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Research

Use of Volumetric Apparent Diffusion Coefficient to Distinguish Between Obstructive and Non-obstructive Azoospermia: A Case-control Study

Obstrüktif ve Obstrüktif Olmayan Azoospermi Ayrımında Volumetrik Görünür Difüzyon Katsayısının Kullanımı: Bir Olgu Kontrol Çalışması

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ABSTRACT

Objective: It is suggested that the use of non-invasive and cost effective imaging modalities, including magnetic resonance imaging (MRI), can be beneficial for detecting areas with spermatogenesis and predicting the presence of sperm in testicles, thereby improving the management of patients with azoospermia.

Methods: This descriptive and analytical study included 38 patients with azoospermia who presented to the Firoozgar and Hazrat Rasoul Akram Hospitals in Tehran, Iran. The patients underwent MRI, testicular biopsy, and hormonal examination. The data were analyzed and compared between the patients with obstructive azoospermia (OA) and non-obstructive azoospermia (NOA).

Results: The present study included 76 testicles from 38 patients with OA (n=14) and NOA (n=24). According to our findings, the patients with OA and NOA did not differ significantly in testosterone (OA: 4.78, NOA: 5.33, p=0.755) and prolactin levels (OA: 10.75, NOA: 9.77, p=0.540). However, those with NOA had significantly higher levels of follicle-stimulating hormone (OA: 4.66, NOA: 20.61, p<0.001) and luteinizing hormone (OA: 3.15, NOA: 12.40, p<0.001), as well as apparent diffusion coefficient (ADC) (OA: 0.96, NOA: 1.16, p<0.001). Moreover, the patients with OA had a significantly higher testis volume (20.37 cm³) compared with those with NOA (8.16 cm³, p<0.001). Additionally, there were significant correlations between pathological grade and the variables of testicular volume (correlation coefficient: 0.672, p<0.001) and ADC (correlation coefficient: 0.480, p<0.001). Finally, the multivariate regression analysis showed a significant relationship between testicular volume and pathological grade. The receiver operating characteristic curves show the performance of ADC [area under curve is 0.954 (95% confidence interval; 0.912-0.995)] between OA and NOA.

Conclusion: The MRI-related parameters of ADC and testicular volume help differentiate and diagnose OA and NOA.

Keywords: Genital diseases, infertility, azoospermia, multiparametric magnetic resonance imaging, volumetric apparent diffusion

ÖZ

Amaç: Manyetik rezonans görüntüleme (MRG) dahil olmak üzere invaziv olmayan ve uygun maliyetli görüntüleme yöntemlerinin kullanımının, spermatogenez bulunan alanları tespit etmek ve testislerde sperm varlığını tahmin etmek için yararlı olabileceği ve böylece azoospermili hastaların yönetimine katkı sağlayacağı öne sürülmektedir.

Gereç ve Yöntem: Bu tanımlayıcı ve analitik çalışmaya, İran'ın Tahran şehrindeki Firoozgar ve Hazrat Rasoul Akram Hastaneleri'ne başvuran 38 azoospermili hasta dahil edildi. Hastalara MRG, testis biyopsisi ve hormonal muayene uygulandı. Veriler analiz edildi ve obstrüktif azoospermili (OA) ve non-obstrüktif azoospermili (NOA) hastalar arasında karşılaştırma yapıldı.

