activity of AP-1 and the orphan receptors Nur77 and Nurr1 in ACTH-secreting tumour cells. They also showed that, in adrenal cortex cells, retinoic acid inhibits corticosterone production and cell proliferation. Castillo et al. (22), meanwhile, demonstrated the effectiveness of 9-cis retinoic acid for treating Cushing's disease in dogs. We speculate that these molecular mechanisms may contribute to the observed decreases in the levels of both ACTH and cortisol following ISO treatment.

We do not know the reasons behind the declines in LH and total testosterone levels in our study. Few studies have investigated the effects of retinoids on androgen metabolism. One previous study reported decreases in the levels of testosterone and the precursor androgen androstenedione in 6/9 acne patients after 12 weeks of ISO therapy (23). However, these researchers did not observe a significant change in LH levels. In a laboratory study, ATRA was found to decrease both basal and LH-stimulated testosterone secretion in cultured testicular cells, these effect being mediated by RARα receptors (24).The decrease in testosterone levels may at least partly explain the effectiveness of this medica-

tion for treating acne. Androgens are important in the pathogenesis of acne because they enhance follicular keratosis and influence sebum production (25). Several studies have demonstrated hyperandrogenaemia in patients with acne vulgaris, typically in conjunction with other clinical signs of hyperandrogenism such as hirsutism, alopecia and/or menstrual disturbances. Estrogen treatments effectively combat acne by lowering levels of androgens, (25) and counteracting their effects on the sebaceous gland. Reducing testosterone levels may also be beneficial in polycystic ovary syndrome, in which hyperandrogenaemia is a well-known pathogenic mechanism.

In conclusion, we have shown in this study that short-term ISO treatment results in mild suppression of pituitary hormones. This effect may be related to the effectiveness of this medication in acne treatment. We propose that retinoids may be tested in the future in the treatment of different pituitary diseases.

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