The role of kidney diffusion tensor magnetic resonance imaging in children

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ABSTRACT

Background: Diffusion tensor imaging (DTI) in magnetic resonance imaging (MRI) provides information about the microstructure of renal tissue and is becoming increasingly useful in the evaluation of relationship between renal structure and function.

Objectives: To investigate, whether DTI allows assessment of renal impairment and pathology in pediatric patients with decreased renal functions.

Materials and methods: Thirty-two pediatric patients and seventeen healthy children were included in this prospective study. For DTI, a respiratory-triggered coronal echo planar imaging (EPI) sequence was performed. Cortical and medullary mean axial and radial diffusivity and fractional anisotropy (FA) were analyzed.

Results: In healthy subjects, the cortical FA values were significantly lower than the medullary FA values (p < 0.001). Cortical and medullary ADC values showed positive correlations (r = 0.499, p = 0.041) and a negative correlation with cortical FA values (r = −0.533, p = 0.028). The eGFR values were negatively correlated with the medullary ADC values (r = −0.484, p = 0.049) in healthy subjects and positively correlated with the medullary values (r = 0.385, p = 0.027). Additionally in the patient group, the age was positively correlated with the medullary ADC values (r = 0.461, p = 0.007). However, the medullary FA values were negatively correlated with the medullary ADC values (r = −0.363, p = 0.038). Tractography of healthy volunteers showed a radial arrangement which converged into the pyramids, whereas renal insufficiency patients had irregular arrangement patterns and architectural distortions in the observed areas.

Conclusions: Renal DTI is a promising diagnostic tool in the assessment of microstructural renal changes and correlates with the eGFR. Therefore, it is possible to estimate the arrangement of the tracks which emanate from the renal medulla. Furthermore, diffusion of the water molecules could be carried out. This study demonstrates the usage of DTI in renal pediatric kidneys. Validations in larger cohort groups with histopathological biopsies are needed.
1. Introduction

The major function of the kidneys is to balance the water and solute concentration. Kidneys do this physiologically by the help of glomeruli and tubules, which enable filtration and reabsorption of water and solutes [1–4]. Understanding the basic mechanisms of water diffusion in the kidneys could help to improve the understanding of kidney pathologies. Laboratory parameters, such as serum creatinine or estimated glomerular filtration rate (eGFR), are commonly used for the evaluation of renal tubular function [5–7].

Diffusion weighted imaging (DWI) visualizes water motion at the molecular level and provides useful information on parenchyma microstructure and function, basically depending on the Brownian motion [5–7]. The apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI [1]. It was shown that ADC values tend to decrease in chronic kidney diseases, depending upon the degree of renal impairment [5,8].

Kidneys have a well-defined anatomical structure with tubules, collecting ducts and vessels radially oriented toward the pelvis and in which molecules move in a preferential direction [9,10]. To investigate molecular diffusion in kidneys, the direction should be evaluated. In healthy kidney vessels, tubules and collecting ducts are involved in water reabsorption and urine formation. These structures have a highly perfectly organized radial arrangement. This kind of arrangement enables motion of water molecules to move in different directions, such as right to left or superior to inferior. Therefore, this is the reason for the anisotropic manner of the molecular diffusion in renal parenchyma [9]. This highly perfectly designed structural organization gets damaged in pathological processes. This relationship was demonstrated by previous studies [5,6,9,11].

DTI enables to measure the diffusion of the water molecules in at least six vectoral ways. The diffusion anisotropy could be used to understand the microstructure of the renal parenchyma. The fractional anisotropy (FA) describes the degree of anisotropy of a diffusion process whereas ADC describes only the averaged diffusivity in the directional way. Therefore, DTI enables to estimate and to measure the vectoral way of least restricted diffusion [3,12,13].

In the literature, the correlation between age-dependent changes and the ability of DTI to estimate renal tissue injuries due to tumors, pyelonephritis and renal artery stenosis was demonstrated. Additionally, it is known that the renal medulla has higher FA values than the cortex [5,9,14].

