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ABDOMINAL IMAGING

ORIGINAL ARTICLE

MRI in the evaluation of the azoospermic male

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PURPOSE
We aimed to show the usefulness of magnetic resonance imaging (MRI) in the evaluation of infertile men and its ability to distinguish obstructive from nonobstructive azoospermia.

METHODS
Between April 2015 and February 2018, 45 azoospermic men underwent scrotal MRI. We evaluated the images with an emphasis on signal characteristics of the testis and morphologic changes typical for obstruction. Testicular volume (TV), apparent diffusion coefficient (ADC) value, T1 and T2 signal ratios (testis/muscle) were measured for every testis. On the basis of histologic results, patients were divided into two groups: obstructive azoospermia (OA) and nonobstructive azoospermia (NOA).

RESULTS
Testes of patients in the OA group had significantly lower ADC values (mean 0.876±101 $\times 10^{-3}$ mm^2/s) than in the NOA group (mean, 1.114±147 $\times 10^{-3}$ mm^2/s). TV was significantly higher in patients with OA (median, 17.61 mL; range, 11.1–38.4 mL) than in those with NOA (median, 10.5 mL; range, 5.2–22.2 mL). ROC analysis showed that both TV and ADC values were highly predictive for distinguishing between OA and NOA patients, with an area under the ROC curve of 0.82 and 0.92 respectively. A cutoff value of ≥12.4 mL could distinguish obstructive from nonobstructive azoospermia with a sensitivity of 92% and specificity of 63%, whereas for ADC measurements a cutoff value of ≥0.952 $\times 10^{-3}$ mm^2/s exhibited a sensitivity of 81% and specificity of 90%. There was no statistically significant difference in T1 and T2 signal ratios between the two groups. Abnormalities typical for obstruction of the male reproductive tract (e.g., dilatation of ejaculatory ducts, prostatic or seminal vesicle cysts) were found in 78% of patients (14/18) in the obstructive group.

CONCLUSION
Scrotal MRI is a very effective tool for the evaluation of azoospermic men and may provide important information facilitating interventional treatment of infertility.

Infertility is a growing problem all around the world. It is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse and affects approximately 48.5 million couples globally. Male factor is solely responsible for infertility in 20% of infertile couples and is contributory in another 30%–40% (1).

Azoospermia is defined as the absence of spermatozoa in the ejaculate and is present in about 10%–20% of infertile men (2). It is classified as obstructive azoospermia (OA) or nonobstructive azoospermia (NOA). OA is caused by obstruction of sperm delivery route at any level (rete testis, efferent ducts, epididymis, vas deferens, and ejaculatory duct). NOA is caused by testicular failure to produce sperm due to various factors. It is of utmost importance to distinguish OA from NOA patients because OA, although rare, is characterized by normal spermatogenesis; thus, those patients are good candidates for sperm retrieval techniques or sometimes for surgical reconstruction, whereas NOA patients should proceed directly to treatment with assisted reproduction techniques such as intracytoplasmic sperm injection (3).

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Specific diagnosis is usually made clinically by an andrologist or urologist based on testicular volume (TV) as well as serum follicle-stimulating hormone (FSH) levels. Men with OA have normal size testes and normal serum FSH, whereas NOA is usually characterized by decreased testicular size and significantly increased serum FSH. However, in a subgroup of patients, testicular biopsy is necessary to make a final diagnosis (4).

Imaging plays an important role in the evaluation of infertile men. Scrotal ultrasound is widely accepted as initial imaging method because it is a gold standard to measure TV and to search for nonpalpable varicocele (5, 6).

Transrectal ultrasonography (TRUS) might be performed in case of obstructive azoospermia to define the level of obstruction and search for correctable causes of infertility (7).

Scrotal magnetic resonance imaging (MRI) despite its high cost and limited availability is becoming increasingly used, particularly as a problem solver to differentiate between benign and malignant lesions found on ultrasonography (US) (8, 9). It is not a well-established examination in the work-up of infertile men; however, it offers many important advantages: Due to its high tissue contrast and multiplanar capabilities, it allows detailed characterization of normal and abnormal scrotal contents and, as opposed to the US, it is not dependent on operator experience. Moreover, it offers a wide field of view that might be adjusted during an examination in order to depict the distal seminal tract, therefore, providing the same information as more invasive TRUS or vasography (7).