Bulgular: Çalışmaya OA (n=14) ve NOA (n=24) tanısı almış 38 hastaya ait 76 testis dahil edildi. Bulgularımıza göre, OA ve NOA tanılı hastalarda testosteron (OA: 4,78, NOA: 5,33, p=0,755) ve prolaktin düzeyleri (OA: 10,75, NOA: 9,77, p=0,540) arasında anlamlı bir fark yoktu. Ancak NOA'lı hastalarda folikül uyarıcı hormon (OA: 4,66, NOA: 20,61, p<0,001) ve luteinize edici hormon (OA: 3,15, NOA: 12,40, p<0,001) düzeyleri ve görünür difüzyon katsayısı (ADC) (OA: 0,96, NOA: 1,16, p<0,001) anlamlı derecede daha yüksekti. Ayrıca OA'lı hastaların testis hacmi (20,37 cm³) NOA'lı hastalara (8,16 cm³, p<0,001) göre anlamlı derecede daha yüksekti. Ayrıca patoloji derecesi ile testis hacmi (korelasyon katsayısı: 0,672, p<0,001) ve ADC (korelasyon katsayısı: 0,480, p<0,001) değişkenleri arasında anlamlı korelasyonlar vardı. Son olarak, çok değişkenli regresyon analizi testis hacmi ile patoloji derecesi arasında anlamlı bir ilişki olduğunu gösterdi. Alıcı işletim karakteristik eğrileri OA ve NOA ayrımında ADC'nin performansını göstermektedir [eğri altında kalan alan: 0,954 (%95 güven aralığı: 0,912-0,995)].

Sonuç: ADC ve testis hacmi gibi MRG ile ilişkili parametrelerin OA ve NOA'yı ayırt etmede ve teşhiste yardımcı olduğu görülmüştür.

Anahtar Kelimeler: Genital hastalıklar, kısırlık, azoospermi, multiparametrik manyetik rezonans görüntüleme, volumetrik görünür difüzyon

INTRODUCTION

As a cause of male infertility, azoospermia is present in 1% of the general population. However, it has been reported in 10-15% of infertile men (1). According to the World Health Organization, investigating male infertility should include a complete medical history and physical examination (2).

Azoospermia can be divided into two general categories: obstructive azaospermia (OA) and non-obstructive azaospermia (NOA), which are critical for differentiation (3). OA can be predicted by normal levels of follicle-stimulating hormone (FSH) and normal volume of both testicles because incomplete spermatogenesis is usually associated with elevated FSH levels in blood samples. However, 29% of men with normal FSH levels exhibit incomplete spermatogenesis (4).

OA and NOA can be differentiated by testicular biopsy. Moreover, the sperm retrieved during the procedure can be successfully used for intracytoplasmic sperm injection (5). In addition to clinical and laboratory investigations, imaging modalities can be used as complementary approaches to illustrate the exact anatomy of the area and the extent of pathology. It has been shown that ultrasound is highly beneficial for investigating the causes of azoospermia, especially OA (6). Additionally, other imaging modalities, such as computed tomography or magnetic resonance imaging (MRI), can be used (7). For example in case of "non-diagnostic" or "inconclusive" findings in ultrasound, MRI of the testicles can be of considerable diagnostic value (8). Up to now, limited studies have investigated the application of functional MRI modalities, such as diffusion-weighted imaging (DWI), magnetic transmission imaging, and hydrogen 1 magnetic resonance spectroscopy (H1MRS), in detecting and localizing the site of spermatogenesis in infertile testes (9).

However, it has been suggested that DWI sequence and apparent diffusion coefficient (ADC) calculation can be beneficial diagnostic tools, providing information regarding structural changes in tissues at the cellular level, leading to a better understanding of tissue characteristics (10,11).

In general, limited studies have investigated the clinical use of DWI sequences in evaluating testicular pathologies, including the diagnosis and localization of non-palpable testicles; differentiating between normal, benign, and malignant lesions; and diagnosing varicocele and testicular torsion (12). ADC values for biological tissues are influenced by several factors, since the interaction of water molecules with tissue components, cell membranes, intracellular organelles, cytoskeleton, and macromolecules restricts their movement (13,14). Thus, the present study aimed to use ADC to distinguish between OA and NOA.

METHODS

Study Design and Setting

This study was conducted based on the Strengthening the Reporting of Observational Studies in Epidemiology Statement (15). In this study, patients with azoospermia were referred to the urology clinics of Firoozgar and Hazrat Rasoul Akram Hospitals in Tehran, Iran, using an easy sampling method. The initial proposal for the study was approved by the Institutional Review Board (IRB) and Ethics Committee of the University of Medical Sciences of Iran (approval ID: IR.IUMS.FMD.REC.1399.284, date: 18.07.2020). This study used recorded patient data, and no intervention was administered to the included population.

