Original Article

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Can Dehydroepiandrosterone-Sulphate be a New Diagnostic Parameter in Idiopathic Hypogonadotropic Hypogonadism?

Dehidroepiandrosterone-Sülfat İdiyopatik Hipogonadotropik Hipogonadizmde Yeni Bir Tanı Parametresi Olabilir Mi?

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ABSTRACT

Objective: Dehydroepiandrosterone (DHEA) and its sulfate derivative DHEA-sulfate (DHEA-s) are major androgen hormones which are synthesis from the adrenal origin. The purpose of this study was to investigate DHEA-s levels in male patients with idiopathic hypogonadotropic hypogonadism (IHH) and to determine whether DHEA-s level are a useful marker for diagnosis of IHH.

Methods: A total of 91 subjects, 31 males with IHH (mean age 19.7±2.6 years) and 60 healthy males (mean age 20.7±2.6 years), were enrolled in this study. The patients with IHH were selected from the subjects who had not yet started treatment for hypogonadism and who had no additional disease, while the healthy control group consisted entirely from individuals admitted to the same hospital outpatient clinic for routine check-ups. Both groups' blood sampling, anthropometric measures, and physical examination were undertaken

Results: Mean DHEA-s level was 133.4±56.5 μg/dL in the IHH group and 433.3±160.3 μg/dL in the control group (p=0.000). The low DHEA-s level in patients with IHH was independent of age, cortisol, and adrenocorticotropic hormone (ACTH) at multivariate logistic regression analysis. The ROC analysis showed that DHEA-s ≤38.2 μg/dL supports a diagnosis of IHH with 100% specificity and 100% sensitivity. DHEA-s was as predictive as total testosterone which is used in the diagnosis of patients with IHH.

ÖZ

Amaç: Dehidroepiandrosteron (DHEA) ve onun sülfat türevi olan DHEA-sülfat (DHEA-s) adrenal kaynaklı majör androjen hormonlardır. Bu çalışmanın amacı, erkek idiyopatik hipogonadotropik hipogonadizmli (İHH) hastalarda DHEA-s düzeylerinin araştırılması ve DHEA düzeyinin İHH tanısında yararlı bir belirteç olup olmadığını belirlemektir.

Yöntemler: Bu çalışmaya 31 İHH'li erkek (ortalama yaş 19,7±2,6 yıl) ve 60 sağlıklı erkek (ortalama yaş 20,7±2,6 yıl) olmak üzere toplam 91 kişi alındı. İHH hasta grubunda yer alan hastalar hipogonadizm için henüz tedavi başlanmamış, yeni tanı konulan ve ek hastalığı olmayan kişilerden, yine sağlıklı grupta polikliniğe rutin kontrol amaçlı başvuran tamamen sağlıklı gönüllülerden seçildi. Her iki grubun da kan örneklemesi, antropometrik ölçümleri ve fiziksel muayenesi yapıldı.

Bulgular: Ortalama DHEA-s düzeyi İHH grubunda 133,4±56,5 μg/dL ve kontrol grubunda 433,3±160,3 μg/dL idi (p=0,000). İHH hastalarında düşük DHEA seviyesi, multivariate logistic regression analizinde yaş, kortizol ve adrenokortikotropik hormondan (ACTH) bağımsızdı. ROC analizi, DHEA-s ≤38,2 μg/dL, %100 spesifite ve %100 sensitivite ile İHH teşhisini desteklediğini göstermiştir. DHEA-s, İHH'li hastaların tanısında kullanılan total testosteron kadar prediktif idi.

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Conclusion: DHEA-s level was significantly lower in the males with IHH compared to controls. Therefore, DHEA-s may be a potential predictive marker for diagnosis of IHH.

