Net Study

Effects of isotretinoin on the thyroid gland and thyroid function tests in acne patients: A preliminary study

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ABSTRACT

Background: Isotretinoin is widely used in the treatment of acne. **Aims:** We investigated the effects of isotretinoin on thyroid function tests and thyroid volume in acne patients. **Methods:** In this prospective study, a total of 104 acne patients were included. Sixty-six patients were treated with isotretinoin for at least 4 months. Thirty eight patients were included in the control group. The levels of thyroid stimulating hormone, free triiodothyronine, free thyroxine, antithyroglobulin and antithyroid peroxidase antibodies were measured and a thyroid ultrasound was performed in all the subjects before treatment and 4 months after treatment. A "p" value of < 0.05 was considered significant. **Results:** In the isotretinoin-treated group, thyroid stimulating hormone levels increased significantly during isotretinoin treatment (P = 0.018). Free triiodothyronine, free thyroxine, anti-thyroid peroxidase levels and thyroid volume decreased significantly during treatment (P = 0.016, P = 0.012, P = 0.006, P = 0.020 respectively). **Limitations:** The major limitation of this study is the lack of follow-up data after the cessation of isotretinoin therapy in acne patients. **Conclusion:** Patients treated with isotretinoin should be monitored with thyroid function tests.

Key words: Acne, isotretinoin, thyroid function test, thyroid volume, vitamin A

INTRODUCTION

Isotretinoin (13-cis retinoic acid), a biologically active metabolite of vitamin A, has been used in the treatment of moderate or severe nodulocystic acne, disorders of sebaceous gland and keratinization and in the prevention of skin cancer.[1-3]

With the increasing use of isotretinoin, especially for the treatment of acne vulgaris and other disorders, the interest in the effect of this retinoid on other organs and the metabolic system has increased considerably.

The effect of vitamin A on the synthesis of thyroid hormone has been known for many years. In 1947, Simkins demonstrated successful treatment of patients with hyperthyroidism with a massive dose of vitamin A.[4] Our literature search revealed three reports about the effects of isotretinoin on thyroid function.[5-7] We evaluated the effects of isotretinoin on thyroid function tests and thyroid volume in acne patients with normal thyroid function. To our knowledge, this is the first clinical study investigating the effects of isotretinoin on both the thyroid function and thyroid volume

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.182794

METHODS

Patients

This prospective study included 104 patients who presented to our dermatology clinic with moderate

How to cite this article: Uyar B, Solak A, Saklamaz A, Akyildiz M, Genç B, Gökduman A. Effects of isotretinoin on the thyroid gland and thyroid function tests in acne patients: A preliminary study. Indian J Dermatol Venereol Leprol 2016;82:587-8.

Received: May, 2015. **Accepted:** December, 2015.

or severe nodulocystic acne between April 2012 and December 2014. Among them, sixty-six patients were treated with isotretinoin for at least 4 months. A control group of 38 patients with moderate or severe nodulocystic acne, matched for age, gender and body mass index was recruited.

Patients with any of the following features were excluded from the study: history of smoking, abnormal blood pressure, body mass index >30 kg/m^2, current use of vitamin A supplements, previous therapy with oral retinoids or hormone therapy for any reason in the last 3 months, previously diagnosed thyroid or pituitary disease, pregnancy, coronary artery disease, diabetes mellitus, chronic renal failure and rheumatic disease. Patients with a recent history of psychiatric, mood or depressive disorders were also excluded from the study.

The baseline thyroid volumes of the subjects in both groups were within normal limits.

The study was approved by the local Medical Ethical Committee and was conducted according to the ethical principles of the Declaration of Helsinki. All the study patients gave written, informed consent to participate.

Isotretinoin therapy

Isotretinoin therapy was initiated at a dose of 0.5–0.8 mg/kg body weight. The drug was administered to acne patients twice daily with meals. Treatment was continued for at least 4 months. Patients in the control group did not receive treatment.

Biochemical parameters

In the study group, biochemical parameters and thyroid volume were screened prior to initiation (pre-treatment) and 4 months after the start of isotretinoin treatment (post-treatment). In the control group, biochemical parameters and thyroid volume were screened at the beginning of the study and repeated after 4 months. These parameters were: free triiodothyronine, free thyroxine, thyroid stimulating hormone, anti-thyroid peroxidase and antithyroglobulin.