It has also been reported that diffusion parameters mainly apparent diffusion coefficient (ADC) may be useful markers of testicular function (10, 11).

The purpose of this study is to show the usefulness of scrotal MRI in the evaluation of infertile men and its capability to distinguish OA from NOA patients.

Main points

- Testicular volume and ADC values are useful parameters in distinguishing patients with obstructive azoospermia (OA) from patients with nonobstructive azoospermia (NOA).
- Patients with NOA usually have atrophic testicles with high ADC values, whereas patients with OA have testicles of normal size with low ADC values.
- In our study, based on testicular ADC values alone, using a cutoff of 0.952 $\times 10^{-3}$ mm^2/s, we were able to make a diagnosis of OA with a sensitivity of 81% and specificity of 90%.
- Abnormalities typical for the obstruction of the seminal tract (e.g., prostatic cysts, the absence of vas deferens, dilatation of ejaculatory ducts or vasa deferentia) are found in the majority, but not in every patient with OA.

Methods

In this prospective study, we enrolled 45 azoospermic men, diagnosed after at least two semen analyses, who were admitted to our Hospital for testicular biopsy and testicular sperm extraction (TESE). This study was approved by the Ethics Committee of our institution, and all patients provided written informed consent before enrollment in the study.

Every patient underwent a detailed physical examination as well as laboratory testing with full sex hormone profile (FSH, luteinizing hormone [LH], testosterone and prolactin). MRI examination of the scrotum and lower pelvis was performed no more than one month before the surgical procedure.

Conventional testicular sperm extraction (cTESE) was performed in every patient by an experienced staff urologist. If a patient had documented history of OA (e.g., previous vasectomy) or on physical examination, there were no appreciable differences in volume and consistency between testes, then unilateral biopsy was performed (n=31). In other cases bilateral biopsy was performed (n=14).

A small part of harvested tissue was sent for the histopathologic analysis and the rest was used for sperm extraction. Testicular histology was classified as: normal, hypospermatogenesis, maturation arrest or Sertoli-cell only syndrome; additionally it was graded using 10-point modified Johnsen score (12).

Exclusion criteria were unrepaired cryptorchidism, claustrophobia and inconclusive biopsy results.

MRI examination

The MRI examinations were held on 1.5 T Siemens Magnetom Aera (Siemens Medical) with the use of auto coil selection option with 20-channel body coil and spine coil. A variety of sequences were performed to assess the morphological and functional changes in the pelvis. In each patient, the same protocol included T2-weighted turbo spin-echo (TSE) sequences in sagittal orientation (TR/TE, 5660/75 ms; slice thickness, 3 mm; gap, 0.3 mm; FOV, 280×280 mm; voxel, 0.9×0.9 mm), T2-weighted TSE in axial orientation (TR/TE, 4000/96 ms; slice thickness, 3 mm; gap, 0.3 mm; FOV, 320×260 mm; voxel, 0.7×0.7 mm), and T2-weighted TSE in coronal orientation (TR/TE, 9600/90 ms; slice thickness, 3 mm; gap, 0.3 mm; FOV, 360×360 mm; voxel, 0.7×0.7 mm). Then T1-weighted TSE sequence in coronal orientation (TR/TE, 550/19 ms; slice thickness, 3 mm; gap, 0.3 mm; FOV, 320×300 mm; voxel, 1.0×1.0 mm) was acquired. Diffusion-weighted imaging (DWI) sequence was acquired in the axial plane using fat-saturated single-shot spin-echo planar imaging sequence with the following parameters: TR/TE, 9600/68 ms; slice thickness, 3.5 mm; gap, 0.35 mm; FOV, 400×400 mm; acquisition voxel, 2.5×2.5 mm; interpolated voxel, 1.3×1.3 mm; number of signals averaged (NSA), 2; five *b* values (0, 100, 500, 800, 1200, 2000 s/mm^2); duration, 5 min 57 s.