Participants

After obtaining written informed consent, the participants were selected and enrolled in the study according to the inclusion criteria. First, demographic characteristics, number of marriages, history of having children, and history of scrotal and inguinal surgeries were obtained from the patients and recorded in the questionnaire.

Inclusion and Exclusion Criteria

Azoospermia patients are based on the results of two semen analysis tests, the necessary hormone tests [testosterone, luteinizing hormone (LH), and FSH, and having a testicular ultrasound]. Patients were unwilling to participate in the study, had single testicle, and were unable to perform MRI.

Data Measurement

According to history, (history of having children and history of vasectomy or scrotal or inguinal surgeries), patients were divided into two groups, obstructive and non-obstructive azoospermia. To increase the accuracy of patient grouping, two criteria (FSH and testicle size) were used in the ultrasound analysis. The groups included the obstructive azoospermia group, which comprised people with normal-sized testicles and normal or slightly increased FSH, and the nonobstructive azoospermia group, comprising patients with reduced testicular size (less than 13 mL) and increased FSH.

Less than one month after MRI, patients were subjected to unilateral or bilateral testicular sampling. The results of the pathological examination of the samples obtained without the knowledge of MRI or other information of the patients were reported, and the patients were divided into 5 different pathological groups. The effects of body mass index (BMI) data, FSH, testosterone, prolactin, LH, testicle volume (TV), age, and testicle size on the occurrence of azoospermia were then evaluated and analyzed.

MRI Protocol

The patients were then subjected to multi-parametric testicular MRI using the Philips 1.5 Tesla (T) system (Ingenia, Philips Healthcare, Netherlands) in the supine position using a multi-channel coil (torso coil). The MRI results were reported by two expert radiologists without any other information about the patient. To determine testis volume and ADC using MRI, testis volume was calculated twice using Lambert's experimental formula (length x height x width x0.71) in cubic centimeters. Then, to determine the final testicular size, the average of the two measurements was considered. The height and width of the testicles were measured in the axial scan, and the length of the testicles was evaluated on sagittal T2-weighted images. Each ADC

value was measured three times in a round region of interest (ROI) with an area of approximately 100 square mm. In the ADC map, ADC was measured quantitatively in the middle portion of the testes, and two measurements were made at different levels just above and below the middle portion. The average ADC value was determined from the average of three measurements. In small and atrophied testes, the ROI area in the middle part and the maximum size of the testis parenchyma were measured without taking the outer part of the extra testis. The ability to distinguish obstructive from non-obstructive azoospermia using T2-weighted sequence DWI data, and ADC values was evaluated and analyzed by the software, and the results were recorded on the checklist.

Histopathological Grading

For this purpose, the biopsied testicle samples were examined by pathologists that were unaware of the MRI findings. Patients with azoospermia were divided into two groups: obstructive azoospermia (normal spermatogenesis and hypo spermatogenesis) and non-obstructive azoospermia (maturation arrest and sertoli cell-only syndrome or del Castillo syndrome and tuberous sclerosis). Based on consultation with pathologists, regardless of whether the patient was obstructed or nonobstructed, the testicle samples were divided into one of these 5 groups, including normal spermatogenesis, hypospermatogenesis, maturation arrest, Sertoli cell-only syndrome, and tuberous sclerosis.

Statistical Analysis

The sample size was measured based on the literature review, which included 30 patients (16). Data were analyzed using Statistical Package for the Social Sciences version 26. To compare the mean of quantitative variables between the two groups, student's t-test (normally distributed random variables based on the result of Kolmogorov-Smirnov test) and non-parametric Mann-Whitney U test (non-normally distributed variables) were used. The Kruskal-Wallis test and Spearman rank correlation coefficient were used according to pathological findings. Finally, logistic regression was used to predict testicular pathological factors. A significance level of 0.05 was considered.

