Should human chorionic gonadotropine treatment increase thyroid volume?

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ABSTRACT

Objective: Our aim was to investigate the thyroid function tests and thyroid volume differences among males with isolated hypogonadotropic hypogonadism (IHH) who take androgen replacement treatment (ART). **Materials and methods:** Forty-four male with IHH with a mean age 33.2 (18-54), diagnosed in Endocrinology and Metabolism Department between September 2013 and September 2014 and 40 healthy male control with a mean age 27.77 (18-55) were involved to study. Patient group was divided to testosterone-treated patients (n = 19) and human chorionic gonadotropine (hCG)-treated patients (n = 25). Patient group was compared in terms of total testosterone, thyroid function tests [thyroid stimulating hormone (TSH), free thyroxine (fT_4)] and thyroid volume, before and 6 months after treatment. Patient group was compared with control group as well. **Results:** When we compared the patient group with the control group, there was no significant difference for age, Body mass index, TSH, fT_4 and thyroid volume between two groups before treatment. There was no difference in terms of TSH, but fT_4, testosterone levels and thyroid volume were significantly higher after treatment, when the patient group was compared before and after treatment (p < 0.05). When we compared testosterone-treated patients and hCG-treated patients; thyroid volume was higher among hCG-treated patients (p = 0.001) but there was no difference for thyroid volume before and after testosterone treatment (p > 0.05). There was no statistically significant correlation between testosterone levels with TSH, fT_4 and thyroid volume (r = 0.09, p = 0.32; r = 0.14, p = 0.11; r = 0.15, p = 0.09, respectively). **Conclusion:** Our study showed that ART increases the thyroid volume especially in hCG-treated patients. Therefore, we suggest that thyroid volume changes should be followed up in hCG-treated patients. Arch Endocrinol Metab. 2015;59(6):482-6

INTRODUCTION

Isolated hypogonadotropic hypogonadism (IHH) may present as an isolated hormonal deficiency (low testosterone and low or normal levels of gonadotropins) secondary to hypothalamic or pituitary defects (1). The goals of therapy for IHH in adolescent or young adult males include the induction of normal puberty and testicular development that allow future fertility. Androgen replacement treatment (ART) that includes testosterone and gonadotropins are used in these patients (2).

Human chorionic gonadotropin (hCG) is a glycoprotein hormone that has structural similarity to thyroid stimulating hormone (TSH). The beta subunit of hCG is unique to hCG but alpha-subunit is identical to that luteinizing hormone (LH), follicle stimulating hormone (FSH) and TSH (3). Human chorionic gonadotropin has thyroid-stimulating activity in bioassays in mice, rats, chicks and men (4-6). The thyroid-stimulating activity of a commercial preparation of hCG was first demonstrated by Burger in a mouse bioassay (7). Subsequently, thyrotrophic activity has been found in several hCG preparations (4,5). These studies showed that hCG is the molar TSH and that 1 Unite hCG has intrinsic thyrotrophic activity equivalent to approximately 0.5 µU TSH in the Mouse bioassay (4). Additionally, hCG stimulates iodide uptake, adenylate cyclase, and DNA synthesis in cultured rat thyroid cells (8). Many investigations have detected that hCG and TSH share not only structural homology but also their receptors show structural similarity as well, and this homology suggests the basis for

the reactivity of hCG with the TSH receptor (9,10). Therefore, high hCG concentrations are associated with thyroid stimulation, both functionally (lower serum TSH concentrations) and anatomically (increased thyroid volume) (11).

There are several conflicting results about the effect of ART on thyroid function tests among males with hypogonadism. Several studies also showed that androgen administration may be associated with increased (12), decreased (13) or unaltered (14) TSH response to thyrotropin-releasing hormone (TRH). But most studies evaluated only patients with primary hypogonadism. So we aimed to investigate whether both hypogonadism and ART (especially hCG) effect the thyroid function tests and thyroid volume in males with IHH.

MATERIALS AND METHODS

Male patients with IHH and healthy male controls who were admitted to Endocrinology and Metabolism Clinic at Kahramanmaras Sutcu Imam University Hospital were included in the study. The study was approved by the ethics committee of Kahramanmaras Sutcu Imam University.

