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KISSPEPTIN IN MALE HYPOGONADISM

Kisspeptin levels in idiopathic hypogonadotropic hypogonadism diagnosed male patients and its relation with glucose-insulin dynamic

Hasan Öztin[1], Eylem Çağıltay[2], Sinan Çağlayan[3], Mustafa Kaplan[4], Yaşam Kemal Akpak[5], Nilay Karaca[6], and Mesut Tığlıoğlu[7]

[1]*Internal Diseases Department, Gülhane Military Medical Academy Military Faculty of Medicine Hospital, Geriatrics Clinic, Ankara, Turkey,* [2]*İzmir Military Hospital, Internal Diseases Clinic, Izmir, Turkey,* [3]*Medipol University Hospital, Endocrinology and Metabolic Diseases Clinic, Istanbul, Turkey,* [4]*Gülhane Military Medical Academy, Haydarpaşa Education Hospital, Internal Diseases Clinic, Istanbul, Turkey,* [5]*Ankara Mevki Military Hospital, Gynecology and Obstetrics Clinic, Ankara, Turkey,* [6]*Bezmialem University Hospital, Gynecology and Obstetrics Clinic, Istanbul, Turkey, and* [7]*Çanakkale Military Hospital, Internal Diseases Clinic, Çanakkale, Turkey*

Abstract

Male hypogonadism is defined as the deficiency of testosterone or sperm production synthesized by testicles or the deficiency of both. The reasons for hypogonadism may be primary, meaning testicular or secondary, meaning hypothalamohypophyseal. In hypogonadotropic hypogonadism (HH), there is indeficiency in gonadotropic hormones due to hypothalamic or hypophyseal reasons. Gonadotropin-releasing hormone (GnRH) is an important stimulant in releasing follicular stimulant hormone (FSH), mainly luteinizing hormone (LH). GnRH omitted is under the effect of many hormonal or stimulating factors. Kisspeptin is present in many places of the body, mostly in hypothalamic anteroventral periventricular nucleus and arcuate nucleus. Kisspeptin has a suppressor effect on the metastasis of many tumors such as breast cancer and malign melanoma metastases, and is called ''metastin'' for this reason. Kisspeptin is a strong stimulant of GnRH. In idiopathic hypogonadotropic hypogonadism (IHH) etiology, there is gonadotropic hormone release indeficiency which cannot be clearly described.

A total of 30 male hypogonatropic hypogonadism diagnosed patients over 30 years of age who have applied to Haydarpasa Education Hospital Endocrinology and Metabolic Diseases Service were included in the study. Compared to the control group, the effect of kisspeptin on male patients with hypogonatropic hypogonadism and on insulin resistance developing in hypogonadism patients was investigated in our study.

A statistically significant difference was detected between average kisspeptin measurements of the groups ($p < 0.01$). Kisspeptin measurement of the cases in the patient group were detected significantly high. No statistically significant relation was detected among kisspeptin and LH/FSH levels. Although a positive low relation was detected between kisspeptin measurements of patient group cases and homeostasis model assessment of insulin resistance (HOMA-IR) measurements, this relation was statistically insignificant. When the patient and control groups were compared for HOMA-IR, no statistically significant difference was detected.

The reason for high kisspeptin levels in the patient group compared to the control group makes us consider that there may be a GPR54 resistance or GnRH neuronal transfer pathway defect. When patients and control groups were compared for HOMA-IR, the difference was not statistically significant. It is considered that kisspeptin is one of the reasons for hypogonatropic hypogonadism and has less effect on insulin resistance.

Keywords

Glucose, Idıopathic hypogonadotropic hypogonadism, insulin, insulin resistance, kisspeptin

History

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Introduction

Hypogonadism is seen commonly in the society and diagnosis period is delayed due to the problems of patients in telling their complaints. It is possible to classify hypogonadism as primary when testicular sourced, secondary when pituitary sourced and tertiary when hypothalamic sourced. Hypogonadism develops due to hormonal or transfer defects formed in hypothalamo-pituitary and testicular/ovarian axis. In hypogonadotropic hypogonadism (HH), hypophyseal follicular stimulant hormone (FSH) and luteinizing hormone (LH) levels are detected low. Hypophyseal FSH and LH are released with gonadotropin-releasing hormone (GnRH) stimulation [1]. Effecting GnRH receptors on pulsatile GnRH gonadotrops, it stimulates gonadotropin gene expression, hormone synthesis and secretion. Hypophyseal gonadotropins take part in steroid production and gametogenesis in males and females. Gonadotropin production requires normal development and functions of GnRH-producing neurons and hypophyseal gonadotrop cells.