RESULTS

Finally, 14 (28 testicles) and 24 patients (48 testicles) were diagnosed as obstructive and non-obstructive. The average ages of patients with and without obstructive azoospermia was 36.32 ± 7.62 and 36.11 ± 8.89 years, respectively (p=0.12).

A significant difference was found between patients with and without obstructive azoospermia in terms of FSH and

LH levels (p<0.05). However, there were no significant differences in testosterone, prolactin, and TV (Table 1).

Based on testicular MRI findings, TV was significantly higher in patients with obstructive azoospermia than in those without (p<0.001), and the mean ADC was lower in patients with obstructive azoospermia (p<0.001) (Table 2).

Based on pathological examination, non-obstructive azoospermia, normal pathology, and tubular sclerosis were not observed in any of the patients with obstructive azoospermia.

The pathology of maturation arrest and sertoli cell-only syndrome formed approximately 79% of the pathologies of non-obstructive azoospermia patients (34 testicles out of 43 testes), and the pathology of hypospermatogenesis and maturation arrest accounted for approximately 76% of the pathology of obstructive azoospermia patients (19 testicles out of 25 testicles).

A significant difference was observed between patients with and without obstructive azoospermia in terms of pathological findings and ADC, TV, and testis volume (p=0.003) (Table 3). There was a positive and significant correlation between the ADC score on MRI and the pathological score (r=0.48, p<0.001). Moreover, the ADC score had a negative and significant correlation with the testis volume (r=-0.676, p<0.001) (Figures 1,2). Receiver operating characteristic curves showing the performance of ADC [area under curve (AUC) is 0.954 confidence interval 95%; 0.912-0.995] between OA and NOA (Figure 3).

DISCUSSION

In the present study, patients with OA had a lower ADC than those with NOA. Compatible with our findings, two studies showed that normal testes had a lower ADC compared with testes with NOA in histopathological investigations (17,18). Moreover, our findings showed that the volume of testis measured in MRI was a significant predictor of pathological findings. According to studies comparing MRI findings between patients with NOA and age-matched controls, the volume of the testis is a significant predictor of spermatozoa in microscopic testicular embryo extraction (microTESE) (19), and patients with NOA and hypospermatogenesis

Table 1. Demographic factors of patients according to the type of azoospermia

Variables	Obstructive (n=28)	Non-obstructive (n=48)	p-value
Age (years), mean ± SD	36.32±7.62	36.11±8.89	0.12
Married, n (%)	20 (71.4)	40 (83.3)	0.08
BMI, mean ± SD	26.2±3.02	28.7±2.54	0.009
Testosterone, mean ± SD	4.78±3.03	5.23±3.88	0.755
Prolactin, mean ± SD	10.75±5.73	9.77±2.25	0.54
FSH, mean ± SD	4.26±2.9	20.61±12.86	<0.001
LH, mean ± SD	3.15±1.62	12.4±7.35	<0.001
TV, mean ± SD	1.31±0.48	1.19±0.4	0.398

SD: Standard deviation, FSH: Follicle-stimulating hormone LH: Luteinizing hormone, TV: Testicle volume

Table 2. MRI findings in terms of the type of azoospermia

Variable	Obstructive	Non-obstructive	p-value
Testicular volume, mean ± SD	20.37±6.6	8.16±3.99	<0.001
ADC, mean ± SD	0.96±0.15	1.16±0.23	<0.001

MRI: Magnetic resonance imaging, SD: Standard deviation, ADC: Apparent diffusion coefficient

Table 3. Frequency of testicular pathology in patients with and without obstructive azoospermia according to ADC in MRI

Pathology findings	Obstructive (n=28)	Non-obstructive (n=48)	p-value
Normal	4 (14.3)	0	
Hypospermatogenesis	15 (53.6)	4 (8.3)	
Maturation arrest	2 (7.1)	20 (41.7)	0.003
Sertoli-cell-only syndrome	4 (14.3)	14 (29.2)	
Tubular sclerosis	0	5 (10.4)	

ADC: Apparent diffusion coefficient, MRI: Magnetic resonance imaging

have significantly higher ADCs than the normal population (20,21). However, the current study compared patients with OA and NOA instead of a normal control group. On the other hand, MRI and ADC have been used to determine the degree of testicular damage in patients with varicocele (22).

