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The Evaluation of Testes by Shear Wave Elastography in Patients with Isolated Hypogonadotropic Hypogonadism

İzole Hipogonadotropik Hipogonadizmli Hastalarda Testislerin Shear Wave Elastografi ile Değerlendirilmesi

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Abstract

Aim: The aim of this study was to evaluate testicular stiffness by shear wave elastography (SWE) in patients with isolated hypogonadotropic hypogonadism (IHH) and to compare it with healthy controls.

Material and Method: In this prospective study, 35 patients with IHH (group 1) and 40 healthy controls (group 2) were evaluated. These two groups were compared in terms of age, testicular volume, and SWE values. In a subsequent analysis, IHH patients were divided into 3 groups: those who were newly diagnosed and did not receive any treatment (group A), those who received testosterone replacement (group B), and those who received human chorionic gonadotrophin alpha (hCG) (group C). Testicular volumes and SWE values were also compared between these subgroups.

Results: Testicular volumes were significantly lower in group 1 than in group 2 (p<.001). Group 1 had significantly higher testicular SWE values than group 2 (p<.001). There was also a negative correlation between the mean value of testicular stiffness and testicular volume in group 1 (r=-0.555, p=.001 for right testes, r=-0.403, p=.016 for left testes). Results of subsequent analysis by treatment status showed that patients in group C had significantly increased testicular volumes. In addition, they tended to have lower SWE values, when compared to groups A and B.

Conclusion: SWE values were significantly higher in IHH patients compared to healthy controls. We found significant improvements in SWE values even in patients receiving short-term hCG replacement. Further research is needed on whether basal SWE values of IHH patients can predict fertility in patients with IHH.

Keywords: Isolated hypogonadotropic hypogonadism, elastography, testicular stiffness, male infertility

Öz

Amaç: Bu çalışmanın amacı, izole hipogonadotropik hipogonadizm (IHH) hastalarında testis sertliğini shear wave elastografi (SWE) ile değerlendirmek ve sağlıklı kontrollerle karşılaştırmaktı.

Gereç ve Yöntem: Bu prospektif çalışmada IHH'lı 35 hasta (grup 1) ve 40 sağlıklı kontrol (grup 2) değerlendirildi. Bu iki grup yaş, testis hacmi ve SWE değerleri açısından karşılaştırıldı. Daha sonra yapılan bir analizde IHH hastaları, yeni teşhis konulan ve herhangi bir tedavi almayanlar (A grubu), testosteron replasmanı uygulananlar (B grubu) ve human koryonik gonadotropin alfa (hCG) alanlar (C grubu) şeklinde üç gruba ayrıldı. Testis hacimleri ve SWE değerleri de bu alt gruplar arasında karşılaştırıldı.

Bulgular: Testis hacimleri grup 1'de grup 2'ye göre anlamlı derecede düşüktü (p<.001). Grup 1'deki olguların testiküler SWE değerleri grup 2'ye göre anlamlı olarak yüksekti (p<.001). Grup 1'deki olgularda testis sertliği ortalama değeri ile testis hacmi arasında da negatif korelasyon vardı (sağ testis için r=-0.555, p=.001, sol testis için r=-0.403, p=.016). Tedavi durumuna göre elde edilen analiz sonuçları, C grubundaki hastaların testis hacimlerinde önemli ölçüde artış olduğunu gösterdi. Ayrıca C grubundaki olgular, A ve B gruplarına göre daha düşük SWE değerlerine sahip olma eğilimindeydiler.