Kisspeptin is a peptide synthesized in hippocampal dentate gyrus (by kiss-1 gene in 1. chromosome). It shows its effect with

Address for correspondence: Nilay Karaca, M.D., Bezmi Alem Vakif University, Medical Faculty, Department of Obstetrics and Gynecology, Adnan Menderes Boulevard, 34093 Fatih, Istanbul, Turkey. Tel: +90 2125232288. Fax: +90 2124531870. E-mail: karacanilay@hotmail.com

GPR54 (G protein-coupled receptor) receptors [2]. Kisspeptin is a strong stimulant of GnRH neurons. That is why it is considered to have a role in HH etiology [2]. Also, it was detected that kisspeptin levels stimulate glucose-dependent insulin secretion in animal experiments made [3]. It was also observed that kisspeptin applied intravenously stimulates insulin secretion. It makes this effect over phospholipase c and mitogen-activated protein kinase [3].

Our aim in this study was to compare kisspeptin levels in young male patients followed with HH diagnosis with healthy individuals and to investigate the role of kisspeptin on hypogonadism etiology and insulin resistance and glucose insulin metabolism.

Materials and methods

A total of 30 male patients over 18 years old who were diagnosed with idiopathic hypogonadotropic hypogonadism (IHH) and applied to Gülhane Military Medical Academy Haydarpasa Education Hospital Endocrinology and Metabolic Diseases Service between November 2011 and May 2012 and who did not use any medicine or have any other diseases which might affect the hormone balance and metabolism were included in the study. The control group was formed with 51 male patients who applied to endocrinology and internal medicine services for different reasons and who were detected to have no hormonal or chronic diseases after the evaluation made. The diagnosis of the disease was made with clinical findings, hormonal examination, laboratory and imaging methods. HH diagnosis was made when LH, FSH, free and total testosterone levels were measured low after the presence of anamnesis and physical examination findings in line with the disease. In the anamnesis, questions such as hypogonadism beginning age, marital status, presence of any kids, libido condition, whether the erection and ejaculation was satisfactory or not were asked. Also, visual and smelling disorders, galactore, whether the patients used any medicine before and the duration were asked. Among physical inspection findings, height, weight, arm span and waist circumference measurements were made. Smell examination was also made. Tanner classification of the patients was evaluated [4]. The patient group consisted of people newly diagnosed with HH and whose treatment continued belonged to onychoid structure in phenotypical terms and were in Tanner stage 1–2.

Smelling defect, a surgical operation which might cause this disease or defined cranial radiological finding, a panhypophyseal disease, primary hypogonadism, hyperprolactinemia, undescended testicle story and use of medicine which might cause hypogonadism were named as exclusion criteria. All the cases included in the study, read and signed disclosure and voluntary consent (acceptance) form and filled in the patient follow-up form including follow-up protocol and the patients were followed-up within the scope of this protocol.

The serum samples of patients who had HH diagnosis, which means patients who have low or normal LH and FSH levels and low testosterone levels, were taken at 8 a.m on an empty stomach. Hettich centrifuge Universal 320 (DJB Labcare Ltd., Milton Keynes, UK) at 5000 rev/min was centrifuged for 5 min and than 2 cc was separated among the remaining serums from venous blood samples taken during routine examinations of the patient and healthy control group and was put in eppendorf tubes for kisspeptin study and after keeping the samples in −80 degree refrigerator, the biochemical parameters were studied together in Gulhane Military Medical Academy Haydarpasa Education Hospital Biochemistry Laboratory. Again, LH, FSH, testosterone, insulin, fasting blood glucose (FBG) examinations in HH patients were studied in Gulhane Military Medical Academy Haydarpasa Education Hospital Biochemical Laboratory and the results were recorded. The homeostasis model assessment of insulin resistance (HOMA-IR) calculated by a formula employing fasting plasma glucose and fasting plasma insulin concentrations (HOMA-IR: fasting plasma glucose (mg/dl) xFasting Plasma insulin (IU/ML)/22.5). Phoenix Pharmaceuticals, Inc. (Burlingame, CA) KISS-1 (113–121)/amide/kisspeptin10/metastin (45–54) amide (human) was performed by EIA kit at the study.