According to our findings, patients with NOA had significantly lower testis volume than those with OA. Compatible with our findings, Regent et al. (23) in Poland showed that patients with NOA had significantly lower testicular volumes than those with OA.

Moreover, another study showed that the FSH and LH levels were significantly higher in patients with NOA than in those with OA, whereas no significant difference was reported in prolactin levels (24). Studies have also shown that MRI is superior to other diagnostic modalities, especially diffusion kurtosis imaging, DWI, and H1MRS, in diagnosing the cause of obstruction in patients with OA (17,25-27). Furthermore, the level of testicular tissue phosphocholine

measured by H1MRS was 3 times lower in areas where only sertoli cells were present compared with areas with normal spermatogenesis (28).

On the other hand, the present study reported a significant relationship between MRI findings and testicular pathology in patients with azoospermia. Compatible with our findings, a study reported a significant relationship between ADC measured by DWI technique and testicular pathology in patients with OA and NOA, showing a positive and significant correlation between ADC value and pathological grade (29). Moreover, the present study reported a significant difference in pathological grade between the patients with OA and NOA azoospermia, showing a significantly lower pathological grade in patients with OA compared with those with NOA. This finding confirmed the correctness of the pathological classification used in the present study. In addition, this classification used the FSH level and testis volume as pre-accepted diagnostic criteria. These variables also showed significant intergroup differences.

The present study revealed a significant relationship between ADC values and testicular pathology. Moreover, pathologies with higher ADC values were associated with higher levels of damage to spermatogenesis. These findings are consistent with two other studies on a similar topic (23,29). It is hypothesized that reduced cell volume in
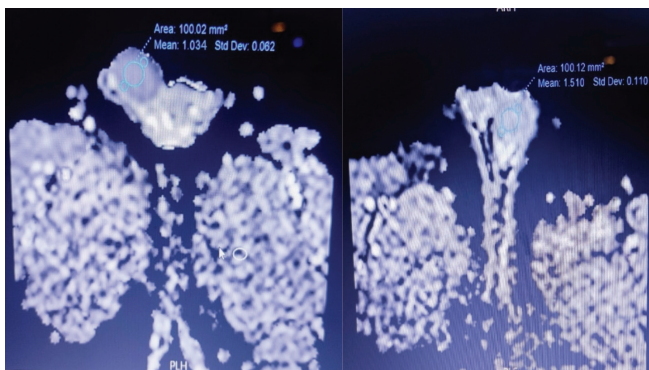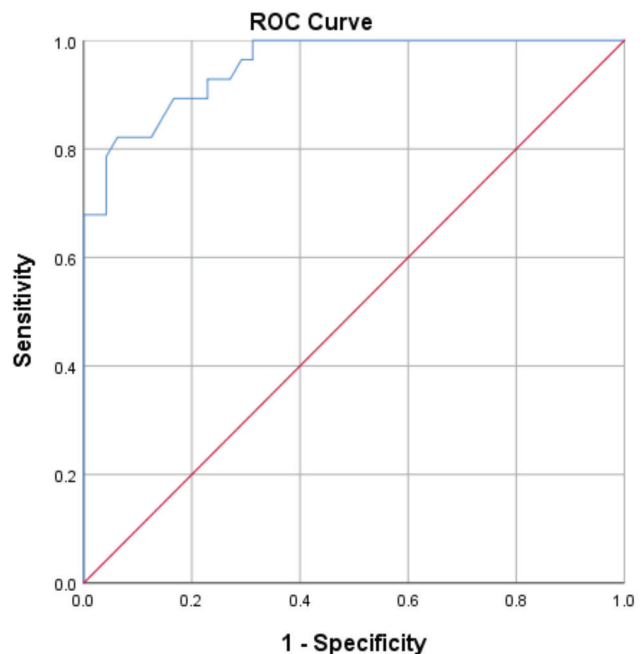