Keywords: Dehydroepiandrosterone, dehydroepiandrosterone-sulphate, idiopathic hypogonadotropic hypogonadism

Sonuç: DHEA-s düzeyi İHH'li erkeklerde kontrollere göre anlamlı olarak daha düşüktü. Bu nedenle, DHEA-s, İHH tanısı için potansiyel bir prediktif belirteç olabilir.

Anahtar Sözcükler: Dehidroepiandrosteron, dehidroepiandrosteron-sülfat, idiyopatik hipogonadotropik hipogonadizm

Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is the deficiency of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). These hormones play a major role in the regulation of the male reproductive endocrine system (1). Since LH and FSH are the trophic hormones of the testis, impairment of the secretion of these pituitary gonadotropins results in low androgen levels. The major androgen hormone is the testosterone which is secreted from the testis.

The IHH is a lifelong disease resulting from GnRH neuron dysfunction and deficiency. Clinical findings in patients with IHH include non-occurrence of puberty and virilization, delayed epiphyseal closure, small testes and penis, and azoospermia (2). The prevalence of IHH is approximately 1/10,000 in males (3).

In males, androgens regulate secondary sex characteristics. These sexual characteristics are largely determined by testosterone (gonadal steroids). Adrenal androgens have a minimal effect on the regulation of sex characteristics. The principal adrenal androgens are dehydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione. The zona fasciculata and the zona reticularis of the adrenal cortex produce a significant quantity of DHEA, an androgen precursor, and androstenedione which is considered a weak androgen. These androgen precursors are converted into more powerful androgens outside the adrenal tissue, and androgens become pathological if specific steroidogenic enzymes are defective. The purpose of this study was to investigate whether DHEA-s, a metabolic by product of testosterone, was a useful marker in the diagnosis of IHH.

Methods

A total of 91 subjects, 31 males with IHH and 60 healthy males, were recruited into the study. The patients in the IHH group were selected from recently diagnosed subjects who were not treated for hypogonadism at the Endocrinology Department of the University of Health Sciences Turkey Erzurum Regional Traning and Research Hospital. The healthy control group consisted of subjects who were admitted for routine check-ups at the Internal Medicine Outpatients clinics in the same hospital. The disease was identified as having total testosterone level <229 ng/dL and free testosterone level <5.1 pg/mL due to the absence or deficiency of pituitary gonadotropins. All patients underwent the GnRH test and no FSH and LH response were observed, and also growth hormone deficiency was excluded. Again, hypothalamus and pituitary gland imagings were performed in all patients. Exclusion criteria were chronic illness, panhypopituitarism, hypo and hyperthyroidsm, nephrotic syndrome, steroid use or use of any drug causing hypogonadism. Also, none of the study subjects was a current smoker or alcohol user. All participants gave their written informed consent to participate in the study and the study was approved by the local ethical committee (2018/05/27).

Total testosterone, free testosterone, LH, FSH, adrenocorticotropic hormone (ACTH), cortisol and DHEA-s levels were investigated in the patient and the control groups. Body mass index (BMI) was calculated by the ratio between weight and height squared in kg/m^2. DHEA-s and ACTH levels were analyzed using Siemens Immulite 2000 XPİ (Siemens Healthcare Diagnostics Inc., Munich, Germany) device by solid-phase, competitive chemiluminescent enzyme immunoassay method. LH, FSH, total testosterone, and free testosterone levels were analyzed using Abbott Architect i2000 SR (Abbott Türkiye, İstanbul, Turkey) device and the chemiluminescent microparticle immunoassay method. Ten cubic centiliter venous blood specimens were collected for hormonal analysis from all patients and healthy volunteers from the antecubital vein between 07:30 and 09:00 in the morning after 12-hour fasting. These specimens were centrifuged for 10 min at 4000 rpm using an Electromag M4808 P Centrifuge device. Data were obtained by analyzing blood specimens in appropriate analyzers.

