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THYROID VOLUME IN YOUNG MALES WITH IDIOPATHIC HYPOGONADOTROPIC HYPOGONADISM VERSUS YOUNG HEALTHY MALES

Ersen Karakılıç[1], Bercem Ayçiçek[2], Mazhar Müslüm Tuna[3], Mehtap Navdar Başaran[4], Mustafa Unal[5], Dilek Berker[6], Serdar Güler[7]

[1]*Canakkale Onsekiz Mart University, Medical Faculty, Endocrinology and Metabolism Division, Canakkale, Turkey*
[2]*Gazi Yasargil Training Research Hospital, Endocrinology and Metabolism Division, Diyarbakir, Turkey*
[3]*Umraniye Training and Research Hospital, Endocrinology and Metabolism Division, Istanbul, Turkey*
[4]*Kanuni Sultan Suleyman Training and Research Hospital, Endocrinology and Metabolism Division, Istanbul, Turkey*
[5]*Istinye University, Endocrinology and Metabolism Division, Istanbul, Turkey*
[6]*Ankara City Hospital, Endocrinology and Metabolism Division, Ankara, Turkey*
[7]*Liv Hospital, Endocrinology and Metabolism Division, Ankara Turkey*

ABSTRACT

Objective: *To evaluate the differences in thyroid volume and thyroid functions between male patients newly diagnosed with idiopathic hypogonadotropic hypogonadism (IHH) and healthy males.*

Material and Method: *A total of 51 consecutively diagnosed male patients with IHH (mean age: 30.1±8.9 years) and 36 body mass index (BMI)- and age-matched healthy controls (mean age: 31.3±5.9 years) were included in the study. All the subjects resided in the same region where mild iodine deficiency was present. Patients with thyroid diseases were excluded. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), IGF-1, prolactin, cortisol, total testosterone, free testosterone, free T4 (fT4), free T3 (fT3), TSH, anti-TPO, and anti-TG were evaluated. Thyroid volumes (TV) were measured using a high-resolution ultrasound operated by an experienced endocrinologist.*

Results: *FSH, LH, total testosterone and free testosterone were lower in patients with IHH than in the control subjects ($p<0.05$). TSH, fT4, fT3, anti-TPO, and anti-TG were found to be similar in both groups ($p>0.05$). Thyroid volume of patients with IHH (mean value of TV=11, 0±6.2 mL) was significantly smaller than in the control subjects (mean value of TV=18, 6±8.1 mL) ($p=0.001$).*

Conclusion: *Young males with newly diagnosed IHH have smaller thyroid volume than healthy males. Thyroid function tests were similar in both groups.*

Keywords: *Hypogonadism, thyroid gland, gonadotropins, thyroid function tests.*

CORRESPONDING AUTHOR: Ersen Karakılıç Endocrinology and Metabolism Division, Medical Faculty, Canakkale Onsekiz Mart University, Canakkale ersenkarakilic@com.edu.tr

EK https://orcid.org/0000-0003-3590-2656 **BA** https://orcid.org/0000-0001-7085-5846 **MMT** https://orcid.org/ 0000-0001-5975-7786

MNB https://orcid.org/0000-0001-7817-2871 **MU** https://orcid.org/ 0000-0001-6640-6298 **DB** https://orcid.org/0000-0002-6388-7505

SG https://orcid.org/0000-0003-2341-4794

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İDİOPATİK HİPOGONADOTROPİK HİPOGONADİZMLİ GENÇ ERKEKLERİN TİROİD HACMİNİN GENÇ SAĞLIKLI ERKEKLERLE KARŞILAŞTIRILMASI

ÖZET

Amaç: İdiyopatik hipogonadotropik hipogonadizmi (İHH) olan sağlıklı erkeklerde tiroid hacmi ve tiroid fonksiyonlarındaki farklılıkları değerlendirmek.

Materyal ve Metot: Yeni tanı konulan 51 İHH'li erkek hasta (ortalama yaş: 30,1±8,9 yıl) ve yaş (ortalama yaş: 31,3±5,9 yıl), vücut kitle indeksi(VKİ) eşleştirilmiş 36 sağlıklı erkek kontrol olarak çalışmaya dahil edildi. Tüm katılımcılar, hafif iyot eksikliğinin bulunduğu aynı bölgede oturuyordu. Tiroid hastalığı olan hastalar çalışma dışı bırakıldı. Folikül uyarıcı hormon (FSH), lüteinizan hormon (LH), IGF-1, prolaktin, kortizol, total testosteron, serbest testosteron, serbest T4 (sT4), serbest T3 (sT3), TSH, anti-TPO, anti-TG değerlendirdi. Tiroid hacimleri (TH) deneyimli bir endokrinolog tarafından yüksek çözünürlüklü bir ultrason kullanılarak ölçüldü.