Sonuç: SWE değerleri IHH hastalarında sağlıklı kontrollere göre anlamlı olarak yüksekti. Kısa süreli hCG replasmanı alan hastalarda bile SWE değerlerinde önemli düzelmeler bulduk. IHH hastalarının bazal SWE değerlerinin IHH'li hastalarda fertiliteyi öngörüp göremeyeceği konusunda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: İzole hipogonadotropik hipogonadizm, elastografi, testiküler sertlik, erkek infertilitesi

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INTRODUCTION

The onset of puberty and achieving fertility depend on the pulsatile release of hypothalamic gonadotropin-releasing hormone (GnRH), which stimulates luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary.[1] A disruption of this axis in the hypothalamic and/or pituitary region results in hypogonadotropic hypogonadism (HH). In general, there are two types of HH, congenital and acquired. The term isolated/idiopathic HH (IHH) refers to HH without anatomical or functional abnormalities in the hypothalamus or pituitary glands.[2] The prevalence of IHH in men is approximately 1:8,000 and is characterized by lack of sexual development and infertility.[3] The first clinically observable sign of puberty in boys is testicular enlargement, but patients with IHH tend to have low testicular volume. Treatment to induce puberty at the right time is critical for sexual, bone, and metabolic health, as well as for psychosocial effects.[4] The treatment regimen for IHH is principally determined by whether the goal is to promote secondary sexual characteristics or to induce fertility.[5] Testicular volume before treatment is thought to be one of the main indicators of spermatogenesis response in patients with IHH who want to have kids.[6,7]

Ultrasonography (US) is a non-invasive, repeatable and inexpensive imaging method commonly used to examine testes. Elastography is a US-based imaging method used to evaluate the stiffness of the tissues.[8] Strain elastography and shear wave elastography are the two types of elastography that are now obtainable.[9] Strain elastography (SE) measures tissue stiffness by applying a compression force to the lesion's surface. The extent of tissue deformation that occurs is related to the stiffness of the lesion. SE is regarded as operator-dependent due to the elastogram's quality depends significantly on the user's examine and application. Shear wave elastography (SWE) generates shear waves in the underlying tissue with varying velocities dependent on the stiffness of the tissue using acoustic radiation force impulses (ARFI). Shear wave velocity readings can be collected as a single value in a fixed region of interest (ROI) or as multiple values for each point in a field of view (FOV). The latter is often referred to as two-dimensional shear wave elastography (2D-SWE).[10] There have been several studies on the use of SWE in normal testis and these studies have provided an adequate basis for more systematic investigations.[11-13]

The aim of this study was to evaluate the testicular stiffness of IHH patients with SWE and to compare the results with the normal healthy control group.

MATERIAL AND METHOD

This was a single-center prospective case-control study conducted between December 2021 and July 2022. The local ethical committee approved the study protocol according to the Helsinki Declaration (29.11.2021-HRU/21.21.05). All participants provided written consent prior to data collection.

Study Participants

Female patients with IHH were not included in the study. A total of 35 male patients with IHH (Group 1) and 40 healthy control males (Group 2) were included in this study. The results of the physical examination, laboratory tests, and radiological imaging were used to diagnose IHH. The following diagnostic criteria were used: a lack of spontaneous puberty before the age of 18, a decrease in testosterone concentration below the normal range for adults, a low or inappropriately normal level of FSH and LH, and a normal result of hypothalamo-pituitary magnetic resonance imaging. None of the patients had hyposmia, anosmia, or a family history of IHH. Patients with IHH who registered to the endocrine outpatient clinic underwent to ultrasound and elastography exams based on these diagnostic criteria. During the ultrasound and elastography examination, the radiologist was unaware of the patients' clinical information. Following an ultrasound and elastography examination the patients were then divided into three groups based on their treatment status. The first group (Group A) consisted of newly diagnosed patients who did not receive any treatment; the second group (Group B) consisted of patients who received parenterally administered testosterone; and the third group (Grup C) consisted of patients who received human chorionic gonadotrophin alpha (hCG). The control group was composed of healthy male employees at our hospital.