Studies in adults have demonstrated the ability to show microstructural changes correlating with functional parameters by utilizing DTI [3,4,9,15–16]. This prospective study’s purpose was to examine the value of renal DTI in children and adolescents.

2. Material and methods

Divided into two cohorts (normal eGFR of ≥60 ml/min/1.73 m² and reduced eGFR between ≥25 ml/min/1.73 m² and <60 ml/min/1.73 m²), a total of 50 children were included in this prospective single center study. A healthy control group consisted of 17 volunteers, the study group of 33 children. The control group consisted of nine males and eight females with a mean age of 8 ± 0.9 years (3.09–14.7 years). The mean age in the study group was 8.5 years ± 0.7 years (3.02–15.3 years), consisting of 20 male and 12 female children. One patient had to be excluded from this study group, as corticomedullary differentiation (CMD) had not been reported.

All of them underwent renal DTI, as further described in the renal MRI acquisition section. The duration of the study was one and half year. To be certain about the absence of renal parenchymal disease, volunteer patients additionally underwent a renal ultrasound examination.

Exclusion criteria were MRI contraindications such as ferromagnetic implants or claustrophobia. Because of a possible risk of nephrogenic systemic fibrosis [17], patients with GFRs lower than 25 were not included in the study. The dimensions and corticomedullar differentiation were controlled before the renal MRI examination. All the values regarding these parameters were within normal values. Regarding the b:0 image values differentiation between the cortex and the medulla could be easily evaluated and able to be understood the object regions and edges.

A study group sub-group, representing patients with renal impairment (eGFR ≥ 25 and equal or lower 40), was defined. eGFRs were calculated from serum creatinine measurements for all subjects based on the revised Schwarz formula for children and adolescent [18]. The patients were sedated under the age of eight. They were sedated by local anesthesiological products.

The study was approved by the institutional review board and written consent was obtained from the parents of all children.

3. Renal MRI acquisition

All subjects were scanned in supine position in an Avanto 1.5 T (T) MRI scanner (Siemens Medical Systems, Erlangen, Germany). Spine array (posterior) and body array (anterior) receiver coils were used to maximize image uniformity. The imaging protocol consisted of a respiratory-gated (axial 2D, 3D) echo-planar fast spin echo sequence (HASTE) and a coronal T2-weighted sequence. After the HASTE sequence, a respiratory-gated, single-shot diffusion tensor imaging – echo planar imaging (DTI-EPI) acquisition was performed on one kidney (b = 0 and 400 s/mm², 6 directions + null, TR/TE = 2000 ms/75 ms, imaging slice thickness = 3 mm, 10 imaging slices/subject). In order to achieve a better resolution and higher SNR values, either the left or right kidney was evaluated. Only single renal evaluation was enough for the determination.

In all children diffusion MR images were acquired prior to the administration of gadolinium. As a routine part of this renal MRI imaging, we had to use the gadolinium administration in order to get the sufficient renal diagnosis except those under eGFR under 25. Although we had to use gadolinium as a part of imaging technique, the renal DTI was evaluated separately in another work station and the
renal MRI determination did not affect the renal DTI results.

4. Imaging post-processing

Image post-processing was performed with Diffusion Toolkit software package (www.trackvis.org, version 0.5). Tractography was reconstructed using a deterministic streamline algorithm. This algorithm was based on a user-defined region of interest. To be continuous and homogeneous within the previous studies, thresholds were set for minimum fractional anisotropy (FA). A region of interest (ROI) analysis of the ADC and FA maps was performed to obtain measures of mean cortical and medullary

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**Fig. 1a.** Shows the descriptive characteristics of healthy volunteers.

**Fig. 1b.** Demonstrates the correlations of parameters that are statically significant.
ADC and FA for each subject. At least three coronal image slices in proximity to the renal hilum were selected for the ROI analysis. Medullary and cortical ROI selections were obtained in the HASTE images with high corticomedullary contrast and high anatomical detail. The ROIs selected in the HASTE images were directly applied to the corresponding (and co-registered) ADC and FA maps to obtain cortical and medullary ADC and FA values. Afterward, the mean of all resulting ADC and FA values was calculated. A Diffusion Ellipsoid is completely represented by the Diffusion Tensor, D. FA is calculated from the eigenvalues \( \lambda_1, \lambda_2, \lambda_3 \) of the diffusion tensors [1]. The eigenvectors \( e \) give the

Fig. 2. (a) Shows the correlations of parameters in the study group patients.