MRI scans were analyzed simultaneously by two radiologists (B.R. and M.S.) with at least 7 years of experience in uroradiology and scrotal imaging. Readers were blinded to the patient's clinical data and biopsy results. The volume of every testis was calculated using syngo.via software by manually tracing entire organ and creating a 3D volume of interest (VOI) (Fig. 1).

The ADC value of every testis was measured by placing at least a 1 cm^2 circular region of interest (ROI) in the midsection of the organ (Fig. 2).

Signal intensity ratios were calculated on both T1-weighted and T2-weighted unenhanced images by dividing signal intensity measured in the center of the testis by signal intensity measured in the center of the skeletal muscle.

Ejaculatory ducts and vas deferens diameters were measured and all the pathologic findings in the scrotum and lower pelvis were reported.

Statistical analysis

The results are presented as mean ± standard deviation (SD) or as median and range where appropriate. The Kolmogorov-Smirnov test was used to assess the normality of the data.

The Mann-Whitney U test was used to determine possible differences in the volume,

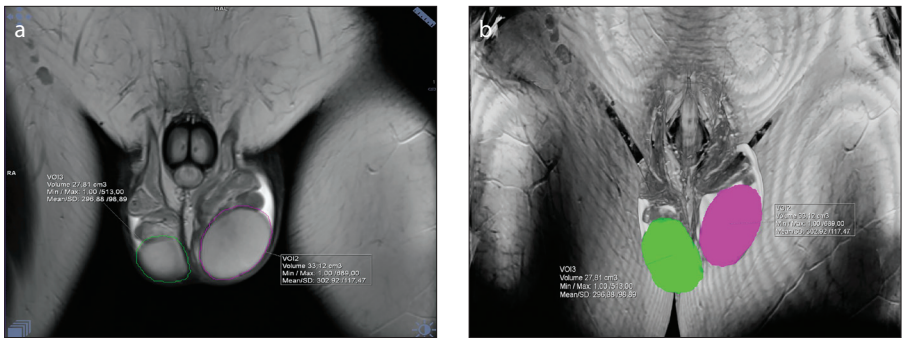

Figure 1. a, b. Measurement of testicular volume using MRI volumetry: **(a)**, coronal T2-weighted image; **(b)**, 3D reconstruction.

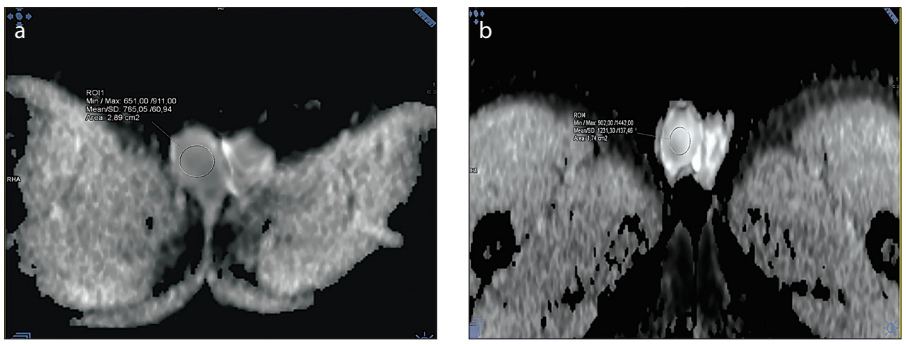

Figure 2. a, b. Examples of apparent diffusion coefficient (ADC) values measured on ADC maps of testes: Image **(a)** belongs to a 36-year-old patient with obstructive azoospermia. Mean ADC value of right testis is 0.77×10^{-3} mm^2/s. Image **(b)** belongs to a 25-year-old patient with nonobstructive azoospermia. Mean ADC value of right testis is 1.23×10^{-3} mm^2/s.