Ultrasound and SWE examination

Ultrasonography and shear-wave elastography examinations of testes was performed by a single radiologist who had 14 years of ultrasonography and 4 years of elastography experience. The examinations were performed by using the Siemens ACUSON S2000 US system (Siemens Medical Solution, MountainView, CA, USA) with a 9L4 probe. The 2D-SWE method utilized in this study was the most recent SWE approach that used acoustic radiation force. While the patient or volunteer were in the supine position, the gray scale US examination of both testes was performed first. Patients with testicular lesions, hydrocele, or varicocele were excluded from the study at this point. All testes were measured in the largest three dimensions (length (L) × width (W) × height (H)), and the testicular volume was then automatically calculated by US device. In order to prevent additional compression and stabilize the elastography images, the linear array transducer was applied very gently to the skin. The sampling box was adjusted to the testis, and a SW quality map was first acquired. Green on the map denotes good SW quality, yellow for marginal SW quality, and red for poor SW quality. After that, SW velocity mode was initialized, and a 2D color map of shear wave velocity (SWV) distribution within the testes was obtained. The color of the map represents the SWV from high (red or orange), intermediate (yellow or green), to low (dark or light blue). A high quality SWE image was selected and the SWV was then measured by a fixed ROI (2×2 mm) in the shear wave velocity map. SWE values were measured in the longest longitudinal plane. SWE values were obtained in both speed mode (m/s) and elasticity mode (kPa). Nine ROI were placed in each testis. Three ROI placed on the upper pole, three on the middle region, and three on the lower pole of the testis (**Figure 1**). Based on the mean value of nine SWE measurements, a statistical analysis was conducted.