Subjects and study protocol

Forty-four male with IHH (patient group) with a mean age 33.2 (18-54) that was diagnosed in Endocrinology and Metabolism Department in Kahramanmaras (a mild iodine deficient city in Turkey) between September 2013 and September 2014 and 40 healthy male control (control group) with a mean age 27.77 (18-55) were involved to study. Patient group was divided into two goups; treated with testosterone (n = 19) and HCG group (n = 25). Patient group was compared in terms of body mass index (BMI), total testosterone (TT), thyroid function tests [TSH, free thyroxine (fT_4)] and thyroid volume, before and 6 months after treatment. These parameters were evaluated between patient and control group as well.

Inclusion criteria

Isolated hypogonadotropic hypogonadism was defined as the presence of clinical symptoms related to hypogonadism (*e.g.* incomplete or delayed sexual development, reduced libido and erectile dysfunction/infertility) and low serum TT levels (< 250 ng/dL), insufficient LH (i.e. low or non-elevated levels), the absence of any

other anterior and/or posterior pituitary hypofunction and pathological findings on a pituitary magnetic resonance image (1).

Exclusion criteria

Patients with previously known history of thyroid disease or receiving any drugs affecting thyroid gland, those with hyperthyroidism, primary or secondary hypothyroidism, euthyroid or hypothyroid Hashimato's disease, thyrotoxicosis (factitia, subacute thyroiditis), and those receiving L-thyroxin suppression therapy, bromocriptine, somatostatin, anti-thyroid drugs, lithium, interferon, perchlorate, and sulfonamides were excluded. Moreover, patients who underwent radiological examination with an iodinated contrast medium within at least 3 days, those who last received drugs including iodine 7 days ago, and those who underwent thyroid operation or received radioactive iodine were not included in the study. Patients with systemic illnesses were excluded, in addition to those who took excessive exercise, used certain medications or as these could affect the metabolism of testosterone and testosterone levels. Secondary causes of hypogonadotropic hypogonadism, such as panhypopituitarism, hyperprolactinaemia and intracranial masses, were excluded before making a diagnosis of IHH.

Biochemical analyses

Blood samples was collected in the morning between 08.00–09.00 hours after an overnight fast to avoid differences because of diurnal variation, especially for hormonal parameters. Normal reference values were as follow FSH (1.42–15.4 mIU/ml), LH (1.24–7.8 mIU/mL), TT (280-1100 ng/dL), prolactin (3–14.7 ng/mL), TSH (0.4-4.2 µIU/mL), fT_4 (0.8-2.7 ng/dL) and Cortisol (5-23 µg/dL). Hormone analyses were carried out using chemiluminescence enzyme immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA, or UniCel DxI 800, Beckman Coulter CA, USA) commercial kits.

Conventional thyroid ultrasonography

Conventional thyroid ultrasonography (US) was performed before and 6 month after the treatment. Each participants underwent a preliminary ultrasonography and it was investigated whether there was any abnormality such as a nodule or parenchymal heterogeneity. All grey scale measurements were performed by the same

endocrinologist with the same US device (Logic P5 System, GeneralElectric Medical Systems, Milwaukee, WI, USA) using a linear transducer of 12 MHz width. While the participant was lying in supine position with the neck in hyperextension, the skin was covered with acoustic material. The thyroid gland was scanned in three dimensions. Depth, width (in transverse plane), and length (in longitudinal plane) of each lobe were measured. Volume of each lobe was calculated using the formula, volume (mL) = $\pi/6$ x width x depth x length (15). Total volume was determined as the sum of the volumes of the lobes except for the isthmus.

Statistical evaluation

The SPSS for Windows (ver. 11.0.; Chicago, IL, USA) was used for statistical analysis. The Student's t-test was used to compare independent variables and dependent variables that were in accordance with a normal distribution, and the variables were expressed as the mean ± standard deviation. Direct relationship between variations was evaluated with pearson correlation test. $P < 0.05$ was defined as statistically significant.

RESULTS

Forty-four male patients with IHH and 40 healthy male controls were involved to the study. The baseline characteristics and thyroid function tests, TT levels, thyroid volume of the male patient with IHH and control group are summarized in table 1. There was no significant difference in terms of age, BMI, TSH, fT_4 and thyroid volume between control group and pre-treatment patient group ($p < 0.05$), but TT levels were significantly lower in patient group ($p < 0.05$).