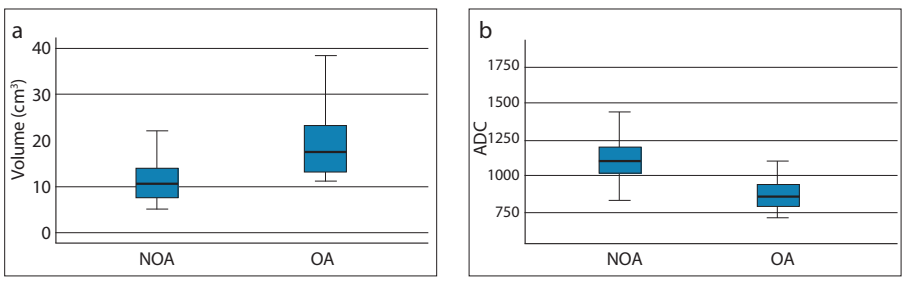

Figure 3. a, b. Box and whisker plot **(a)** shows comparison of testicular volumes between obstructive azoospermia (OA) and nonobstructive azoospermia (NOA) patients. Box and whisker plot **(b)** shows comparison of testicular ADC values (×10^{-3} mm^2/s) between OA and NOA patients.

T1 signal ratio, and T2 signal ratio between NOA and OA groups. The Student's t-test was used to determine possible differences in the ADC values between the two groups.

A receiver operating characteristic (ROC) curve analysis was used to determine the ability of TV and ADC to distinguish between OA and NOA patients. The area under the ROC curve (AUC) was calculated, and the cutoff values with the best sensitivity and specificity were determined using Jouden's index.

Statistical analysis was performed using SPSS version 20.0 (IBM, Inc.) and reviewed by a biostatistician. The data were considered significant when $P \leq 0.05$.

Results

During the study period we examined a total of 45 patients. One patient had an inconclusive biopsy report and one was excluded due to unrepaired cryptorchidism. Hence 43 azoospermic males were included in our analysis. They were divided into two groups according to the testicular biopsy reports: OA group (18 patients with normal or nearly normal spermatogenesis) and NOA group (25 patients with severely impaired spermatogenesis, maturation arrest or Sertoli cell-only syndrome).

One patient in the NOA group had undergone unilateral orchidectomy, therefore we analyzed 49 testes in NOA group and 36 testes in OA group.

Serum concentrations of hormones and mean modified Johnsen scores are presented in Table 1.

Demographic data analysis revealed no significant difference between the two groups in age distribution (mean, 32.4±5.6 years for OA group and 33.4±5.3 years for NOA group; $P = 0.53$).

TV was significantly higher in the OA group ($P < 0.001$). Median TV in patients with OA was 17.61 mL (range, 11.1–38.4 mL) and in patients with NOA, 10.5 mL (range, 5.2–22.2 mL).

ADC values of testicular parenchyma were significantly lower in patients with obstructive azoospermia ($P < 0.001$). Mean ADC in OA group was 0.876±101 ×10^{-3} mm^2/s (range, 0.711–1.100 ×10^{-3} mm^2/s) and 1.114±147 ×10^{-3} mm^2/s in NOA group (range, 0.897–1.650 ×10^{-3} mm^2/s). No significant differences between groups were observed in the T1 and T2 signal ratios. Detailed results are presented in Table 1 and illustrated on the plots (Fig. 3).

ROC analysis showed that both TV and ADC values were highly predictive for distinguishing between OA and NOA patients, with an area under ROC curve of 0.82 (CI 95%, 0.73–0.91) and 0.92 (CI 95%, 0.77–0.96) respectively. A cutoff value of ≥12.4 mL could distinguish OA from NOA with a sensitivity of 92% and specificity of 63%, whereas for ADC measurements a cutoff value of ≥0.952 ×10^{-3}mm^2/s exhibited a sensitivity of 81% and specificity of 90%.

Because volume ROC curve is biconvex, we determined the alternative cutoff value of 14.8 mL with higher specificity and lower sensitivity (Table 2, Fig. 4).

Abnormalities typical for seminal tract obstruction were found in 78% (14/18) of patients assigned by a biopsy to the OA group and were not found in NOA patients (0/25). Specific findings are listed in Table 3 and presented in Fig. 5.

Discussion

The development of assisted reproductive techniques (ART) has revolutionized the management of infertile couples, greatly improving birth rates in male factor infertility (13).

