Role of diffusion-weighted magnetic resonance imaging of testes in patients with testicular varicocele

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Varicocele, characterized by varicosity of the pampiniform venous plexus of the spermatic cord, is a common pathology of the testes [1]. Though commonly found in adolescents and young adults (approximately 15% of adult males) the incidence in patients attending infertility clinics and in those with secondary infertility can be as high as 40% and 80% respectively [2-4]. Ninety percent of varicoceles affect the left side while only 10% are bilateral [5]. First described in the 16th century by a French surgeon, Ambroïse Paré (1500-1590), as caused by melancholic blood it was not until the late 19th century that a relationship between infertility and varicocele was proposed by Barfield, a British surgeon [6].

Colour-flow Doppler ultrasonography plays a vital role in the imaging of varicocele by defining the anatomic and physiologic aspects of varicoceles in real-time. The reflux flow in the pampiniform plexus of veins is identified by the colour of the signal. Clinically, varicocele is defined as the presence of 3 or more veins, with one of them having a minimum resting diameter of 3 mm or an increase in venous diameter with the Valsalva manoeuvre [7]. While colour Doppler ultrasound can predict the outcome of microsurgical subinguinal varicocelectomy [8] testicular ultrasound is the most accurate and reproducible method to assess testicular volume and significant testicular size variations. A volume difference variation of upto 2 ml depends on the measurement technique used. Hence, only a size variation of greater than 2 ml by ultrasound is considered the best indicator of testicular damage [1]. In addition to identifying the enlargement of the pampiniform plexus with reflux of blood into its tributaries Venography can also identify collateral vessels and the incompetent valves though being replaced by tests that are less invasive, less time consuming and have lower exposure to radiation [9].Intra-abdominal pathology should always be excluded in elderly patients with sudden onset of varicocele, right-sided varicoceles and a varicocele that is not reduced in the supine position by abdominal ultrasound or CT scan [9].

Of the many mechanisms that have been proposed, such as induced testicular hypoxia by venous stasis and small vessel occlusion, leading to Leydig cell and germinal cell dysfunction [10], retrograde blood flow of adrenal and renal metabolites in the spermatic vein [11], increased testicular and scrotal temperature [12], reduction of gonadotropin and androgen secretion [13], alterations in the axis lamina propria-extracellular matrix-(ECM-) germinal epithelium [14], and increased nitric oxide (NO) production within dilated spermatic vein [15] the pathogenesis of testicular damage by varicocele still remains controversial. Histopathology may reveal a thickened tubular basement membrane, thickened interstitial blood vessel walls, luminal narrowing, and increased interstitial fibrous tissue [16-18]. For purpose of providing information about tissue integrity, DWI is
one of the latest upcoming technology [19]. Only few researchers have performed studies related to the application of DWI on the testis.

Till now, many studies have been carried out in different countries on DWI of scrotal abnormalities. However, there have been only limited studies on DWI of testis in patients with varicocele. To our knowledge no such study has been carried out in India till now.

In this study, we have evaluated the changes in apparent diffusion coefficient (ADC) values of the testes in patients presenting with varicocele and compared it with normal population. In addition, we also evaluated the correlation between the ADC values to the testicular varicocele grading.
Methods and materials

A total of 30 consecutive patients with varicocele presenting to the Infertility clinic & Urology OPD of Saveetha Medical College Hospital were taken into the study after obtaining approval from institutional review board. The clinical diagnosis of varicocele was made following a physical examination in those patients presenting with infertility, testicular pain, or both. They will also be examined by colour Doppler ultrasound to confirm the diagnosis. Patients who present with any of the exclusion criteria will be excluded from the study. The clinical examination of the patient will be done by palpation and inspection with the patient standing before and during Valsalva maneuver. The classification of clinical varicocele will be based on the guidelines of WHO classification (Table 1)

Table 1. WHO classification of varicocele:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>Palpable during valsalva maneuver</td>
</tr>
<tr>
<td>2</td>
<td>Palpable without the Valsalva maneuver</td>
</tr>
<tr>
<td>3</td>
<td>Visible through the scrotal skin</td>
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Patients with testicular torsion, trauma, tumors, history of scrotal surgery, hernia or previous varicocele repair were excluded from the study.

Thirty healthy volunteers were taken into study. Colour Doppler USG of the patients will be done using a 5-12 MHz high frequency transducer. The diameters of the short axis and refluxes of the largest veins of the pampiniform plexuses will be measured with the patient in a resting supine position and during Valsalva maneuver. These measurements will be done separately for both testes. The patient will be confirmed to have varicocele if a tubular or oval structure with a diameter or 2mm or more is detected, if there is a venous flow in and around the testis, and if there is a positive response to the Valsalva maneuver.

Diffusion weighted Magnetic Resonance Imaging (MRI) will be done using 1.5T MRI unit with the patient lying in a supine position with a 16-channel body coil placed over the pelvic region. Diffusion weighted images (DWI) directed at the lower abdomen will be collected. Single-shot spin-echo echo-planar DW images with b values of 0, 400 and 800 s/mm² will be obtained using the parameters: TR/TE, 6000/88; FOV, 180mm; matrix, 128x256; slice thickness, 4mm; interslice gap 1mm ; slice number, 20; and number of signals averaged 4. The DWI data will be used to generate ADC maps. Images will be taken 5mm distally from the capsule to avoid artifacts. The measured circular region of interest areas will be set at approximately 0.5cm². A total of three measurements will be
made from the same level (Fig. 1, Fig 2). The mean of the three ADC values will be used for the evaluations and statistical analysis. T2 weighted axial images will also be taken with TR/TE, 4000/110; FOV, 180mm; matrix, 256x256; slice thickness, 4mm; interslice gap 1mm; slice number, 20; and number of signals averaged 4.