Figure 1. Examples of ADC value measurement in ADC map of testicles

ADC: Apparent diffusion coefficient
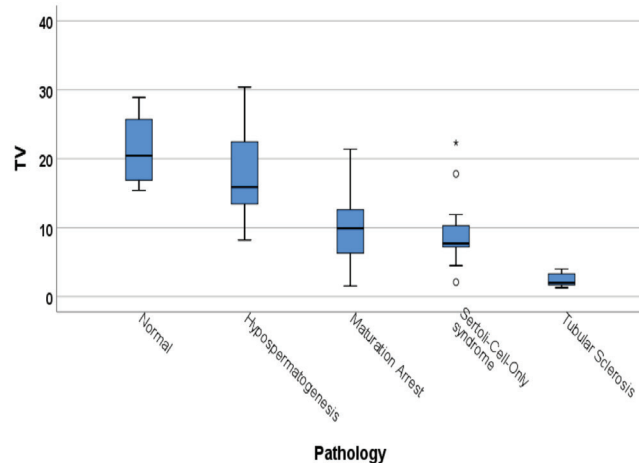
Figure 2. TV changes according to testicular pathological findings in patients with azoospermia

TV: Testicle volume

Figure 3. ROC curves showing the performance of the apparent diffusion coefficient [AUC is 0.954 (CI 95%; 0.912-0.995)] between obstructive and non-obstructive azoospermia

ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

severe pathologies of spermatogenesis and the absence of different cell lines in testicular parenchyma allow for the free movement of water molecules, thereby increasing their diffusion. However, the hypersignalisation of DWI and decreased ADC reported in patients with testicular malignancies in the present study can be explained by the hypercellularity of tumoural tissue and impedance against the movement of water molecules.

Our results showed no significant correlation between ADC and age. However, the size of the testis and testicular parenchyma decreases with age (17), owing to the loss of germ cells and Sertoli cells, leading to reduced length and diameter of the seminiferous tubules (26). Other changes include the formation of peritubular fibrotic tissue, thickening of the tunica propria (the outermost layer of the venom), and increased numbers of Leydig cells, which increase resistance (30).

Finally, this study reported that patients with OA had significantly higher BMIs than those with NOA. Although obesity has been proven to play an important role in oligospermia and azoospermia, defective spermatogenesis due to reduced androgen levels can also explain the decreased muscle mass observed in patients with NOA. Moreover, hypoandrogenism can cause obesity in men (31).

Our study has some limitations; one of the important ones is the small sample size and the non-random sampling method, which introduces bias. Moreover, without a comparison with a healthy control group, the study findings on testicular volume and ADC values in patients with OA and NOA might lack context. Therefore, it is suggested that a large number of participants in a cohort with case-control design study with healthy subjects can be provided clearer guidance regarding the use of this imaging protocol.

CONCLUSION

DWI-based imaging modalities and calculation of quantitative diffusion values, such as ADC, can be beneficial in differentiating OA from NOA. According to our findings, the ADC value and volume of the testis were significantly related to the testicular pathological grade reported in histopathological examinations. Among all study variables, only testis volume had a predictive value for pathological grade.

Acknowledgements

ETHICS

Ethics Committee Approval: The initial proposal of the work was approved by the Institutional Review Board (IRB) and Ethics Committee of the of Iran University of Medical Sciences Iran (approval ID: IR.IUMS.FMD.REC.1399.284, date: 18.07.2020).

Informed Consent: This was a retrospective study which informed consent of patients was waived by the Institutional Review Board (IRB) and Ethics Committee of the of Iran University of Medical Sciences.

Authorship Contributions

Surgical and Medical Practices: F.M., M.A.G., R.M., Concept: M.G., M.M., Design: M.M., Data Collection or Processing: M.M., F.M., M.A.G., Analysis or Interpretation: S.S, Literature Search: M.M., Writing: M.G., M.M.

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

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