Fasting blood samples were obtained by venepuncture of the large antecubital veins after a12-h fasting period. The samples were centrifuged immediately, the plasma separated and all samples were studied using the same kits. Free triiodothyronine (normal 2.3–4.2 pg/ml), free thyroxine (normal 0.98–1.63 ng/dl), thyroid stimulating hormone (normal 0.35–5.5 uU/ml), anti-thyroid peroxidase (normal 0–34 IU/ml) and antithyroglobulin (normal 5–115 IU/ml), were measured using electrochemiluminescent immunoassay methods.

Assessment of thyroid volume

Thyroid measurements were performed using a real-time ultrasound scanner with a 7.5 MHz, 50 mm linear transducer. Patients were examined in a supine position with the neck maximally extended.

Longitudinal and transverse scans of each thyroid lobe and isthmus were performed to obtain length, width and depth in centimeters. The thyroid volume was calculated by adding the volumes of each lobe and the isthmus. The lobar volume was calculated using the rotation ellipsoid model formula 14.15: V_{Lobe} (ml) = $\pi/6$ × width of the lobe (cm) × depth of lobe (cm) × length of the lobe (cm). The isthmus volume was calculated using the following formula: $V_{Isthmus}$ (ml) = $\pi/6$ × width of the isthmus (cm) × depth of isthmus (cm) × length of the isthmus (cm).

Statistical analyses

The normality of data was analyzed using the Kolmogorov–Smirnov test. All numerical variables with a normal distribution were expressed as the mean ± standard deviation while data that was not normally distributed was expressed as the median (interquartile range). For comparison between the pre- and post-treatment data of the treatment group and between the initial data and the data obtained after 4 months of the control group, the paired sample *t*-test was used for homogenous data. A Wilcoxon signed rank test was used for analysis of non-homogenous data. The statistical analyses were carried out using the Statistical Package for the Social Sciences version 20 (SPSS, Chicago, IL, USA).

RESULTS

There were 14 (21.2%) males and 52 (78.8%) females in the isotretinoin-treated group and 8 (21.1%) males and 30 (78.9%) females in the control group not treated with isotretinoin. The mean age of the isotretinoin-treated group was 22.68 ± 4.51 years (age range of 18–36 years). The mean age of the control group was 23.82 ± 4.38 years (age range of 18–39 years). Comparisons of the thyroid function tests and thyroid volumes before and after isotretinoin treatment in the isotretinoin-treated group and the initial and

later values in the control group are summarized in Table 1. We found that levels of thyroid stimulating hormone (P = 0.018) increased significantly during isotretinoin treatment. Free triiodothyronine, free thyroxine and anti-thyroid peroxidase levels as well as thyroid volumes decreased significantly during treatment in acne patients (P = 0.016, P = 0.012, P = 0.006, P = 0.020 respectively). There was no significant difference in the levels of antithyroglobulin. Pre-treatment and post-treatment values of thyroid stimulating hormone [Figure 1] and thyroid volume [Figure 2] have been represented as box- plots.

In the control group, there was no statistically significant difference between the initial and later values of thyroid stimulating hormone, free triiodothyronine, free thyroxine, anti-thyroid peroxidase, antithyroglobulin levels and thyroid volume (P = 0.532, P = 0.357, P = 0.539, P = 0.722, P = 0.952, P = 0.249 respectively).

DISCUSSION

It has long been known that high doses of vitamin A can interfere with the effects of thyroid hormone metabolism. Sadhu and Brody demonstrated a 10% decrease in oxygen consumption, a depressed metabolic rate and, interestingly, a 35% decrease of thyroid weight in euthyroid rats given high doses of vitamin A.[8]

The effect of vitamin A and retinoids on the hypothalamic-pituitary-thyroid axis has been well recognized but poorly understood.[9,10]

Retinoids can affect cell growth, differentiation, function and metabolism via two groups of nuclear hormone receptors: retinoic acid receptors and retinoid X receptors. These receptors also mediate the activity of steroid and thyroid hormones.[11]

Recent studies have shown that hypothalamic-pituitary-thyroid function is primarily affected by retinoid X receptor-selective retinoids (called rexinoids).[12,13] *In vitro* studies, animal models and human trials have demonstrated that rexinoids can suppress thyroid stimulating hormone.[12-17] The effects of retinoids on thyroid function and thyrotrope function appear to be through a retinoid X receptor-mediated or rexinoid pathway.[9,10,12,13,16] Isotretinoin, a biologically active metabolite of vitamin A, is a weak retinoic acid receptor agonist. Janssen *et al*. suggested that although retinoid X receptor-selective retinoids suppress the thyroid stimulating hormone (TSH) level, retinoic acid receptor-selective retinoids such as isotretinoin may not suppress it.[18] The observation in our study that thyroid stimulating hormone levels increased in parallel with isotretinoin therapy supports the hypothesis that isotretinoin affects thyroid gland by different mechanisms than retinoid X receptor-selective retinoids.