Parameters examined in the study were stated as average ± standard deviation. Number cruncher statistical system (NCSS) 2007 & power analysis and sample size (PASS) 2008 statistical software (Kaysville, UT) program was used for statistical analysis. While study data were evaluated, Student's *t* test was used in intergroup comparisons of parameters demonstrating normal distribution in addition to definitive statistical methods (average, standard deviation, median, frequency and rate) and Mann–Whitney U test was used in intergroup comparisons of parameters not demonstrating normal distribution. Spearman's correlation analysis was used in the evaluation of relations between parameters. Significance was evaluated on $p<0.05$ and $p<0.001$ level.

This thesis study was made in Gulhane Military Medical Academy Haydarpasa Education Hospital Endocrinology and Metabolism service after 8 February 2012 and b.30.2.ist.0.30.90.00/4289 consent was taken from İstanbul University Cerrahpaşa Faculty of Medicine Ethics Committee. Consent was taken from Epidemiological Study Group of our hospital for the scientific convenience of the study and cost recovery. No intervention was made on the patients apart from the routine examinations and also no interventions which might worsen the course of the disease or hurt the patient.

Results

The ages of the cases were between 20 and 38 and the average age was 23.77 ± 4.37 years. 30 hypogonad cases included in the study were defined as ''Patient Group'' and 51 normal cases were defined as ''Control group''. Average age was 21.17 ± 0.77 in the patient group and 25.19 ± 4.86 in the control group. When patient and control groups were compared, no statistically significant difference was determined in demographical characteristics ($p>0.05$) (Table 1).

A high statistically significant difference was determined between FSH, LH, testosterone and kisspeptin measurements of the cases according to the groups ($p<0.01$). While FSH, LH and testosterone measurement averages of the cases in the patient group were observed significantly low, kisspeptin levels were determined significantly high (Table 2). No statistically significant difference was determined when both groups were evaluated for HOMA-IR, insulin and BFG (Table 2).

Table 1. Evaluation of demographical information according to the groups.

	Evaluation groups		
	Patient group ($n=30$)	Control group ($n=51$)	
	Avr ± SD	Avr ± SD	*p*
Height (cm)	173.10 ± 6.45	175.73 ± 6.32	0.077
Weight (kg)	71.20 ± 13.30	73.00 ± 13.03	0.553
BMI (kg/m^2)	23.75 ± 4.25	23.63 ± 4.13	0.903
Arm span (cm)	176.43 ± 6.04	175.28 ± 6.82	0.448
Waist circumference (cm)	89.07 ± 11.70	91.68 ± 8.72	0.295

*Student's *t* test analysis was used in this table. BMI: body mass index.

No significant result was achieved in the comparison of kisspeptin values and other parameters in patient and control groups (Table 3). A positive relation was determined between HOMA-IR measurements and waist circumference measurements of patient group cases and this was a high statistical significance ($r = 0.539$; $p = 0.002$; $p < 0.01$) (Figure 1). There is also a positive statistically significant relation between HOMA-IR measurements and BMI measurements of patient group cases ($r = 0.406$; $p = 0.026$; $p < 0.05$) (Figure 2) (Table 4).

Table 2. Evaluation of biochemical results according to the groups.