Bulgular: FSH, LH, total testosteron ve serbest testosteron IHH hastalarında kontrol deneklerine göre daha düşüktü. Her iki grupta da TSH, sT4, sT3, anti-TPO, anti-TG benzer bulundu (p>0,05). İHH (ortalama TH değeri=11, 0±6,2 mL) olan hastaların tiroid hacmi, kontrol grubundakilerden anlamlı ölçüde daha küçüktü (ortalama TH değeri=18, 6±8.1 mL) (p=0,001).

Sonuç: Yeni tanı konulan İHH'lı genç erkeklerde tiroid hacmi genç sağlıklı erkeklerden daha düşüktür. Tiroid fonksiyon testleri her iki grupta benzerdi.

Anahtar kelimeler: Hipogonadizm, tiroid bezi, gonadotropinler, tiroid fonksiyon testleri.

INTRODUCTION

Idiopathic hypogonadotropic hypogonadism (IHH) is caused either by deficient production, secretion or action of gonadotropin-releasing hormone (GnRH), a key neuropeptide that orchestrates mammalian reproduction. IHH is separated into two main categories: anosmic HH (Kallmann syndrome), which is based on the presence of an impaired sense of smell, and congenital normosmic IHH. The incidence of IHH is nearly 1–10:100,000 live births, with approximately 2/3 and 1/3 of cases arising from Kallmann syndrome (KS) and idiopathic HH, respectively.[1] Isolated GnRH deficiency occurs more commonly in males than in females.[2,3]

IHH is characterized either by incomplete or absent puberty and infertility. IHH may present solely as congenital GnRH deficiency or be associated with other developmental anomalies such as cleft lip or palate, dental agenesis, ear anomalies, congenital hearing impairment, renal agenesis, bimanual synkinesis or skeletal anomalies.[4]

Patients with IHH have low testosterone levels with depressed or inappropriately normal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It is known that gonadotropins FSH, LH, and human chorionic gonadotropin (hCG) are all glycoprotein hormones made up of an alpha and a beta subunit; the alpha subunit in the gonadotropins is the same one that occurs in thyroid-stimulating hormone (TSH). Recent investigations have clarified the structural homology of not only the gonadotropins and TSH molecules, but also of their receptors, and this homology suggests the basis for reactivity of gonadotropins with TSH receptors.[5]

In recent years, several studies have investigated the effects of gonadotropin levels on the thyroid gland. Some studies showed that the administration of androgens may be associated with increased, decreased or unaltered response of TSH to thyrotropin-releasing hormone (TRH).[6-8] However, many of these studies were based on thyroid function tests in patients with primary hypogonadism. Therefore, the authors aimed to investigate whether thyroid functions and thyroid volume differs or not between males with IHH and a healthy (control) group.

MATERIAL AND METHOD

The study population comprised patients admitted to the Endocrinology and Metabolism Clinics at a Research Hospital. The hospital serves as a center for patients with rare disorders. All subjects resided in the same country.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Table 1. Clinical characteristics of the idiopathic hypogonadotropic hypogonadism (IHH) patients and controls

	IHH (N:51)	Control (n:36)	*p*
Age, year	30.1±8.9	31.3±5.9	0.318
Weight, kg	76.6±15.7	75.1±10.9	0.697
Height, cm	167.8±37.6	173.0±5.5	0.418
BMI, kg/m²	25.5±6.5	25.1±3.7	0.874

BMI: Body mass index, **IHH:** idiopathic hypogonadotropic hypogonadism

Subjects

A total of 51 patients newly diagnosed with IHH (mean age: 30.1±8.9 years) and 36 healthy controls (mean age 31.3±5.9 years) admitted to the hospital between 2011–2015 were included in the study. Patients with known thyroid disease were excluded from the study. IHH patients did not receive any replacement therapy prior to evaluation.