A literature review revealed three clinical studies studying the effects of isotretinoin on thyroid function which had differing results .[5-7] The results of our study and previous trials examining the effects of isotretinoin treatment on thyroid gland are summarized in Table 2.

Marsden *et al*. studied seven patients with severe rosacea who received isotretinoin 1 mg/kg/day for 12 weeks and found a significant decrease in total thyroxine, free thyroxine index and total triiodothyronine. They found that mean total triiodothyronine declined from

Table 1: The values of thyroid function tests, related antibodies and thyroid volumes in isotretinoin-treated group (n=66) and control group (n=38)

Laboratory parameters	Mean±SD or median (IR)		*P*	Mean±SD or median (IR)		Control group *P*
	Pre-treatment	Post-treatment		Control group initial	Control group after	
TSH (mIU/L)	1.84±1.02	2.27±1.07	0.018	1.61±0.71	1.70±0.98	0.532
FT3 (pg/ml)[a]	3.28 (0.79)	3.11 (0.47)	0.016	2.91 (3.21)	2.96 (3.50)	0.357
FT4 (ng/dl)	1.20±0.26	1.07±0.19	0.012	1.16±0.25	1.19±0.36	0.539
Anti-TPO (IU/ml)[a]	13.34 (20.77)	7.65 (8.23)	0.006	19.50 (57.25)	19.17 (75.77)	0.722
Anti-Tg (IU/ml)[a]	10.25 (26.65)	13.11 (8.50)	NS	27.59 (57.25)	25.45 (61.67)	0.952
Thyroid volume (ml)	9.46±2.10	8.95±1.91	0.020	8.48±0.95	8.44±0.91	0.249

[a]A Wilcoxon signed ranks test was used for comparison of anti-TPO, anti-Tg, FT3 levels and a paired samples *t*-test was used for other parameters. SD: Standard deviation, FT3: Free triiodothyronine; FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, Anti-Tg: Anti-thyroglobulin, Anti-TPO: Anti-thyroid peroxidase, NS: Not significant. IR: Interquartile range

2.2 nmol/L (pre-therapy) to 2.0 nmol/L at 12 weeks of therapy and continued to fall, reaching a nadir of 1.8 nmol/L 4 weeks after stopping therapy. They found no significant change in serum thyroid stimulating hormone (TSH) from the basal state.[5]

O'Leary *et al.* studied 24 women with acne vulgaris who received isotretinoin 1 mg/kg/day for 16 weeks. They studied serum free thyroxine, total triiodothyronine (before and 16 weeks after the therapy) and thyroid stimulating hormone (before and 8 weeks after the therapy). There was no significant change in serum free thyroxine. Like Marsden *et al.*, they did not find a significant change in thyroid stimulating hormone with up to 8 weeks of therapy. In contrast, O'Leary *et al.* observed no significant change in total triiodothyronine.[6]

Karadag *et al.* initiated isotretinoin 0.5–0.75 mg/kg in 47 acne patients. They found that levels of free triiodothyronine, thyroid stimulating hormone and thyroid stimulating hormone receptor antibody decreased significantly at 3 months of isotretinoin therapy. Karadag *et al.* stated that there were no significant changes in the levels of thyroglobulin, antithyroglobulin or anti-thyroid peroxidase after commencing isotretinoin treatment.[7] In contrast to the above studies, our study revealed a statistically significant increase in thyroid-stimulating hormone ($P = 0.018$).

Several studies have indicated that isotretinoin and other retinoids affect cell cycle progression, differentiation, apoptosis and cell survival in a variety of cell types.[19-25] Interestingly, isotretinoin treatment of mice results in both decreased hippocampal neurogenesis and a reduction in the hippocampal volume.[23,24] The reason for the increase in thyroid stimulating hormone observed in our study may be a reduction in thyroid volume as a result of the direct apoptotic effect of isotretinoin on the thyroid cells. Isotretinoin is known to increase iodine uptake in thyroid cancers, facilitating therapy.[26-28] This effect may also have induced volume reduction in the thyroid gland. As a result of the reduction in thyroid volume, free triiodothyronine and free thyroxine levels may have decreased and thyroid stimulating hormone level may have increased.