Total testosterone levels, thyroid function tests and thyroid volume changes, before and after treatment, in patient group were summarized in table 2. In patient group, there was no significant difference according to TSH levels, before and after treatment ($p > 0.05$), but fT_4, TT levels and thyroid volume (8.76 ± 1.13 mL and $9.02 \pm 0,99$ mL; before and after treatment, respectively) were significantly higher after treatment ($p = 0.001$).

We also analyzed the patients according to the treatment type (Table 3). In hCG-treated group, thyroid volume was significantly higher after treatment ($8.28 \pm$

Table 1. The baseline characteristics and thyroid function tests, total testosterone levels, thyroid volume of the male patients with IHH and controls

Parameters	Patient group (n = 44)	Control group (n = 40)	p
Age (year)	32.47 ± 9.30	28.77 ± 9.68	0.078
BMI (kg/m²)	27.33 ± 6.61	26.5 ± 7.06	0.605
FSH (mIU/mL)	1.82 ± 1.68	5.1 ± 2.21	< 0.001
LH (mIU/mL)	1.44 ± 1.24	3.71 ± 1.50	< 0.001
TT (ng/dL)	98.65 ± 69.69	460.52 ± 90.36	< 0.001
TSH (mIU/mL)	1.41 ± 0.79	1.70 ± 0.94	0.133
fT_4 (ng/dL)	1.16 ± 0.19	1.10 ± 0.14	0.128
Prolactin (ng/mL)	7.64 ± 3.39	7.85 ± 2.77	0.772
Cortisol (mcg/dL)	19.23 ± 1.14	19.36 ± 1.22	0.623
GH (ng/mL)	1.86 ± 0.55	2.04 ± 0.75	0.261
TV (mL)	8.62 ± 1.46	8.78 ± 0.81	0.558

IHH: ısolated hypogonadotropic hypogonadism; BMI: body mass ındex; FSH: follicle stimulating hormone; LH: luteinizing hormone; TT: total testosterone; TSH: thyroid stimulating hormone; fT_4: free thyroxine; GH: growth hormone; TV: thyroid volume.

Table 2. Total testosterone levels, thyroid function tests and thyroid volume changes before and after treatment in patient group

Parameters	Before treatment n = 44	After treatment n = 44	p
BMI (kg/m²)	27.3 ± 3.90	27.1 ± 5.10	0.620
TT (ng/dL)	98.65 ± 69.70	434.83 ± 138.64	< 0.001
TSH (mIU/mL)	1.45 ± 0.75	1.39 ± 0.56	0.627
fT_4 (ng/dL)	1.16 ± 0.19	1.34 ± 0.49	0.024
TV (mL)	8.76 ± 1.13	9.02 ± 0.99	0.001

BMI: body mass index; TT: total testosterone; TSH: thyroid stimulating hormone; fT_4: free thyroxine; TV: thyroid volume.

1.04 mL and 8.68 ± 0.95 mL, before and after treatment, respectively) (p = 0.001), but in group treated with testosterone, thyroid volume was similar before and after treatment (9.39 ± 0.95 mL and 9.47 ± 0.88 mL, respectively) (p > 0.05). There was no significant difference according to TSH levels in hCG-treated group compared before and after treatment (p > 0.05), but there was a borderline significant higher fT$_4$ levels after treatment (p = 0.057). In group treated with testosterone, fT$_4$ and TSH levels were not significantly different before and after treatment (p > 0.05).

When we analysed both patient (n = 44) and control group (n = 40) there was no significant correlation between TT levels and TSH, fT$_4$, thyroid volume (r = 0.09, p = 0.32; r = 0.14, p = 0.11; r = 0.15, p = 0.09, respectively).