Fig. 2 (continued)
directions in which the ellipsoid has major axes, and the corresponding eigenvalues give the magnitude of the peak in that direction.

5. Statistical analysis

Among both cohorts, mean medullary and cortical diffusion parameters (ADC, FA) as well as eGFRs were compared using two-tailed Student’s t tests. Mean cortical and medullary ADC and FA were also plotted as a function of eGFR for all subjects and Pearson’s correlation coefficients (R) were determined. Multivariable regression was used to analyze the dependence of whole-kidney region-of-interest tractography volume on FA, eigenvectors and renal function diagnosis.

As statistical software (SPSS Statistics 21, IBM, USA) was used, P-values lower than 0.05 were assumed to be statistically significant.
6. Results

Comparison between the two groups showed that the FA values in the medulla were significantly lower (p < 0.001) in the study group than in the control group. Additionally, the ADC cortex, ADC medulla, and FA cortex were statistically significant lower values (p = 0.049, 0.001, and 0.001 respectively) in the study group compared to the control group. However, the \( k \) values did not show statistically significant differences between the cortical values in both groups (p = 0.121). (Compare Table 2a.)

Within the stepwise regression analysis result medullar tract length showed linear regression with ADC of the medulla (p = 0.015) in study group population. Additionally medullar FA results showed partial regression with ADC medulla when eGFR was less than 60 in the study group (p = 0.029).

7. Control group

The mean value of the eGFR in the control group was measured to be 84 mL/min (range 72–119 mL/min) (Fig. 1a).

8. Study group

In the cortical regions, ADC values were significantly (p < 0.001) higher in the cortex than in the medulla. In opposite, the FA values were significantly (p < 0.001) higher in the medulla than in the cortex. (Fig. 2a and b) (Tables 1a–1c).

Multivariate stepwise regressions in the impaired renal function subgroup (eGFR ≤ 40) showed statistically differing FA values (p = 0.04), when compared to the control group. (The graphics of the detailed analysis are shown in Fig. 3.)

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### Table 1b
The DTI results of \( t \)-test for the patient group.

<table>
<thead>
<tr>
<th>Paired differences</th>
<th>Mean</th>
<th>Std. deviation</th>
<th>Std. error mean</th>
<th>95% confidence interval of the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1 medullarFA - adcmedulla</td>
<td>-1.646212</td>
<td>0.045584</td>
<td>0.007935</td>
<td>-1.662375 to -1.630049</td>
</tr>
<tr>
<td>Pair 2 facortex - adccortex</td>
<td>-1.993091</td>
<td>0.094447</td>
<td>0.016441</td>
<td>-2.026580 to -1.959602</td>
</tr>
<tr>
<td>Pair 3 ( \lambda1 )korteks - ( \lambda1 )medulla</td>
<td>0.823939</td>
<td>0.137862</td>
<td>0.023999</td>
<td>0.775056 to 0.872823</td>
</tr>
<tr>
<td>Pair 4 ( \lambda2 )korteks - ( \lambda2 )medulla</td>
<td>0.197576</td>
<td>0.182962</td>
<td>0.031850</td>
<td>0.132700 to 0.262451</td>
</tr>
<tr>
<td>Pair 5 ( \lambda3 )korteks - ( \lambda3 )medulla</td>
<td>0.213939</td>
<td>0.136655</td>
<td>0.023788</td>
<td>0.165483 to 0.262395</td>
</tr>
<tr>
<td>Pair 6 facortex - medullarFA</td>
<td>-0.235364</td>
<td>0.023817</td>
<td>0.004146</td>
<td>-0.243809 to -0.226919</td>
</tr>
</tbody>
</table>

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### Table 1c
The DTI correlation values of \( t \)-test for the patient group.