STATISTICAL ANALYSIS:

Diffusion Weighted Magnetic Resonance Imaging (DWI) was done for all participants and the data was used to generate ADC maps which were expressed as arithmetic means and SDs. A one-way analysis of variance with a post hoc Bonferroni test was used to analyze normally distributed continuous data. Independent sample Student t tests were used to compare continuous variables between the groups. The association between venous diameters and mean ADC values in patients with varicocele was analysed using Pearson correlation coefficient. A two-sided p value <0.05 was considered statistically significant.
Fig. 1: Testicular diffusion weighted image of healthy 28-year-old man. Apparent diffusion coefficient (ADC) map shows ADC values of $1038.33 \times 10^{-3}$ s/mm$^2$ in right testicular parenchyma. Min = Minimum, Max = Maximum.
Fig. 2: Testicular diffusion weighted imaging of 30-year-old man with right sided varicocele. Apparent diffusion coefficient (ADC) map shows ADC values of ipsilateral and contralateral testicular parenchyma are 882 and 960 $\times$ 10$^3$ s/mm$^2$ respectively. Min = Minimum, Max = Maximum.

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Results

The ADC values of both ipsilateral and contralateral testicular parenchyma in patients with varicocele were lower than those of healthy age-matched controls (Fig.3, Fig.4). In patients with varicocele, the mean ADC values were significantly negatively correlated with venous diameters during rest (Fig.5A) and during Valsalva maneuver (Fig.5B). ADC values decreases as grading increases (Fig.6).

- The ADC values of group 1 were lower than those of group 3 (p < 0.001)
- The ADC values of group 2 were also reduced compared with group 3(p < 0.001)
- No statistically significant differences were identified between groups 1 and 2 (p = 0.989)

(Group 1 = Testicles ipsilateral to varicocele.
Group 2 = Testicles contralateral to varicocele.
Group 3 = Healthy volunteer control subjects.)
Fig. 3: p < 0.05 was considered statistically significant. Group 1 = Testicles ipsilateral to varicocele. Group 2 = Testicles contralateral to varicocele. Group 3 = Healthy volunteer control subjects.

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Fig. 4: Box plots depict testicular apparent diffusion coefficient (ADC) values for each group. Group 1 = testicles ipsilateral to varicocele or varicoceles. Group 2 = testicles contralateral to varicocele or varicoceles. Group 3 = healthy volunteer control subjects. The ADC values of group 1 and group 2 were lower than those of group 3 (p < 0.001) No statistically significant differences were identified between groups 1 and 2 (p = 0.989)
**Fig. 5:** Relationship between changes in testicular apparent diffusion coefficient (ADC) values and venous diameters in patients with varicocele. A and B, Scatterplots depict relationship between changes in testicular ADC values and venous diameters during rest (A) and during Valsalva maneuver (B).

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<tr>
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<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
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<tr>
<td>Testicular ADC value</td>
<td>0.951 ± 0.02</td>
<td>0.884 ± 0.03</td>
<td>0.848 ± 0.03</td>
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<tr>
<td>(x10^{-3} s/mm^2)</td>
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<tr>
<td>Mean ± SD</td>
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**Fig. 6:** WHO classification of varicocele. Grade 1 - Palpable during valsalva manuevere. Grade 2 - Palpable without the Valsalva maneuver. Grade 3 - Visible through the scrotal skin.

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Conclusion

With respect to diffusion weighted imaging of testes in patients with testicular varicocele, this is the first study in Indian population.

In our study,

- We calculated the normal testicular ADC values from control group.
- We found that ADC values of both ipsilateral and contralateral testicular parenchyma were significantly lower than that of healthy volunteers.
- Mean ADC values were significantly negatively correlated with venous diameter.
- ADC values decreases as grading increases.

A preliminary study was done on diffusion-weighted MRI of the testes in patients with varicocele by Karakas et al (2014) where similar results were obtained as in our study. In our study, we also found that ADC values decreases as grading increases.

The limitation of our study was lack of histopathological diagnosis.

Though the pathogenesis of testicular damage by varicocele remains controversial many mechanisms have been proposed such as: induced testicular hypoxia by venous stasis and small vessel occlusion leading to Leydig cell and germinal cell dysfunction, retrograde blood flow of adrenal and renal metabolites in the spermatic vein, increased testicular and scrotal temperature, reduction of gonadotropin and androgen secretion, alterations in the axis lamina propria-extracellular matrix- (ECM-) germinal epithelium, and increased nitric oxide (NO) production within dilated spermatic vein. The histopathology of testes in patients with varicocele has revealed findings of a thickened tubular basement membrane, thickened interstitial blood vessel walls, luminal narrowing, and increased interstitial fibrous tissue. DWI is one of the latest upcoming technology for providing information about tissue integrity. Decrease in the ADC values can be considered an indirect indicator of testicular damage as evidenced in our study.

Tsili et al (2014) had reported that normal testicular tissue were different among age groups and that ADC values of normal testicular tissue increase with advancing age.

Paduch et al (2004) had reported that testicular ultrasound is the most accurate and reproducible method to assess testicular volume and significant testicular size variations and had noted that a volume difference of less than 2 ml can be due to the measurement technique alone. Hence a size variation of greater than 2 ml by ultrasound should be
considered the best indicator of testicular damage and should serve as the minimal requirement for surgical repair of the adolescent varicocele.

Based on the results of our study, early detection of testicular damage and the degree of testicular fibrosis due to varicocele can be identified by using DWI. The measurement of testicular ADC values may be used as an indirect diagnostic indicator in the detection of testicular damage and can be considered as a requirement for surgical repair. Also post surgical diffusion imaging of the testes can be done and ADC values can be calculated to assess the improvement.
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