Original Article

Male Idiopathic Hypogonadotropic Hypogonadism: Serum Insulin-like Growth Factor-1 and Oestradiol Levels

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Abstract

Background: Idiopathic hypogonadotropic hypogonadism (IHH) is a form of male infertility caused by a congenital defect in the secretion or action of gonadotropin-releasing hormone from the hypothalamus. Oestradiol emerged as the main sex steroid in the regulation of the hypothalamic–pituitary–testicular axis, reproductive function and growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis in men. Moreover, GH/IGF-1 axis has been suggested to play a role in IHH. **Aims:** This study evaluated serum IGF-1 in IHH men and controls. Furthermore, we evaluated the association between serum total oestradiol (TE2) and IGF-1 levels in patients and controls. Parameters including age, body mass index and fertility history were analysed. **Settings and Design:** This prospective study was conducted at the Royan institute. **Materials and Methods:** In 20 men with IHH and 20 controls, serum IGF-1 levels were estimated using chemiluminescence immunoassay and serum E2 levels were assessed by means of the electrochemiluminescence method. **Statistical Analysis Used:** Kolmogorov-Smirnov test, parametric t-test or the Mann-Whitney and the Pearson correlation coefficient were performed. SPSS version 22 was used for the analysis of data. **Results:** There was a significant decrease in serum IGF-1 levels in IHH patients compared with controls (145.1 ± 8.9 ng/ml vs. 229.6 ± 7.3 ng/ml $P < 0.001$, respectively). Furthermore, a significant decrease was observed in TE2 levels in IHH male patients (12.3 ± 2.5 pg/ml) compared with controls (31.9 ± 5.3 pg/ml $P < 0.001$). A positive correlation was observed between serum IGF-1 and TE2 levels in the total number of participants, suggesting that E2 deficiency in IHH cases can explain the lower levels of serum IGF-1. **Conclusions:** These findings suggest that the reduction in IGF-1 levels may be associated with the influence of E2 on the GH/IGF-1 axis, and may confirm the role of the GH/IGF-1 axis in IHH. Further investigations will be required to determine the exact mechanisms by which E2 and IGF-1 affect the reproductive neuroendocrine function.

Keywords: *Oestradiol, hypothalamic-pituitary axis, idiopathic hypogonadotropic hypogonadism, insulin-like growth factor-1*

Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is defined through delayed or absent sexual development that results in low serum testosterone levels, decreased spermatogenesis and low or inappropriately normal levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH), but with normal levels of other pituitary hormones; Growth hormone (GH), prolactin (PRL),

Received: 13-09-2022 **Revised:** 27-11-2022
Accepted: 28-11-2022 **Published:** 30-12-2022

Access this article online

Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/jhrs.jhrs_132_22

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How to cite this article: Salehisedeh N, Parhizkar A, Yaghmaei P, Sabbaghian M. Male idiopathic hypogonadotropic hypogonadism: Serum insulin-like growth factor-1 and oestradiol levels. J Hum Reprod Sci 2022;15:351-6.

thyroid-stimulating hormone (TSH)) and no anatomical and functional abnormalities of the hypothalamic-pituitary (HP) axis.[1-3] It is primarily defined by idiopathic gonadotropin-releasing hormone (GnRH) deficit in production, secretion and action.[4-7]

Insulin-like growth factor-1 (IGF-1) stimulates GnRH promoter activity *in vitro*,[8,9] and also stimulates the release of GnRH from GnRH neuronal cell lines (GT1-7 cells).[10] In addition, GH and IGF-1 affect the migration of GnRH neurons (GN11) from the olfactory placode to the hypothalamus-preoptic area in foetal life and stimulate GnRH post-natal life secretion.[11] In the human GnRH (hGnRH) promoter, it has been shown an AP-1 site that mediates IGF-1 stimulation of hGnRH promoter activity *in vitro*.[9]

Oestradiol is known as a critical player in male reproductive function and in controlling the HP–testicular (HPT) axis.[12,13] E2 directly inhibited pituitary gonadotropin production to reduce sensitivity to GnRH.[14,15]. Furthermore, E2 reduced GnRH pulse frequency through an action site in the hypothalamus and reduced responsiveness to GnRH in the pituitary, therefore, decreased LH pulse amplitude.[16] A study on male IHH has reported that the predominant negative effect of E2 on LH occurs in the hypothalamus.[17] E2 may indirectly regulate GnRH neurons through functions on oestrogen receptor α (ER) in kisspeptin, neurokinin B and dynorphin-expressing neurons in the infundibular nucleus of the hypothalamus.[18] Furthermore, ER is expressed by hGnRH neurons.[19]