Differentiating OA from NOA is crucial for the management of infertile men because patients with obstruction may be sometimes good candidates for cost-effective

Table 1. Baseline characteristics, laboratory results and testicular parameters grouped by type of azoospermia

	Nonobstructuctive azoospermia		Obstructive azoospermia	
	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)
Age (years)	33.4 (±5.3)	34.0 (7.0)	32.4 (±5.6)	33.5 (7.2)
FSH (mIU/mL)	22.18 (±13.07)	21.88 (22.14)	4.61 (±2.54)	4.50 (3.45)
LH (mIU/mL)	10.61 (±2.83)	11.10 (3.76)	4.40 (±1.38)	4.05 (2.30)
Testosterone (nmol/L)	13.53 (±4.56)	13.37 (7.58)	17.46 (±3.72)	17.29 (8.08)
Prolactin (ng/mL)	12.92 (±7.36)	10.82 (10.89)	6.86 (±2.75)	6.20 (4.50)
mJs	4.65 (±1.67)	4 (3)	9.78 (±0.43)	10 (0.25)
T1 SR	1.68 (±0.27)	1.62 (0.30)	1.69 (±0.19)	1.70 (0.27)
T2 SR	10.10 (±2.37)	9.86 (2.72)	10.46 (1.50)	10.60 (2.50)
ADC ($\times 10^{-3}$ mm^2/s)	0.11 (±0.15)	0.11 (0.19)	0.88 (±0.10)	0.86 (0.15)
Volume (mL)	11.86 (±6.38)	10.50 (6.51)	18.98 (±6.89)	17.61 (10.29)

SD, standard deviation; IQR, interquartile range; FSH, follicle-stimulating hormone; LH, luteinizing hormone; mJs, modified Johnsen score; SR, signal ratio; ADC, apparent diffusion coefficient.

Table 2. Cutoff values and their diagnostic accuracy for distinguishing obstructive azoospermia from nonobstructive azoospermia

Parameter	Cutoff	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	J
ADC ($\times 10^{-3}$ mm^2/s)	0.952	0.92 (0.77–0.96)	81%	90%	85%	86%	0.71
Volume (mL)	12.4	0.82 (0.73–0.91)	92%	63%	65%	91%	0.55
	14.8		58%	84%	72%	73%	0.42

AUC, area under the ROC curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; J, Youden's index; ADC, apparent diffusion coefficient.

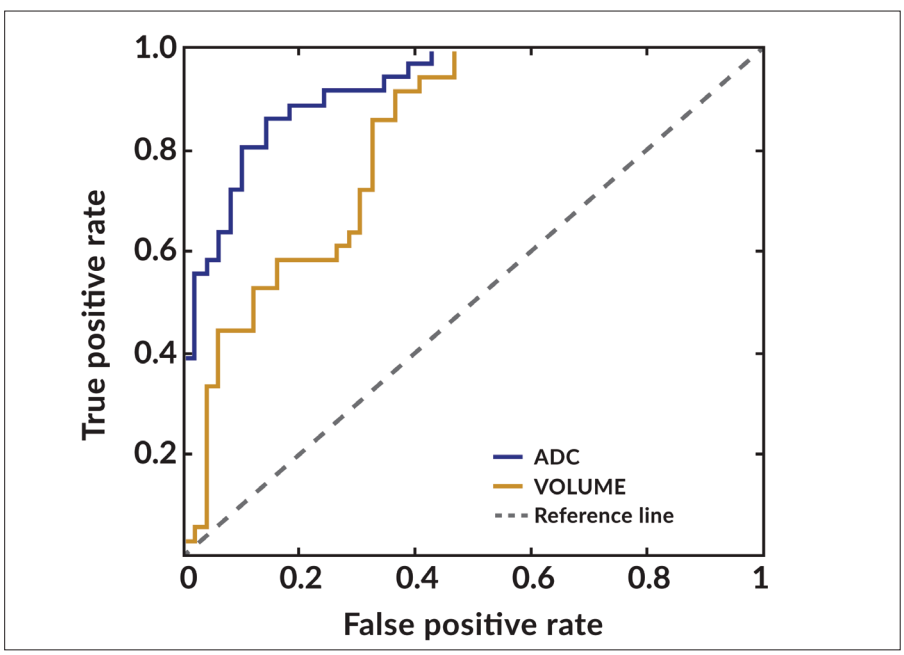

Figure 4. ROC curves showing the diagnostic performance of testicular volume and ADC values in differentiating between OA and NOA patients.

surgical procedures like transurethral resection of ejaculatory ducts (TURED) or even vasoepididymostomy (14, 15).