Statistical Analysis

After analysis of the variance, comparisons between groups were done using Student's t-test or Mann-Whitney U test for continuous data. Unless otherwise stated, the results were expressed as mean ± stadart deviation. One-tailed Pearson's correlation test or Spearman correlation test was performed to find out the correlation between various variables. Logistic regression analysis was performed whenever it was appropriate. ROC curve analysis assessed the cut-off DHEA-s level with the best diagnostic accuracy for detecting IHH. $p<0.05$ was considered statistically significant. The statistical analysis was performed using SPSS version 19.0 software program (IBM-SPSS, Chicago, USA).

Results

There wasn't any significant difference between sociodemographic characteristics of the patient and the healthy control groups. The mean ages were 19.7±2.6 years in the patient group and 20.7±2.6 years in the control group (p=0.1). BMI values in the patient and the healthy control groups were 21.9±4.8 kg/m^2 and 25.4±7.8 kg/m^2, respectively (p=0.1). The sociodemographic characteristics of both groups are summarized in Table 1.

The mean DHEA-s values were 133.4±56.5 µg/dL in the IHH group and 433.3 ± 160.3 µg/dL in the control group (p<0.001). The total testosterone levels in the patient and control groups were 28.0±26.3 nmol/L and 568.1±288.0 nmol/L, respectively (p<0.001). In the patient and the control groups, the free testosterone levels were 9.7±14.3 pg/mL and 18.0±9.0 pg/mL, respectively (p=0.006). The FSH levels were 1.6±2.4 mIU/mL and 4.3±5.4 mIU/mL (p<0.001), and the LH levels were 0.7±0.9 mIU/mL and 4.2±2.6 mIU/mL (p<0.001) in the patient and the control groups, respectively. The results are summarized in Table 1.

Table 1. Clinical and biochemical characteristics of the patient and control groups

	IHH	Control	p value
Total number of patients	31	60	
Age (years)	19.7±2.6	20.7±2.6	0.1
Weight (kg)	62.8±16.8	66.1±18.5	0.7
Height (cm)	168±9	162±16	0.2
BMI (kg/m²)	21.9±4.8	25.4±7.8	0.1
DHEA-s (µg/dL)	133.4±56.5	433.3 ± 160.3	0.000*
Total testosterone (nmol/L)	28.0±26.3	568.1±288.0	0.000*
Freetestosterone (pg/mL)	9.7±14.3	18.0±9.0	0.006*
FSH (mIU/mL)	1.6±2.4	4.3±5.4	0.000*
LH (mIU/mL)	0.7±0.9	4.2±2.6	0.000*
ACTH (pg/mL)	23.1±10.4	24.3±13.0	0.7
Cortisol (µg/dL)	13.9±4.1	15.9±5.3	0.7
p<0.05 significantly*			

ACTH: Adrenocorticotrophic hormone, BMI: Body mass index, DHEA-s: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