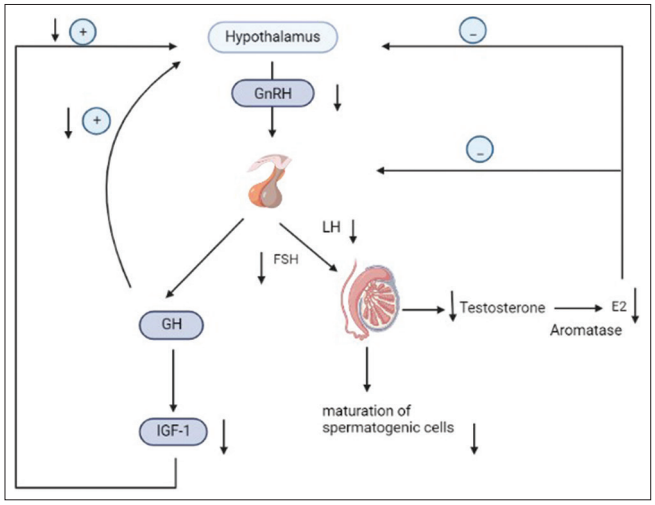

Figure 1: Schematic illustration of the effects of GH/IGF-1 and E2 on HPT axis. GH/IGF-1 axis stimulates GnRH secretion in (GT1-7 cells) GnRH neurones. Hypothetically, this stimulatory effect may reduce due to decreased levels of IGF-1 in IHH patients. The image was created in Biorender.Com. LH = Luteinizing hormone, FSH = Follicle-stimulating hormone, GnRH = Gonadotropin-releasing hormone, GH = Growth hormone, IGF-1 = Insulin-like growth factor-1, HPT = Hypothalamic–pituitary–testicular, IHH = Idiopathic hypogonadotropic hypogonadism

The cascade of hormonal events is shown in Figure 1.

However, only a few studies have investigated the serum levels of IGF-1 in IHH patients.[20,21] To obtain a better understanding of the role of IGF-1 and oestradiol in IHH, the present study was conducted to investigate the relationship between serum IGF-1 and E2 as two important regulatory factors in the HPT axis.

Materials and Methods

This single-centre study with ethic code: IR.ACECR.ROYAN.REC.1398.010 was approved at the research ethics committee of Royan Institute, Tehran, Iran. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013. All the volunteers gave their written informed consent before the start of the study. Men who used any anabolic medication were excluded from the study. General health history was obtained at the initial visit. Based on the clinical history, physical examination and routine laboratory measurements, men with diabetes, endocrine, renal, liver and cardiovascular diseases were not included in this story.

Patients with idiopathic hypogonadotropic hypogonadism

This study was conducted on 20 male IHH subjects referred to Royan institution, from November 2018 to May 2019. The mean age was 34.1 ± 3.1 (range, 30–40) years; the mean body mass index (BMI) was 23.8 ± 3.8 (range, 18.2–33.6 kg/m^2). IHH patients were characterised by (1) incomplete or absent puberty by the age of 18 years, (2) decreased serum T levels below 2.5 ng/ml in the existence of low serum LH and FSH levels below 1.2 mIU/ml and 2 mIU/ml, respectively, (3) standard hypothalamus and pituitary magnetic resonance imaging findings and (4) normal sense of smell and normal karyotypes (46, XY). Detailed physical investigations were completed, including evaluation of the testis volume by Prader orchidometer. All patients had previous treatment, although there had been a washout period of 4 months before entering the study.

Controls

Twenty men were evaluated in our department because they belonged to couples presenting with infertility of female origin. The mean age was 35.3 ± 2.6 (range, 31–40) years; the mean BMI was 24.1 ± 2.5 (range, 18.4–27.7 kg/m^2). They were selected for the assessment of normal semen analysis according to WHO 2010; (sperm concentration: 15 × 10^6 sperm/ml, Percentage motility: 40%, 1.5 Ml volume)[22], testicular

volume more than 15 ml (Prader orchidometer), normal serum concentrations of LH, FSH, and T.

Sample size

G Power version 3.1 software (G power Source Company Ltd. offers alternative energy services) was used to calculate the sample size. Considering the comparison of the mean of the two independent groups of the study, an independent *t*-test was used. To determine the sample size, type I error 0.05 and type II error 0.2 (power 0.8) were considered.