	Evaluation groups		
	Patient group (n =30)	Control group (n = 51)	
	Avr ± SD	Avr ± SD	p
†FSH (mlU/ml)	1.13 ± 1.12 (0.92)	4.22 ± 2.79 (3.20)	0.001‡
†LH (mlU/ml)	0.49 ± 0.51 (0.36)	3.81 ± 1.49 (3.50)	0.001‡
†Testosterone (nmol/l)	2.71 ± 5.91 (1.09)	5.72 ± 1.89 (5.75)	0.001‡
*FBG (mg/dL)	78.97 ± 10.87	78.18 ± 8.17	0.713
†Insulin (IU/mL)	10.21 ± 4.98 (8.65)	9.73 ± 6.27 (8.00)	0.396
†Kisspeptin	4.20 ± 10.65 (3.65)	2.95 ± 1.18 (2.81)	0.001‡
†HOMA-IR	2.02 ± 1.06 (1.77)	1.82 ± 1.32 (1.39)	0.311

Tests used:
*Student's t test.
†Mann–Whitney U test.
‡$p < 0.01$
FSH: follicle stimulating hormone; LH: luteinizing hormone; FBG: fasting blood glucose; HOMA = homeostatic model assessment; IR = insulin resistance

Table 3. Evaluation of FSH, LH, FBG, insulin and Homa-IR relation for all groups.

	Evaluation groups			
	Patient group ($n = 30$)		Control group ($n = 51$)	
	Kisspeptin r	p	Kisspeptin r	p
FSH	0.109	0.573	0.049	0.731
LH	0.246	0.198	−0.053	0.714
Insulin	0.242	0.205	−0.133	0.363
HOMA-IR	0.250	0.191	−0.069	0.628
Testosterone	−0.068	0.728	−0.009	0.950

The test used in this table is r = Spearman's rho.

Discussion

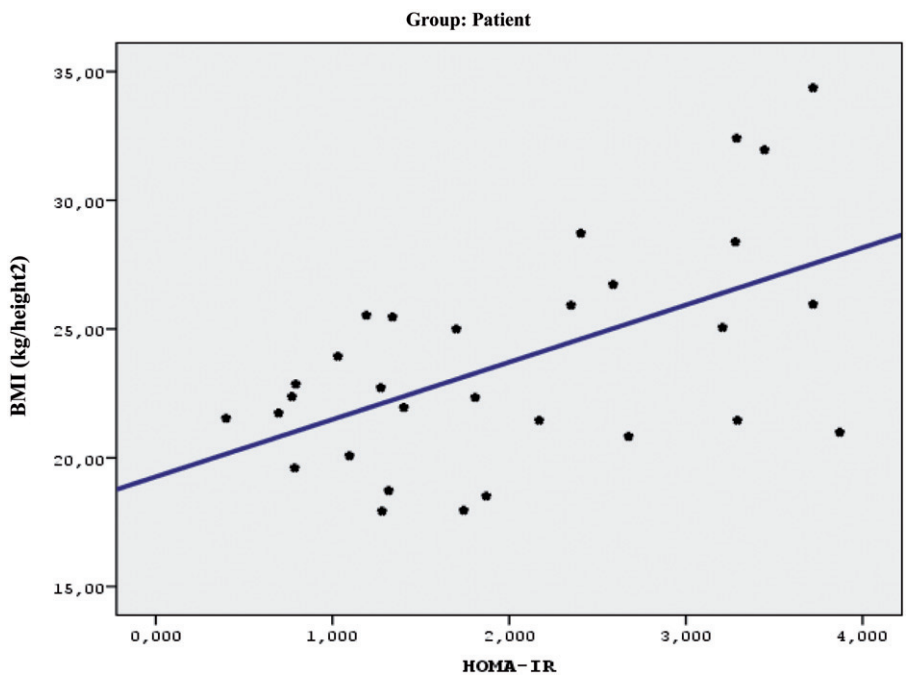
In this study, kisspeption levels were found high in IHH cases. This result demonstrates that kisspeptin may play a role in IHH etiology over hypothalamo-pituitary-gonadal axis.

Reproduction disorders constitute social, medical and economical problems for both the patient and the society. Hormones and peptides similar to kisspeptin playing role in the development and functions of hypothalamo-pituary-gonadal axis were defined in recent years for this reason. There are also studies showing that kisspeptin has a stimulating effect on GnRH [5]. It demonstrated kisspeptin's role in GnRH's organization in animal experiments made [6].