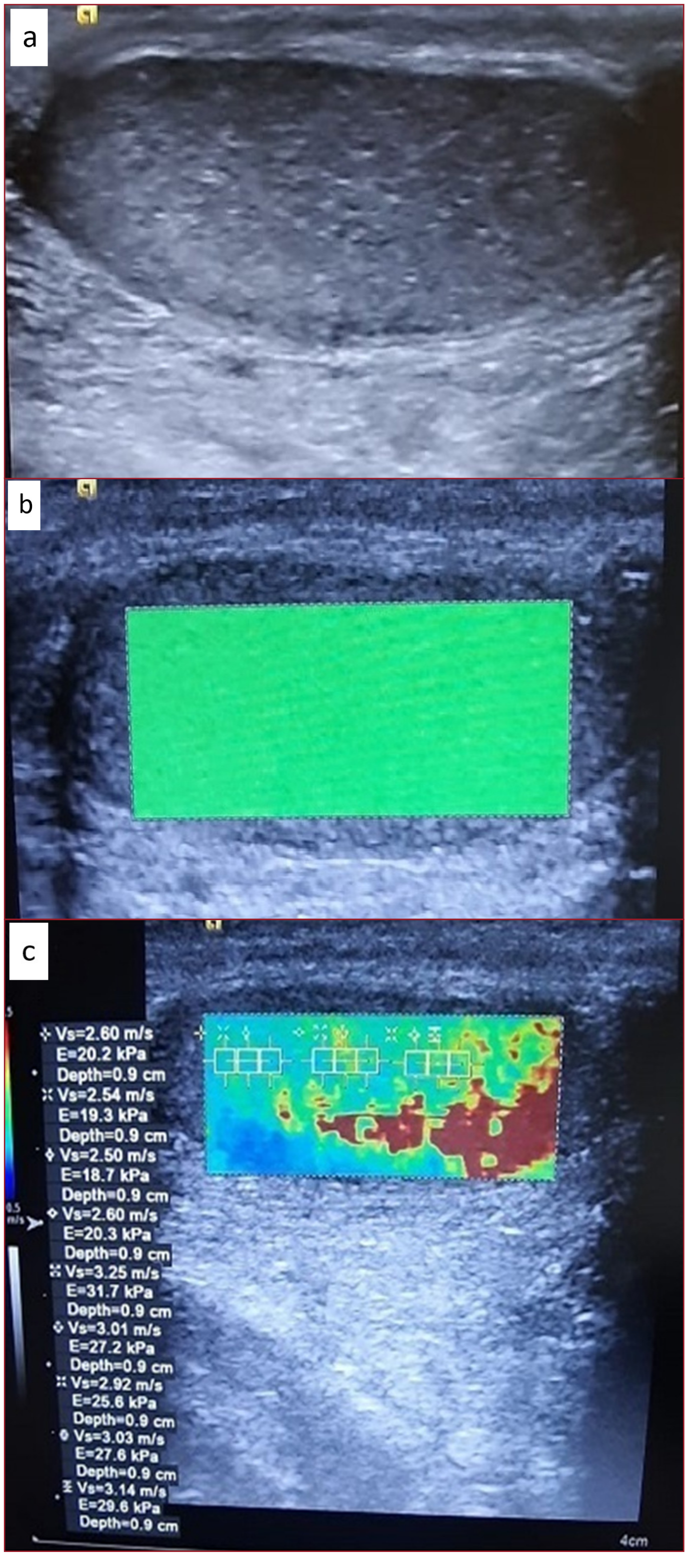

Figure 1. a) Gray scale image of testis of a 32-year-old male patient with a diagnosis of IHH (Group A). Note the heterogeneous echotexture of the testis. b) The quality map of same patient. c) Three measurements were obtained from each part of testis in the longest longitudinal plane. SWE images were displayed in speed mode (m/s) and elasticity mode (kPa).

Statistical Analysis

The Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago IL, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to verify the normality of the data. According to the distribution of the data, the mean±standard deviation or median and interquartile range were calculated. The continuous variables were analyzed using independent samples t-tests or Mann-Whitney U tests, based on their distribution. We compared categorical variables with the Chi-square test. Homogeneity of variances was evaluated with Levene's test. If the data were normally distributed, one-way analysis of variance (ANOVA) was used to compare three or more groups. In post-hoc analyses, Tukey's test was used if homogeneity of variance was assumed. Whenever normality tests failed, the Kruskal-Wallis test was used to compare three or more groups and pairwise comparisons were conducted for subgroup analysis.

RESULTS

In this study, 75 participants were included, 35 patients with IHH in group 1 and 40 healthy controls in group 2. Group 2 had a higher mean age, but this difference was not statistically significant(group1: 25.97±6.06, group 2: 29.02±7.29, p=.054). In the group 1 patients, the right testicular volume (RTV) was 4.45±2.83 ml and the left testicular volume (LTV) was 4.22±2.58 ml, which was significantly lower than the testicular volumes in group 2 (RTV: 13.74±2.46ml, LTV: 13.50±2.38ml (p<.001 for both). On the basis of elasticity and velocity parameters, IHH patients had mean SWE values of 14.88±4.01 kPa and 2.20±0.29 m/s for right testes, and median 14.6 (11.52-16.42) kPa and 2.20 (1.95-2.33) m/s for left testes. In the control group, the mean SWE values were 5.17±1.22 kPa and 1.29±0.15 m/s for right testes, and median 4.28 (3.77-5.79) kPa and 1.24 (1.18-1.43) m/s for left testes. Patients in group 1 had significantly higher stiffness values in both testicles than those in group 2 (p<.001) (**Table 1**).

Table 1. Group-wise baseline characteristics of subjects

Parameters	Healthy control	IHH	P-value
Age (years)	29.02±7.29	25.97±6.06	.054[a]
RT Volume (ml)	13.74±2.46	4.45±2.83	<.001[a]
LT Volume (ml)	13.50±2.38	4.22±2.58	<.001[a]
RT-SWVV (m/s)	1.29±0.15	2.20±0.29	<.001[a]
LT-SWVV (m/s)	1.24 (1.18-1.43)	2.20(1.95-2.33)	<.001[b]
RT-EM (kPa)	5.17±1.22	14.88±4.01	<.001[a]
LT-EM (kPa)	4.28 (3.77-5.79)	14.6 (11.52-16.42)	<.001[b]

Abbreviations: IHH; Isolated hypogonadotropic Hypogonadism, SWVV; Shear Wave Velocity Values, EM; Elastic Modulus RT; Right Testis, LT; Left Testis. Data areexpressed as the mean and Standard deviation or median (first and third quartile) values. p value< 0.05 was considered significant. Significant p values are highlighted in bold .a: Independent samples t-test. b: Mann-Whitney U test

Correlation analysis showed that the volume of the testicles increased with increasing age in patients with IHH (r=0.423, p=.011 for right testes, r=0.460, p=.005 for left testes). There was also a negative correlation between the mean value of testicular stiffness and testicular volume (r=-0.555, p=.001 for right testes, r=-0.403, p=.016 for left testes) (**Table 2**).