Hormone analysis

Blood samples were collected in red plain blood collection tubes (Hebei Xinle Sci and Tech CO., Ltd), between 8 and 10, in the morning. Serum was separated from the blood samples and labelled with a code and serum samples were then stored in a freezer at –70°C. Samples were kept for not more than 4 months and were then analysed.

Levels of serum FSH and LH were estimated using the ELISA method (commercial kit, Stat Fax 3200). Total oestradiol (TE2) and thrombin time (TT) levels were measured using the electrochemiluminescence method by Roche kit and Cobas 6000 analyser. For all subjects, serum IGF-1 levels were assessed from blood samples by means of chemiluminescence immunoassay (the DiaSorin LIAISON system). Reference ranges are based on those used by some commercial and reference-laboratory ranges and vary by laboratory [Table 1].[4]

Statistical analysis

All results are reported as individual values in the figure and as means ± standard deviation (SD) in the table and text. At the first, we used the Kolmogorov–Smirnov test to check the normality of variables. Hormonal parameters were compared using a parametric *t*-test or the Mann–Whitney. We used the Pearson correlation coefficient to examine the relationship between variables. SPSS version 22 (SPSS 22, Inc., Chicago, IL, USA) was used for the analysis of data. $P < 0.001$ was considered to denote significant differences. Figure 2 has been made in Microsoft Office Excel.

Results

Kolmogorov–Smirnov test was used to check the normality of variables, and all the variables were normal. Mean IGF-1 levels in groups are revealed in Table 1. The patients with IHH (145.1 ± 8.9 ng/ml) had meaningfully lower levels of IGF-1 levels than controls (229.6 ± 7.3 ng/ml; $P < 0.001$). Serum IGF-1 levels in patients and controls were within the normal range.[23] Mean ± SD TT, LH, FSH and TE2 in the control and patients are shown in Table 1. Compared with patients, controls had higher TT, LH, FSH and E2 levels. Linear Pearson's correlations were accomplished to define the trends of serum IGF-1 levels relating to the serum TE2 levels in the total number of patients and controls. The combined population of men with IHH and controls had a positive association between serum TE2 and IGF-1 levels [Figure 2].

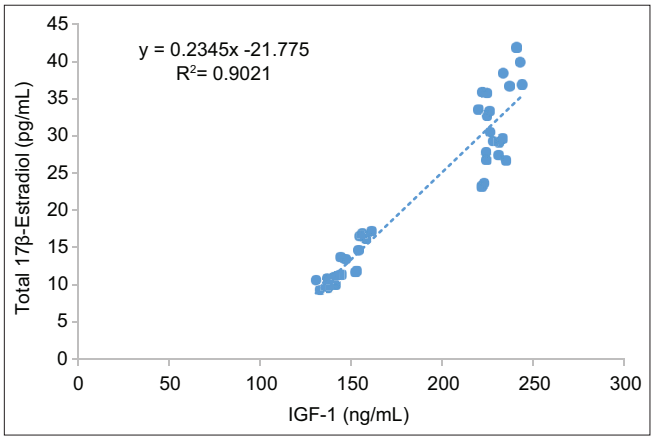

Figure 2: Correlation between serum IGF-1 and TE2 levels in combined population of controls and patients with IHH; $P < 0.001$. IHH = Idiopathic hypogonadotropic hypogonadism, IGF-1 = Insulin-like growth factor-1, TE2 = Total oestradiol

Table 1: Clinical and laboratory characteristics of patients and controls (mean±standard deviation)

	Patients	Control	Reference range	*P*
N	20	20		
Age (years)	34.1±3.1	35.3±2.6		0.185
BMI (kg/m^2)	23.8±3.8	24.1±2.5		0.770
Right testis volume (mL)	4.6±1.5	15.4±0.4		<0.001
Left testis volume (mL)	4.8±1.5	15.4±0.4		<0.001
FSH (µ/mL)	0.8±0.4	7.3±1.2	2-10 (µ/mL)	<0.001
LH (µ/mL)	0.4±0.3	7.6±0.6	1.2-8.6 (µ/mL)	<0.001
Total testosterone (ng/mL)	0.4±0.5	5.5±1.3	2.49-8.36 (ng/mL)	<0.001
Total E2 (pg/mL)	12.3±2.5	31.9±5.3	25.8-60.7 (pg/mL)	<0.001
IGF-1 (ng/mL)	145.1±8.9	229.6±7.3		<0.001

BMI=Body mass index, LH=Luteinising hormone, FSH=Follicle-stimulating hormone, IGF-1=Insulin-like growth factor-1

Discussion

The present study is a human study with a total number of 40 participants. This study aimed to investigate serum IGF-1 levels in 20 men with IHH and 20 controls. There is a negative correlation between circulating IGF-1 levels and age; peaking during puberty and gradually declining throughout adult life,[24,25] hence two groups of participants with matched ages were used in this study. We observed that serum IGF-1 levels were lower in men with IHH than in the controls. GH was not measured in the present study, but this finding possibly supports the role of the GH/IGF-1 system in IHH.