There are some studies showing the relation between insulin resistance and kisspeptin [7]. Although no relation is observed between kisspeptin measurements and HOMA-IR in IHH cases in our study. It was reported that testosterone application lowers insulin resistance in replacement doses in middle-aged males and also the fasting plasma insulin levels [8]. On the contrary, it was shown that testosterone treatment did not have an effect on insulin resistance in male cases with physiological levels of serum testosterone concentration [9].

Better comprehension of physiological and pathophysiological steps on reproduction is important for genetical applications, development of new treatment options and individualization of these. We think that the role of kisspeptin on gonadal axis may contribute in the development of new treatment methods. Although it is considered that kisspeptin may be used in the treatment of GnRH treatment theoretically, still there is no use of it in practice. The most important reason for this is kisspeptin's low stability [10]. With the understanding of the physiological role of gonadotropins, beginning of producing recombinant gonadotropins used commonly for treatment today may prepare appropriate conditions for peptide production. The interpretation

Figure 1. Distribution of HOMA-IR and BMI measurements.



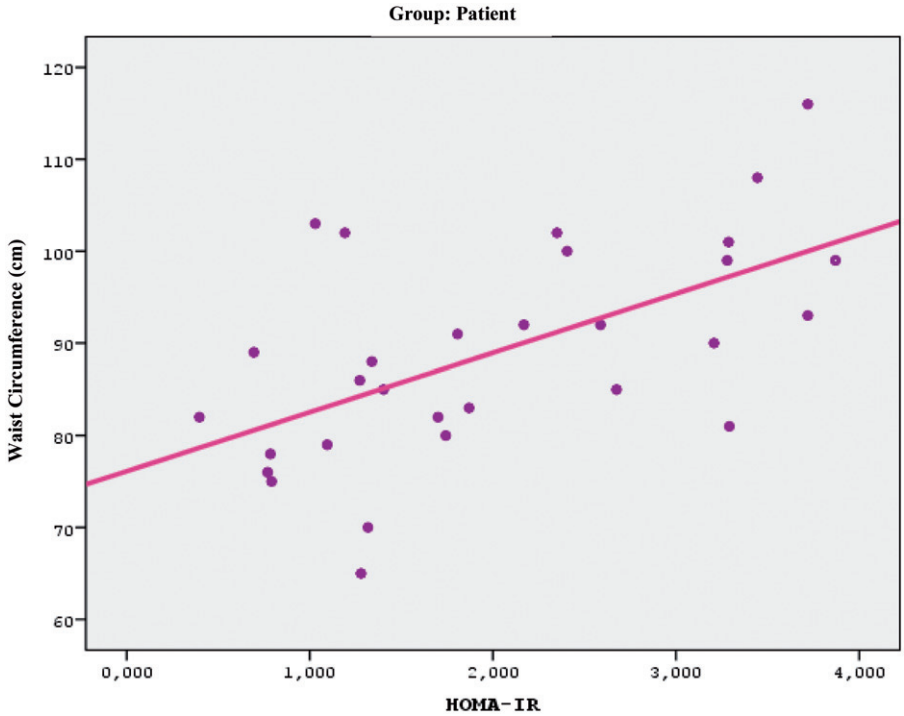


Figure 2. Distribution of HOMA-IR and waist circumference measurements.

Table 4. Relation of waist circumference and BMI measurements with HOMA-IR measurement in the patient group.

	HOMA-IR	
	r	*p*
Waist circumference	0.539	0.002†
BMI	0.406	0.026*

The test used in this table is r = Spearman's rho.
*$p < 0.05$
†$p < 0.01$

of the results should be done carefully due to some factors in our study. First of all, the number of cases included in the study is low.

It was detected that kisspeptin was high in IHH cases and had no relation with insulin resistance in our study. The reason for high kisspeptin levels in the patient group makes us consider that there may be a GPR54 resistance or GnRH neuronal transfer pathway defect. Investigating the presence of GPR54 receptor resistance in these cases may make a new contribution. Longitudinal and controlled new studies are needed in order to evaluate the relation between kisspeptin and insulin resistance in IHH cases.

Declaration of interest

All authors declare no conflict of interest.

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