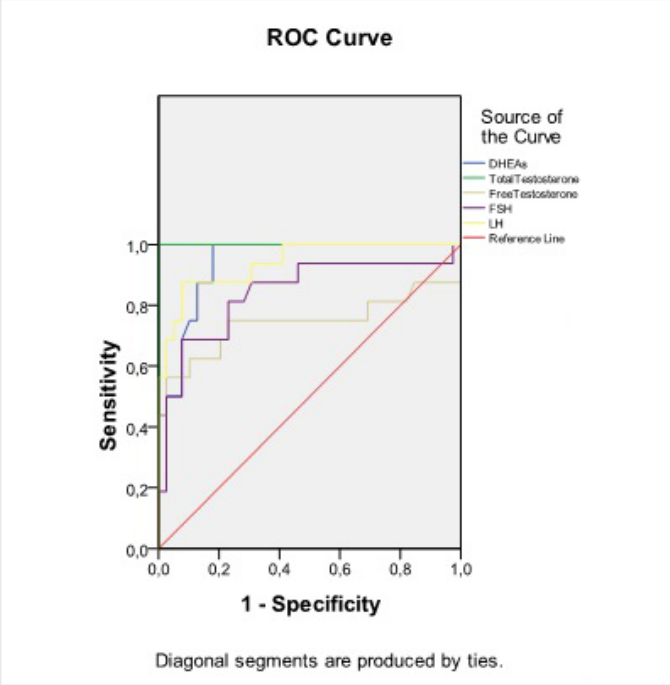

Figure 1. ROC curve

The ACTH levels in the patient and the control groups were 23.1±10.4 pg/mL and 24.3±13.0 pg/mL (p=0.7), and the cortisol levels were 13.9±4.1 µg/dL and 15.9±5.3 µg/dL (p=0.7), respectively (Table 1). At the correlation analysis, the DHEA-s level exhibited the positive correlations with the total testosterone (p=0.02, r=0.411), free testosterone (p=0.01, r=0.412), cortisol (p=0.005, r=0.321), ACTH (p=0.01, r=0.382), LH (p<0.001, r=0.432) and prolactin levels (p=0.01, r=0.295), and BMI (p=0.01, r=0.307). The data obtained are shown in Table 2.

Multiple regression analysis of the DHEA-s level and the other risk factors were performed. Low DHEA-s level was found to be an independent risk factor from age and cortisol and ACTH levels in patients with IHH. The data obtained are shown in Table 3. The ROC curve of DHEA-s level predicting IHH is shown on the Figure 1. The AUC of the DHEA-s was 0.95 (p<0.001). The cut-off point of DHEA-s level was ≤38.2 µg/dL (sensitivity: 100%; specificity 100%).

Discussion

In the present study, it was be detected that the DHEA-s level in males with IHH was much lower than the healthy subjects.

Table 2. The correlation relationship between DHEA-s and other factors

	r (correlation coeffcient)	p
Height (cm)	0.107	0.4
Weight (kg)	0.219	0.08
Age(years)	0.190	0.08
BMI (kg/m²)	0.307	0.01*
T. testosterone (nmol/L)	0.411	0.02*
F. testosterone (pg/mL)	0.412	0.01*
Cortisol (µg/dL)	0.321	0.005*
ACTH (pg/mL)	0.382	0.01*
FSH (mIU/mL)	0.05	0.6
LH (mIU/mL)	0.432	0.000*
Prolactin (ng/mL)	0.295	0.01*

ACTH: Adrenocorticotrophic hormone, BMI: Body mass index, DHEA-s: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

Table 3. Multivariate regression values

Variables	DHEA-s	
	β	p
Age (years)	0.8	0.4
ACTH (pg/mL)	1	0.2
Cortisol (µg/dL)	0.8	0.1

ACTH: Adrenocorticotrophic hormone, DHEA-s: Dehydroepiandrosterone sulfate

The DHEA-s level was determined in patients on the basis diagnostic phases. The DHEA-s level was found lower in the patients. This is one of the first studies to show that the DHEA-s is an easily identifiable marker that can be used in the diagnosis of IHH. We found out that the DHEA-s level ≤38.2 µg/dL predicted the diagnosis of IHH with 100% sensitivity and 100% specificity.

Puberty is a process that begins prenatally and ends in adulthood with the autoregulation of all hormonal secretions. This continuity is based on the equilibrium between neurohormones (GnRH), neurotransmitters (biogenic amines), pituitary gonadotropin (FSH, LH) secretion, and final organ reaction (testis or ovarium) (4). Normal pubertal development involves the release of GnRH from the hypothalamus and activation of the hypothalamic-pituitary-gonadal (HPG) axis, followed by activation in the hypothalamic-pituitary-adrenal axis. This enables the individual to achieve full sexual maturity. Testosterone release in males begins with the effect of GnRH and subsequently of LH and FSH after the onset of pubertal development. As pubertal development continues, adrenal androgens are secreted from the adrenal gland under the effect of ACTH. Adrenarche is referred to the developmental changes concluding with the increased androgen secretion from the adrenal glands (5).