IHH was defined as the presence of clinical symptoms related to hypogonadism (e.g., incomplete or delayed sexual development, reduced libido and erectile dysfunction/infertility), low serum total testoterone (TT) levels (<2.5 ng/mL) along with insufficient LH and FSH levels (i.e. low or non-elevated levels), the absence of any other anterior and/or posterior pituitary hypofunction and pathological findings, as observed on a pituitary magnetic resonance imaging. Before diagnosing IHH, repeated measurements of TT levels were obtained in the morning to confirm initial low levels. Sex hormone-binding globulin (SHBG) was also measured. Patients with systemic illnesses and eating disorders were excluded, in addition to those who undertook excessive exercise, who used certain medications (e.g., opiates or high-dose glucocorticoid therapy) or those who had abnormal SHBG levels, as these could affect the metabolism of testosterone and thus the testosterone levels. Secondary causes of hypogonadotropic hypogonadism, such as primary or secondary hemochromatosis, panhypopituitarism, hyperprolactinemia and intracranial masses, obesity and metabolic syndrome were excluded before making a diagnosis of IHH.

Biochemical Analyses

All blood samples were taken in the morning between 8:00 and 9:00 am, after 12 h overnight fast. Serum TSH (0.27-4.2 mIU/mL), free thyroxin (ft4) (0.93-1.7 ng/dL), free triiodothyronine (ft3) (2.0-4.4 pg/mL), anti-thyroglobulin (anti-Tg) (<115 IU/mL) and thyroid peroxidase anti-body (anti-TPO) (<34 IU/mL) were measured by electrochemiluminescence immunoassays (DXI 800 Beckman Coulter, Ireland). Serum levels of FSH (1.5-12.4 mIU/mL), LH (1.7-8,6 mIU/mL), total testosterone (2.18-9.05 ng/mL), free testosterone (8.7-30 pg/mL), prolactin (4.04-15.2 ng/mL), IGF-1 (ng/mL) (normal reference range adjusted by age: 150–385), and cortisol (6.7-22.6 µg/dL) were measured with the electrochemiluminescence microparticle immune method (paramagnetic particle, electrochemiluminescence immune assay) using a Roche Hitachi Cobalt 600 device.

Magnetic Resonance Imaging

Tesla dynamic-enhanced pituitary and cranial magnetic resonance imaging was performed before making a diagnosis of IHH, to exclude intracranial/pituitary masses.

Thyroid Volume

Thyroid ultrasonography was performed by a single endocrinologist for all patients using a 12 MHz linear probe (Hitachi EUB 8500). The thyroid gland volume was calculated according to the ellipsoid formula: volume (mL): length (cm)×width (cm)×depth (cm)×0.52.9

Statistical Analyses

SPSS for Windows (ver. 11.0.; Chicago, IL, USA) was used for statistical analysis. The Shapiro–Wilk test was performed to test for normal distribution. Student's t-test was used to compare independent variables that abided by normal distribution, and the variables were expressed as mean and standard deviation. The Mann–Whitney U-test was used to test the independent variables without normal distribution, and they were expressed as median and interquartile range. An alpha value of 0.05 was accepted as statistically significant.

RESULTS

The study included 51 IHH patients and 36 healthy males in two groups. There was no significant difference in age (30.1±8.9 vs. 31.3±5.9) and body-mass index (25.5±6.5 kg/m² vs. 25.1±3.7 kg/m²) between the subjects in the two groups (Table 1).

Hormonal Evaluation

The mean FSH, LH, total testosterone and free testosterone levels were found to be significantly lower in the IHH group. Prolactin, IGF–1 and cortisol levels were similar in both groups (Table 2).

Thyroid Hormones, Thyroid Autoantibodies and Thyroid Volume

The mean TSH, fT4, fT3, anti-TPO and anti-TG levels were found to be similar between the two groups (Table 3). The mean thyroid volume in the IHH group (11.0±6.2 mL) was significantly lower than in the healthy control group (18.6±8.1 mL, *p*: 0.001) (Table 3).

DISCUSSION

IHH is a rare disease and presents with low LH, FSH, and testosterone levels. There are a very limited number of studies describing the relationship between hypogonadism and thyroid hormones, and these studies mostly investigated patients with primary hypogonadism. The present study is different as it aimed to investigate whether or not there are any differences in thyroid functions and thyroid volume between young males with IHH and healthy controls.