<table>
<thead>
<tr>
<th>Correlations</th>
<th>adccortex</th>
<th>medullattractlength</th>
<th>adcmedulla</th>
<th>facortex</th>
<th>( \lambda1 )korteks</th>
<th>( \lambda1 )medulla</th>
<th>( \lambda2 )korteks</th>
<th>( \lambda2 )medulla</th>
<th>( \lambda3 )korteks</th>
<th>( \lambda3 )medulla</th>
<th>eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>aage Pearson's Correlation</td>
<td>0.461</td>
<td>0.007</td>
<td>0.461</td>
<td>0.007</td>
<td>0.461</td>
<td>0.007</td>
<td>0.461</td>
<td>0.007</td>
<td>0.461</td>
<td>0.007</td>
<td>0.461</td>
</tr>
<tr>
<td>medullattractlength Pearson's Correlation</td>
<td>-0.527</td>
<td>0.002</td>
<td>0.096</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
</tr>
<tr>
<td>adcmedulla Pearson's Correlation</td>
<td>-0.527</td>
<td>0.002</td>
<td>1.000</td>
<td>0.345</td>
<td>0.049</td>
<td>0.345</td>
<td>0.049</td>
<td>0.345</td>
<td>0.049</td>
<td>0.345</td>
<td>0.049</td>
</tr>
<tr>
<td>( \lambda2 )korteks Pearson's Correlation</td>
<td>-0.461</td>
<td>0.007</td>
<td>0.096</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
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<tr>
<td>( \lambda2 )medulla Pearson's Correlation</td>
<td>0.392</td>
<td>0.024</td>
<td>0.096</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
</tr>
<tr>
<td>( \lambda3 )korteks Pearson's Correlation</td>
<td>0.476</td>
<td>0.005</td>
<td>-0.346</td>
<td>0.644</td>
<td>0.048</td>
<td>0.644</td>
<td>0.048</td>
<td>0.644</td>
<td>0.048</td>
<td>0.644</td>
<td>0.048</td>
</tr>
<tr>
<td>( \lambda3 )medulla Pearson's Correlation</td>
<td>0.440</td>
<td>0.010</td>
<td>0.096</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR Pearson's Correlation</td>
<td>0.385</td>
<td>0.027</td>
<td>0.096</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
<td>0.495</td>
<td>0.001</td>
</tr>
</tbody>
</table>
In contrast to the control group, tractography in the study group did not demonstrate a strict radial arrangement of the fibers extending from the proximal portion to the Henle loop. The tracks were loosely arranged along the displaced parenchyma in the study group. This resulted in hollow spaces without tracts in the location of the dilated renal calyces or parts of the renal pelvices, especially in the patients with diagnosed ureteropelvic junction (UPJ) obstruction (Figs. 4a and 4b).

9. Discussion

The main objective of the study was to assess the feasibility and potential benefits of diffusion tensor imaging in pediatric kidney diseases. We acquired diffusion MR images of sufficient quality to perform DTI tractography in a cohort of children with normal and abnormal renal functional parameters based on the eGFR values.

The renal parenchyma is divided into cortex and medulla which is totally different in a histological and morphological point of view. Mainly the cortex part is responsible for the ultrafiltration of plasma. This ultrafiltrate moves through the medullary pyramids. Between the medullary pyramids there are also vessels which pass transverse and parallel to the tubules, enabling active secretion and reabsorption of solutes. In the renal pelvic region, the ultrafiltration moves to the renal papillas ending into minor and major calyx forming the urine [1,2,9].

The formation of urine and ultrafiltration of the kidney needs a nearly perfectly designed microstructural arrangement, in both the cortex and the medulla. In the cortex, there are randomly arranged fibers extending from proximal portions of the glomerule to the distal parts of the convoluted tubules. The fiber network system in the medulla consisted of a parallel vascular network design. The tubulous structures, including the ascending and descending portions of the Henle loop are also found in this parallel designed portion system. In this volumetric design within the comparison of medulla with the cortical region, the fibers found in the medulla were thinner than the cortical tubules [1,9,13,16].