DISCUSSION

Isolated hypogonadotropic hypogonadism is a rare but treatable disease. Androgen replacement treatment (testosterone or gonadotropin treatment) have been used to in these patients (2). There was limited data about the effects of sex hormones and hCG on thyroid functions and thyroid volume among hypogonadal male patients (14,16-18). Spitz and cols. (16), evaluated the effect of estrogens and androgens on TSH secretion in hypogonadal male and female patients. Male patients showed a transient reduction in serum T4 during hCG therapy. In this study, the male patients with hypogonadism had TSH responses to TRH similar to those of the male controls. Sowers and cols. (17), found that there were no significant changes in serum T4, T3, or TSH in euthyroid men that was under hCG treatment in the supraphysiological doses. In this study, commercial hCG in doses of 100,000 and 150,000 IU produced a small thyroid-stimulating effect. Additionally, Burman

and cols. (14), showed that testosterone treatment had no significant effect on any of thyroid parameters in the patients with the Klinefelter's syndrome. On the contrary, Morley and cols. (18), mentioned that androgen administration has been reported with decreased TSH responses to TRH in the men with primary hypogonadism. In our study, TSH and fT$_4$ levels were similar between healthy controls and male patients with IHH (before treatment). After ART, TSH levels didn't change significantly but fT$_4$ levels increased significantly. In subgroup analysis we detected that this fT$_4$ increase was due to group treated with hCG, so we speculated that this increase may be due to thyrotrophic activity of hCG. In group treated with hCG, fT$_4$ levels increased after treatment but still within the normal range and this may be the cause of similar TSH levels before and after treatment.

Hyperthyroidism or increased thyroid function have been reported in many patients with trophoblastic tumors. These cases, considerably increased hCG levels and suppressed TSH levels suggest that hCG has thyrotropic activity. Human chorionic gonodotropine and human TSH belong to the biochemically closely related glycoprotein hormone family, they are potentially cross-reactive at the receptor level (8). *In vitro*, hCG has a weak intrinsic thyroid-stimulating activity, being able to stimulate iodine uptake, generation of cAMP, 3,5,3'-triodothyronine secretion, and even growth of thyroid cells (19-21). In our study thyroid volume was similar between healthy control and male patients with IHH (before treatment). But after treatment thyroid volume significantly increased in patient group (p < 0.05). In subgroup analysis there was no thyroid volume difference in testosterone-treated group but in group treated with hCG there was a significant increase (p = 0.001). We think that this change was due to thyroid-stimulating activity of hCG as well.

Table 3. Body mass index, total testosterone levels, thyroid function tests and thyroid volume changes according to the treatment type

Parameters	TT group Pre-treatment n = 19	TT group Post-treatment n = 19	HCG group Pre-treatment n = 25	HCG group Post-treatment n = 25	p*	p**
BMI (kg/m²)	28.9 ± 5.1	28.46 ± 4.03	27.5 ± 6.6	27.97 ± 9.12	0.834	0.915
TT (ng/dL)	133.04 ± 72.87	446.10 ± 155.24	72.52 ± 55.43	426.26 ± 127.23	< 0.001	< 0.001
TSH (mIU/mL)	1.65 ± 0.88	1.41 ± 0.45	1.30 ± 0.60	1.37 ± 0.63	0.296	0.540
FT$_4$ (ng/dL)	1.21 ± 0.19	1.31 ± 0.31	1.12 ± 0.18	1.36 ± 0.60	0.227	0.057
TV (mL)	9.39 ± 0.95	9.47 ± 0.88	8.28 ± 1.04	8.68 ± 0.95	0.374	0.001

TT: total testosterone; HCG: human chorionic gonadotropin; BMI: body mass index; TSH: thyroid stimulating hormone; fT$_4$: free thyroxine; TV: thyroid volume.

* The statistical comparison of pre and post-treatment in the group treated with testosterone; ** The statistical comparison of pre and post-treatment in the group treated with HCG.

Several physiological and pathological factors as iodine supply, age, sex, weight, height, BMI, and body surface area can influence thyroid volume (22). Thyroid volume is reported to increase dependent to age or body surface (23). In addition to, in an iodine replete area, thyroid volume was inversely related to the median urinary iodide (24). In our study, there was no significant difference according to BMI and age in patient and control group. The location of the participants was the Mediterranean region and this region is a mild iodine deficient area. So we don't think that this thyroid volume difference was due to age, BMI and iodine status.

In conclusion, this is the first study investigating changes on thyroid volume and thyroid function of ART in males with IHH. Our study showed that ART increases the thyroid volume especially in patients treated with hCG. Therefore, we suggest that thyroid volume changes should be followed in patients treated with hCG. More studies are required to explain the changes of thyroid volume in males with IHH.

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