Table 2. A correlation analysis of group 1 patients regardless of their treatment status

		RT Volume (ml)	LT volume (ml)	RT-SWV (m/s)	LT-SWV (m/S)
Age (years)	r value	.423*	.460**	-.142	.052
	p value	.011	.005	.415	.793
RT Volume (ml)	r value		.944***	-.555**	-.392*
	p value		<.001	.001	.020
LT Volume (ml)	r value			-.531**	-.403*
	p value			.001	.016
RT-SWVV (m/s)	r value				.761***
	p value				<.001

Abbreviations: RT; Right Testis, LT; Left Testis, r: Pearson's correlation, p value< 0.05 was considered significant. Significant p values are highlighted in bold

In the final analyses, patients were divided into three groups according to their treatment status (Group A, B, and C) (**Table 3**). The mean age of patients in group A was significantly lower than those in group B and C (p=.001). There was a significant increase in mean testicular volume in group C patients when compared with both group A and B (p<.001). The values of testicular stiffness in group C patients were significantly lower than those in group A. However, there was no significant difference between group A and group B in terms of testicular stiffness.

Table 3. The comparison of IHH patients based on their treatment status

	Group A (n:11) (Treatment-naive)	Group B (n:10) (IM testosterone)	Group C (n:14) (hCG alpha)	p value
Age (years)	20.90±3.93[a**b**]	29.20±3.64	27.64±6.49	.001
RT Volume (ml)	2.21±1.35[b***c*]	3.98±2.59	6.26±2.04	<.001
LT Volume (ml)	2.20±1.07[b***c*]	3.68±2.64	6.19±1.97	<.001
RT-SWVV (m/s)	2.36±0.28[b*]	2.20±0.28	2.06±0.24	.032
LT-SWVV (m/s)	2.21±0.24	2.24±0.26	2.05±0.29	.200
RT-EM (kpa)	17.18±4.18[b*]	14.95±3.97	13.04±3.10	.033
LT-EM (kpa)	14.89±3.36	15.50±3.77	12.96±3.80	.215

Abbreviations: HCG; Human chorionic gonadotrophin, IM; Intramuscular, SWVV; Shear Wave Velocity Value, EM; Elastic Modulus, RT; Right Testis, LT; Left Testis
Data are expressed as the mean and standard deviation. p value<.05 was considered significant. Significant p values are highlighted in bold
The definition of post hoc analysis: a: between group A and B, b: between group A and C, c: between group B and C, *: p value between .05-.01, **: p value between .01-.001, ***: p value<.001

DISCUSSION

The most important distinguishing feature of this study is that SWE was used for the first time to determine testicular stiffness in patients with IHH. It was already expected that testicular volumes would be lower in patients with IHH than in healthy controls. These patients also displayed a significant increase in testicular stiffness in comparison to healthy controls. One of the most interesting aspects of our study is the observation that the degree of stiffness in the testicles may vary according to the treatment regimen used. Despite a relatively limited number of patients and a relatively short treatment period, we found significant differences in testicular volume increase and reduced testicular stiffness in patients receiving human chorionic gonadotropin alpha versus other groups. This could indicate that optimal hormone replacement therapy (LH and FSH) is associated with improved testicular parenchyma in patients with IHH. There is already evidence to suggest that testosterone replacement alone is not sufficient to stimulate testicular growth or spermatogenesis in patients with IHH.[6]