The DHEA and its sulfate conjugate (DHEA-s) are the major steroids secreted from the adrenal glands (6). DHEA-s is the adrenal androgen most present in the circulation. It is regarded as a marker of the onset of adrenarche, and also plays a role in the pubertal development (7). Androgens and estrogens are synthesized from DHEA. DHEA forms from a series of metabolic pathways using cholesterol as a substrate. In the final stage, androgens are synthesized from DHEA with the effect of 17,20-lyase (8,9).

The DHEA, a metabolic by-product in the biosynthesis of the male sex hormone testosterone, follows a circadian rhythm that peaks in the mornings. In contrast, DHEA-s has a relatively stable concentration throughout the day, and it is used as a useful biomarker of adrenal androgen secretion and DHEA. DHEA-s is released from the zona reticularis of the adrenal cortex as a response to ACTH. Production reaches a peak in young adulthood and then decreases by 2-4% a year (10,11).

Since the patient group enrolled in this study had testosterone deficiency due to IHH, and since both the patient group and the control group consisted of young males, we did not determine the age-dependent decrease in the DHEA-s levels. This study investigated the practicability and effectiveness of measuring DHEA-s levels in the diagnosis of patients with IHH characterized by the absence or deficiency of pubertal development.

Previous studies in the literature have investigated the DHEA and DHEA-s levels in panhypopituitarism and pubertal disorders. Differing opinions have been reported on the subject. Giton et al. (12) reported significantly lower DHEA-s level in the patients diagnosed as having IHH and panhypopituitarism compared to the control group. Cohen et al. (13). investigated the levels of adrenal androgens such as DHEA, DHEA-s, and androstenedione in 90 patients with delayed puberty. The DHEA-s level was low in all patients and the authors reported that the DHEA-s level was able to identify 89% of patients with hypogonadotropic hypogonadism. They concluded that measurement of serum DHEA-s levels could be a considerable assistance in the early diagnosis of conditions that might lead to delayed puberty (13). In our study, we also showed that low-level DHEA could identify IHH with 100% sensitivity and 100% specificity.

Rohayem et al. (14) investigated the usefulness of gonadal activity, growth axis activation, and adrenarche markers due to the limited specificity and sensitivity of diagnostic parameters indistinguishing between the constitutional delay of growth and puberty (CDGP) and IHH, and the difficulty in establishing the diagnosis. Seventy four subjects with delayed puberty were enrolled, 24 with hypogonadotropic hypogonadism, 22 classified as pre-pubertal CDGP (PP-CDGP) and 28 with early-pubertal CDGP (EP-CDGP). The LH, FSH, testosterone, inhibin B, and the Anti-Mullerian hormone levels of all patients were investigated. In addition, insulin-like growth factor (IGF)-1, IGFBP3, INSL3, and DHEA-s levels were also investigated in 9 patients in the IHH group, 8 in the PP-CDGP group and all patients in the EP-CDGP group. DHEA-s level was assessed as a marker of adrenarche, and no significant difference was determined between the three groups.

Conclusion

Although we observed no significant difference between the IHH and the control groups in terms of ACTH and cortisol levels in this study, we determined a significant difference in terms of DHEA-s levels. In conclusion, we think that DHEA-s level is as practicable and predictable marker of total testosterone levels in the diagnosis of patients with IHH.

Ethics

Ethics Committee Approval: The study was approved by the local ethical committee (2018/05/27).

Informed Consent: All participants gave their written informed consent to participate in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: K.Ç., H.K., M.B., A.Ç., Ş.C.A., Design: K.Ç., A.Ç., Ş.C.A., Data Collection or Processing: K.Ç., H.K., M.B., A.Ç., Ş.C.A., Analysis or Interpretation: K.Ç., H.K., M.B., A.Ç., Ş.C.A., Literature Search: K.Ç., H.K., M.B., Writing: K.Ç., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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