However, more importantly, the outcomes of testicular sperm extraction combined with intracytoplasmic sperm injection in the OA group are better due to normal spermatogenesis (16).

Many authors have reported that TV correlates directly with testicular function and that it can be used to distinguish NOA from OA patients (17–19). It is easily evaluated by clinical examination, but US is widely accepted as the gold standard to measure the TV and the formula $L \times W \times H \times 0.71$ is proposed to be the most accurate (5).

MRI volumetry is an alternative method which offers high repeatability and its accuracy is not affected by operator experience. Kabay et al. (20) demonstrated in their study that TV measurements with MRI using the Cavalieri principle have better correlation with actual TV than US measurements. In agreement with previous reports, our study also showed that patients with OA have significantly larger testis than those with NOA and our cutoff volume of 12.4 mL for discriminating between the two groups was similar to other studies (11, 21).

ADC is a measure of the magnitude of the diffusion of water molecules calculated using DWI (22). Normal testes appear slightly hypointense on ADC maps because in testicular parenchyma water molecules are confined to densely packed seminiferous tubules which causes restriction of diffusion. It has been reported that ADC values of normal testes increase with advancing age (23).

To our knowledge, there have been only two reports regarding MRI diffusion parameters of testes in the evaluation of male infertility. Tsili et al. (10) compared ADC and fractional anisotropy (FA) in testes of patients with NOA and normal controls. They found that both parameters are significantly increased in the NOA group; moreover, they showed that differences in ADC values in testes of infertile men depend on the severity of spermatogenesis impairment.

Han et al. (11) assessed retrospectively the usefulness of TV, ADC, and normalized ADC in predicting the histopathologic grade of azoospermia and in differentiating OA from NOA. They reported that both ADC and normalized ADC are significantly increased in NOA patients and that TV is decreased. Our results are similar to theirs, although Han et al. (11) found volume

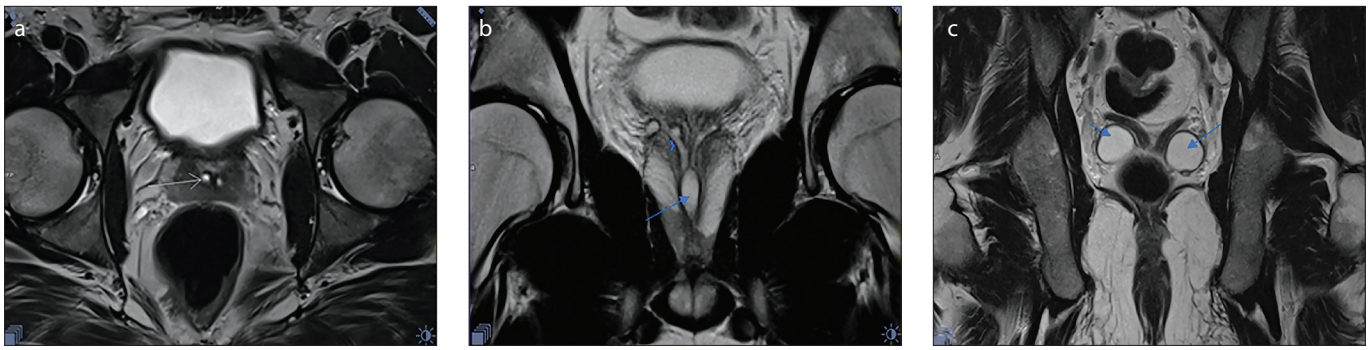

Figure 5. a–c. Examples of seminal tract abnormalities found with MRI in patients with OA: **(a)**, bilateral dilatation of ejaculatory ducts *(arrow)*; **(b)**, prostatic cyst *(arrow)* with dilatation of terminal vas deferens *(arrowhead)*; **(c)**, cysts of seminal vesicles *(arrows)*.