The effectiveness of SWE in assessing the stiffness of tissues or lesions has been demonstrated in a variety of organs, including the thyroid, breast, and liver.[14-16] In recent years, SWE has become one of the more common methods for evaluating testicles. A significant increase in testicular stiffness was observed with the SWE method in patients with testicular tumors, varicocele and torsion.[17-21] Based on a meta-analysis of studies that used the SWE to distinguish between malignant and benign testicular lesions, the researchers found that the pooled sensitivity was 87% and the pooled specificity was 81%. As a general rule, malignant lesions are considered to be harder than benign lesions.[22] It should be noted, however, that stiffness measurements of some benign lesions with calcification may be higher and, stiffness measurements of some malignant lesions with necrosis and liquefaction may be lower.[17] In varicoceles, stiffer testicles are thought to be associated with germ cell atrophy, thickened tubular basement membranes, and increased interstitial fibrosis.[18] In both animal and human studies, testicular torsion has been associated with increased testicular stiffness. Increased stiffness is believed to be associated with increased intratesticular pressure due to venous obstruction, tissue edema, bleeding and necrosis.[20,21]

A number of studies have demonstrated that infertile males have increased testicular stiffness.[23-26] Urologists use tissue palpation to assess scrotal stiffness, but it is a subjective tool that requires experience. An abnormal spermiogram may indicate parenchymal damage. Due to the invasive nature of testicular biopsy, it is no longer routinely recommended for assessing histological features of parenchymal damage.[27] According to an experimental study on white rabbits, increased testicular stiffness after testicular torsion was positively correlated with impaired spermatogenesis.[23] In a study involving 1,116 men undergoing in vitro fertilization treatment, increased testicular stiffness was found to be inversely related to total sperm count. This condition has been linked to fibrotic thickening of the walls of seminiferous tubules in the testicles.[24] It was also observed in another study by Erdogan et al. that infertile men exhibited significantly higher testicular SWE values than healthy controls. They also stated that testicular stiffness increased with decreasing testicular volumes. The increased testicular stiffness values have been attributed to parenchymal damage that impairs spermatogenesis.[25] In the study conducted by Illiano et al. similar findings were reported as well.[26] In testicular biopsy samples taken from azoospermic males, Li et al. observed an increase in the thickness of lamina propria and a decrease in the diameter of seminiferous tubules and spermatogenetic epithelium height.[28]

In our patient group, in addition to increased testicular stiffness, we also found a decrease in testicular echo and heterogeneity on gray scale imaging. According to histopathological findings in patients with IHH, the seminiferous tubules are separated by an interstitial space that consists of blood vessels, connective tissue cells, and collagen fibers. However, typical adult Leydig cells were not detected. Moreover, only immature sertoli cells and early type A spermatogonia were found in the cords.[29] This findings suggests that increased testicular stiffness in IHH patients may be related to increased connective tissue.

The Study's Strengths and Limitations

Our study had some limitations. Firstly, the study included a relatively small number of patients. Secondly, all SWE measurements were performed by a single radiologist, and only one measurement was taken. However, we believe that taking nine separate measurements from each part of the testis would result in a higher level of accuracy. A third limitation involves the lack of analysis of sperm parameters and the inability to compare histopathological findings among patients. One of the strengths of our study is that testicular stiffness in IHH patients was evaluated with SWE for the first time in the literature. A further noteworthy finding was the significant reduction in testicular stiffness observed in patients receiving hCG alpha in comparison to those receiving testosterone replacement therapy.

CONCLUSION

Testicular stiffness was significantly higher in IHH patients than in healthy controls. A significant improvement in testicular stiffness was observed in patients treated with hCG alfa compared with those treated with testosterone. In patients with IHH, detection and monitoring of testicular stiffness using the SWE may be useful in demonstrating the effectiveness of treatment. Future prospective studies with a larger sample size are needed to confirm this study's findings..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Non-interventional Clinical Researches Ethics Committee (Date: 29.11.2021, Decision No: HRU/21.21.05).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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