IHH is caused by an isolated failure of release, action or both of the GnRH.[26] It has been indicated that in patients with IHH, variants of the IGF-1 gene have been described but it remains to be confirmed if these variants play a role in the pathogenesis of IHH.[27] Other study has also shown that GH and IGF-1 have a stimulatory effect on the migration of GnRH neurons and GnRH secretion.[11]

In men with isolated hypogonadotropic hypogonadism, GH and IGF-1 secretion have been reported to be lower before therapy with sex steroids.[21] In another study, serum IGF-1 levels have been shown to be within the normal range in men with IHH and increased after gonadotropin replacement therapy.[20] Furthermore, it has been indicated that in HH patients, the plasma concentration of IGF-1 increased after testosterone therapy,[28] because testosterone has a stimulatory influence on the GH axis.[29,30]

We also found a significant E2 deficiency in the serum of patients with IHH than in controls, which is in accordance with the published result.[31] The substrate–product link between TE2 and TT[31] explains lower E2 levels in patients compared with controls. LH is considered to regulate E2 secretion by Leydig cells in a positive way,[31-33] therefore, lower TE2 levels in IHH patients can be correlated with circulating LH deficit.[31] ERβ expression has been documented in the somatotroph, and both subtypes of oestrogen receptors regulate the GH gene expression.[34]

We noted a positive association amongst serum E2 and IGF-1 levels, which is logical, given the significant role of E2 in the regulation of IGF-1 secretion,[35] and suggests that the lower levels of IGF-1 in IHH men are related to the circulating E2 shortage. Compared with testosterone, E2 becomes clear as the significant sex steroid in the regulation of the GH-IGF-1 axis in men.[12] An intense positive correlation has been reported between GH secretion and E2 concentration as the main determinant of GH secretion in men.[36] The results of the present study confirm that a linkage exists between levels of serum IGF-1 and sex steroids. Compared with controls, men with aromatase deficiency had GH shortage and decreased levels of IGF-1,[35] suggesting that oestrogen shortage may interfere with the normal development of the somatotropic axis in aromatase-deficient patients. HP–adrenal axis centrally regulates endocrine actions and controls the operation of the GH/IGF-1 system.[37] This regulation requires the integrity of the hypothalamus, pituitary and liver, as reviewed in.[38] Thus, there may be mechanisms for thorough maturation of the GH-IGF-1 axis and this procedure may fail in men with IHH due to the E2 reduction.

These findings could point to a link between E2 deficiency and reduction in the levels of serum IGF-1 in male IHH patients and possibly indicate the role of the GH/IGF-1 axis in IHH. However, additional work remains to be needed to enlighten the influences of E2 on HPT and the GH/IGF-1 axis in particular and the molecular mechanisms of the interactions between E2 and IGF-1.

It has been reported that serum IGF-1 levels in children with HH are lower than in those with delayed puberty.[39] In previous study, it has been demonstrated that GH and IGF-1 can directly stimulate GnRH secretion.[11] The results of the present study can provide evidence supporting the role of the GH-IGF-1 axis in IHH and possibly have therapeutic value in clinical practice. To evaluate the role of GH and IGF-1 for the treatment of IHH, animal studies should be carried out.

Limitation in our study was that follow-up visits by the patients were unlikely because the patients had been referred to the institution from other towns, and then returned to their provinces after completing detailed investigations. Therefore, we could not assess the effect of the testosterone and/or gonadotropin replacement therapies applied to patients.

Conclusions

We observed a positive correlation between serum IGF-1 and E2 levels in the participants of this study. With previous basic and clinical data, these findings may explain clinical data, addressing the role of E2 on the GH/IGF-1 axis in IHH.

Acknowledgements

We appreciate all patients who cooperated in this research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability and sharing statement

Data supporting the results are included in the published article and the authors' are willing to share the data on request.

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