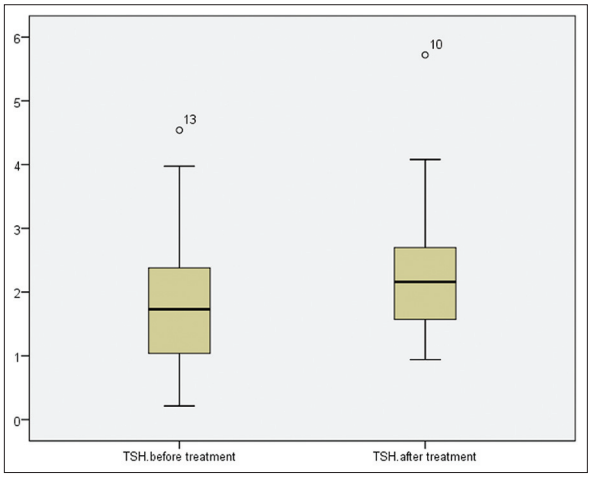

Figure 1: Pre- and post-treatment values of thyroid stimulating hormone levels are presented by box- plots graphics

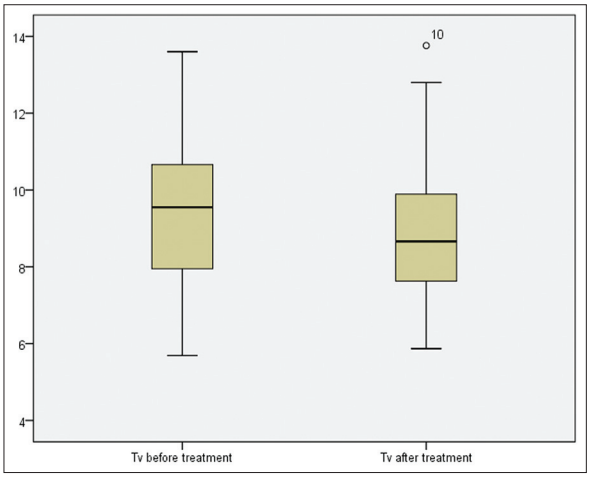

Figure 2: Pre- and post-treatment values of thyroid volume levels are presented by box- plots graphics

Table 2: Previous clinical trials and our study examining the effects of isotretinoin on thyroid gland

Study	Patients	Dose/duration	Decreased	Increased	No change
Marsden *et al.*[5]	7 rosacea patients	1 mg/kg/day/12 weeks	TT4, TT3, free thyroxin index		TSH
O'Leary *et al.*[6]	24 women with acne	1 mg/kg/day/12 weeks (for TSH 8 weeks)			TSH, FT3, FT4
Karadag *et al.*[7]	47 acne patients	0.5-0.75 mg/kg/day/12 weeks	FT3, TSH, TRAb		Thyroglobulin, anti-Tg, anti-TPO, FT4
Uyar *et al.*	66 acne patients	0.5-0.8 mg/kg/day/16 weeks	FT3, FT4, anti-TPO, thyroid volume	TSH	Anti-Tg

FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, Anti-Tg: Anti-thyroglobulin, Anti-TPO: Anti-thyroid peroxidase, TRAb: Thyroid-stimulating hormone receptor antibody

We enrolled patients with normal thyroid function. None of the patients experienced clinical symptoms of hypothyroidism such as increased sensitivity to cold, unexplained weight gain, puffy face, hoarseness, thinning hair, slowed heart rate or impaired memory after isotretinoin therapy for 4 months. Some of the symptoms were ignored because they might also occur as a result of isotretinoin treatment such as fatigue, dry skin, depression, muscle weakness, elevated blood cholesterol level, muscle aches, tenderness and stiffness and constipation. However, drug usage in patients who have thyroid dysfunction or are clinically hypothyroid may worsen metabolic pathology and induce irreversible hypothyroidism.

The major limitation of this study is the lack of follow-up data after the cessation of isotretinoin therapy. Another limitation is that we could not analyze men and women separately.

In conclusion, the increasing number of studies assessing the effects of isotretinoin on the thyroid gland will help clinicians to predict its side effects and to plan treatment accordingly. The next step in generating such data could possibly be expanding our study to include more patients and a longer follow-up.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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