In a previous study with a small population, fibers extending throughout the whole kidney did not show significant differences between kidneys with normal or abnormal function [9]. Our study's results support this finding, although whole renal fiber tracts were significantly higher in the study group than in the control group. This is most likely due to increasing number of fibers with patient age and was not statistically significant in the multivariate regression analysis. Similar findings have been reported in other previous studies [5,6,8,9]. On the other hand, based on the regression analysis, the medullar FA could have a critical role in the determination and estimation of the renal parenchymal injury.

In the evaluation of the fractional anisotropy maps, corticomedullary differentiation detected in the study group was fairly poor when compared with the healthy volunteers. The insufficient resolution of the FA maps between the regions could be as a result of the injury to the loss of fiber tract organization. This could also be due to the
capacity of detecting DTI in the thinner fibers, which could be related to the Tesla magnitude. On the other hand, Jaimes et al. did a study with a 3T machine reporting similar results [9].

Regarding the patient group, there is a decrease in diffusion anisotropy obtained. This could be caused within the structural parenchymal alterations, such as interstitial fibrosis, tubular atrophy and cellular infiltration, basically involving pathologies the medullar part of the renal system. Previously particularly including the small group studies presenting the reduction in the medullary fractional anisotropy values was reported [4–6,8,9]. In our study group, there were seventeen patients with eGFR less than 40 ml/min/1.73 m². In this group we identified that only medullary FA could be a promising diagnostic tool in the assessment of radial fiber arrangement and its correlation with eGFR. Based on our study report, we could use the medullary FA as a marker of renal structural integrity alteration, potentially useful index for the diagnosis and outcome of kidney disease.

Hueper et al. [11], hypothesize that the majority of chronic diseases affecting the renal parenchyma probably alter directed diffusion (FA) before free diffusion (ADC). Previous studies mention that ADC and FA are also influenced by different several factors as in the renal medulla. In think age of the water molecules and physiology there could be high alterations during the movement of the transportation [6,9]. ADC is mainly influenced by perfusion, whereas the FA is related to the water molecule transport in the collecting tubules.

These comments also suggested that DTI is the most appropriate technique for functionally evaluating the kidney as compared to DWI, and the medullary FA represents the most sensitive parameter in detecting renal damage in different diseases.

The limitations of the study include a small study population of 49 children. There were no patients with an eGFR lower than 25 ml/min/1.73 m² and only seventeen with an eGFR between 25 ml/min/1.73 m² and 40 ml/min/1.73 m². We avoided inclusion of patients with a eGFR lower than 25 ml/min/1.73 m² because of potentially harmful MRI contrast agent effects [17]. Due to the restricted study population, age-dependencies in renal diffusion parameters were not assessed explicitly. Regarding this, we noticed similar results as in the literature [9]. Additionally, we did not consider or compare different b values in the evaluation of DTI imaging, which possibly could help to optimize acquisition technique. Previous studies demonstrated the effects of different b values [19–21], that influence the FA values regarding the limitations for the specific chronic kidney diseases should be evaluated.

![Partial Regression Plot](image)

Fig. 3. (a–f) Figures are enabled from the regression plot of the test of multivariate step logistic regression test. In this graphics the selected cases represent eGFR of 40. The number of selected cases is seventeen kidneys. The unselected cases are the children who have eGFR greater than 40. (a) Shows the relationship of medullar trace length with age. (b) Shows the relationship of ADC medulla with medullar trace length. (c) Shows the partial regression plot of medullar FA and age. (d) Shows the scatter plot of medullar FA. (e) Shows the partial regression plot of medullar FA and ADC medulla values. (f) Shows the histogram of selected histogram in the relationship of frequency.
Fig. 3b (continued)

Fig. 3c (continued)
Fig. 3d (continued)

Fig. 3e (continued)
10. Conclusions

Our prospective study showed the capability of renal DTI in the usage of alterations induced by various chronic kidney diseases. DTI enables to understand the renal anisotropy based on physiology without contrast media administration. Medullary FA values seem to be the best promising tool in the association within the complementary of laboratory and morphological parameters.
Conflict of interest

The authors declare that there are no conflict of interests.

References