Glycoprotein hormones like FSH, LH, hCG and TSH have some similarities not only in their structures, but also in their receptors. Glycoprotein hormones are heterodimeric proteins with a common α-subunit and hormone-specific β-subunit. Glycoprotein hormones bind to the large extracellular domain of the receptor and cause a conformational change in the receptor that leads to the activation of G-protein and thus the intracellular signaling pathway.[10,11]

Thyrotrophic effects of gonadotropins are well known, particularly for hCG.[5,12] Furthermore, it was shown that LH binds to the TSH receptor and stimulates adenylate cyclase potently, with a thyrotropic action on the human thyroid.[13,14] It was also demonstrated that LH binds to recombinant TSH receptor and is about 10 times as potent as hCG in increasing cAMP.[6]

To our knowledge, there are only two studies that studied the relationship between thyroid volume and gonadotrophic hormones. These similar studies involving polycystic ovarian female patients reported that LH levels may also have a positive effect on thyroid volume.[15,16] It was established that gonadotropin levels had no effect on thyroid functions and the effect of LH on thyroid volume was independent of insulin resistance in these studies.

Thyroid volume may be affected by variables such as age, gender, anthropometric values, amount of iodine and underlying autoimmune thyroid disease.[17-19] In the present study, there was no difference between the groups in terms of these anthropometric, demographic features and iodine status that could affect thyroid volume.

Table 2. Hormone levels in the idiopathic hypogonadotropic hypogonadism (IHH) patients and controls

	IHH Mean±SD	IHH Median (Min-Max)	Control Mean±SD	Control Median (Min-Max)	*p*
FSH, mIU/mL	1.3±1.8	0.7(0.07-9.0)	3.9±2.6	2.8(1.6-10.0)	<0.001
LH, mIU/mL	0.7±1.0	0.2(0.03-5.10)	4.4±1.8	4.2(2.0-8.2)	<0.001
Total testosterone, ng/mL	0.6±0.6	0.3(0.03-2.4)	4.6±1.6	4.3(2.6-9.0)	<0.001
Free testosterone, pg/mL	3.0±2.9	2.0(0.2-14.0)	17.4±7.0	16.2(8.8-29.7)	<0.001
Prolactin, ng/ml	11.0±14.7	8.3(5.1-28.7)	9.3±3.7	8.5(4.5-19.0)	0.241
IGF-1, ng/mL	225.0±150.0	243(125.0-474.0)	199.2±49.5	184.0(134.0-334.0)	0.634
Cortisol, µg/dL	16.1±7.7	15.2(7.0-32.3)	16.1±4.4	18.0(7.1-25.0)	0.867

IHH: Idiopathic hypogonadotropic hypogonadism, **FSH:** follicle-stimulating hormone, **LH:** luteinizing hormone, **IGF-1:** insulin-like growth factor 1, **SD:** standard deviation.

Table 3. Thyroid hormone, autoantibody levels and thyroid volume

	IHH Mean±SD	IHH Median (Min-Max)	Control Mean±SD	Control Median (Min-Max)	*p*
TSH, mIU/L	2.3 ±1.5	2.1(0.3-7.7)	2.2 ±1.2	2.0(0.7-5.3)	0.769
fT4, ng/dL	1.1 ±0.2	1.1(0.9-1.6)	1.2 ±0.2	1.2(0.7-1.5)	0.105
fT3, pg/mL	3.2 ±0.7	3.1(2.1-4.7)	3.3 ±0.5	3.3(2.2-4.8)	0.092
Anti-TPO, IU/mL	7,6 ±4.9	7.7(0-22)	7.9 ±5.5	6(0-20)	0.682
Anti-Tg, IU/mL	12.4 ±5.0	11.7(3.0-19.7)	15.2 ±6.9	11.0(10.0-25.0)	0.529
Thyroid volume, mL	11.0 ±6.2	10.2(2.0-34.3)	18.6 ±8.1	16.6(5.5-37.7)	0.001

TSH: Thyroid stimulating hormone, **fT4:** free thyroxine, **fT3:** free triiodothyronine, **Anti-TPO:** thyroid peroxidase antibody, **Anti-Tg:** antithyroglobulin antibody, **SD:** standard deviation.

Another study examined thyroid volume in males with IHH with a small group of subjects.[20] The study examined thyroid volume in males with IHH and found no difference between them and a control group. However, in the same study, significant growth in thyroid volume was observed in the group treated with hCG, while no change in thyroid volume was observed in the testosterone replacement group. Although there is a dramatic difference between the conclusion of this study, the significant increase in thyroid volume in the hCG treatment group supports our results.

CONCLUSION

For the first time, the present study revealed that thyroid volume was significantly smaller in young men with IHH.

*The authors declare that there are no conflicts of interest.

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