Table 3. Abnormalities of seminal tract found in patients with obstructive azoospermia

MRI finding	n
Bilateral absence of the vas deferens	4
Ejaculatory duct dilatation	3
Dilatation of distal part of vas deferens	3
Prostatic cyst	3
Seminal vesicle cyst or dilatation	2
The absence of the seminal vesicles	2
Enlargement of epididymis	1
Total number of MRI findings	18

Two patients presented with two abnormalities and one with three abnormalities.

measurements to yield higher diagnostic value in distinguishing OA from NOA patients than testicular ADC and normalized ADC measurements. In their study, AUC for volume measurements was 0.92 with a cutoff value of 13.06 and AUC for ADC measurements was 0.741 with a cutoff of 1.031 $\times 10^{-3}$ mm^2/s. In our study, ADC measurements exhibited better performance in distinguishing OA from NOA than volume measurements with AUC 0.92 and 0.82, respectively. Differences between our studies are most probably caused by small patient populations and methods, particularly different imaging protocols.

Unfortunately, in both studies there was a significant overlap of ADC values between the OA and NOA groups; therefore, further research is needed to find what other factors determine the testicular ADC value.

In the literature, there are many reports showing the usefulness of scrotal and transrectal US in the evaluation of the azoospermic male. Abdulwahed et al. (19), examined 268 azoospermic patients; using scrotal US they were able to detect NOA with 75% sensitivity and 78% specificity and OA with 29.8% sensitivity and 87% specificity. The most common findings in the NOA group were decreased TV and varicocele whereas in patients with OA the most common findings were spermatocele, epididymitis, and duct ectasia.

TRUS, due to its low cost and availability, is currently the modality of choice for assessing the actual cause of OA. It enables high-resolution imaging of the prostate, seminal vesicles, and vas deferens and reliable diagnosis of congenital and acquired abnormalities implicated in the cause of obstructive azoospermia. Approximately 75% of patients with OA have structural abnormality visible on TRUS (24). Du et al. (25) reported a sensitivity of 95.3% and specificity of 97.2%, using a combined assessment of scrotal US and TRUS in differentiating between OA and NOA.

MRI is superior to TRUS in the evaluation of distal seminal tract due to its high soft-tissue contrast and multiplanar capabilities (26, 27). With MRI it is possible to depict the absence of intraabdominal part of vas deferens, which is crucial for the diagnosis of congenital absence of vas deferens (CAVD). CAVD is often accompanied by seminal vesicle (SV) anomalies (agenesis or hypoplasia), which are also easily diagnosed with MRI (28). OA patients sometimes present with SV dilatation (>15 mm), SV cysts (>5 mm in diameter) or signs of chronic prostatitis, like coarse calcifications and prostatic heterogeneity. With MRI, ejaculatory duct diameter of more than 2 mm can be used as a diagnostic criterion of ejaculatory duct obstruction (29). In the present study, we found seminal tract abnormalities in 78% of patients in the OA group, which is a similar value to that reported in previous TRUS studies (27, 29).

In summary, based on our results, testes of patients with OA are significantly larger and have lower ADC values than testes of patients with NOA. ADC measurements exhibited better performance in distinguishing OA from NOA than volume measurements. Abnormalities typical for seminal tract obstruction were found in the majority but not in every patient with OA.

This study has some limitations. First, we examined a relatively small number of patients, therefore, it was not possible to correlate ADC values with different histological stages of NOA testes. Second, as a gold standard, we used testicular biopsy and it has been reported that regions of different levels of spermatogenesis might be present even within the same testis (30). Third, we did not have a control group of healthy individuals.

In conclusion, MRI examination of the scrotum and lower pelvis combines the most important features of both scrotal US and TRUS giving information about testicular volume and seminal tract abnormalities as well as having the added value of functional assessment in form of DWI. Scrotal

MRI is a promising tool for the evaluation of infertile men, but further studies are necessary for it to claim its place in daily clinical practice.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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