Abdominal Radiology (2019) 44:1867–1872
https://doi.org/10.1007/s00261-019-01933-4

KIDNEYS, URETERS, BLADDER, RETROPERITONEUM

Diffusion tensor imaging of the kidney in healthy controls and in children and young adults with autosomal recessive polycystic kidney disease

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Published online: 19 February 2019

Abstract

Objective To compare diffusion tensor imaging (DTI) of the kidneys and its derived parameters in children with autosomal recessive polycystic kidney disease (ARPKD) versus healthy controls.

Methods In a prospective IRB-approved study, we evaluated the use of DTI to compare kidney parenchyma FA values in healthy controls (age-matched children with no history of renal disease) versus patients with ARPKD. A 20-direction DTI with *b*-values of $b = 0$ s/mm^2 and $b = 400$ s/mm^2 was used to acquire data in coronal direction using a fat-suppressed spin-echo echo-planar sequence. Diffusion Toolkit and TrackVis were used for analysis and segmentation. TrackVis was used to draw regions of interest (ROIs) covering the entire volume of the renal parenchyma, excluding the collecting system. Fibers were reconstructed using a deterministic fiber tracking algorithm. The FA values based on the ROI data, mean length, and volume of the tracks based on the fiber tracking data were recorded.

Results Eight healthy controls (mean age = 12.9 years ± 4.0; 1/8 males) and six ARPKD participants (mean age = 13.8 years ± 8.5; 5/6 males) were included in the study. Compared to healthy controls, patients with ARPKD had significantly lower FA values (0.33 ± 0.03 vs. 0.25 ± 0.02, $p = 0.002$) and mean track length (16.73 ± 3.43 vs. 11.61 ± 1.29 mm, $p = 0.005$).

Conclusion DTI of the kidneys shows significantly lower FA values and mean track length in children and young adults with ARPKD compared to normal subjects. DTI of the kidney offers a novel approach for characterizing renal disease based on changes in diffusion anisotropy and kidney structure.

Keywords DTI · Kidney · ARPKD · Magnetic resonance imaging · Urology · Diffusion tensor imaging

Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is a hereditary ciliopathy that is an important cause of progressive chronic kidney disease (CKD) in children. Patients with ARPKD have enlarged cystic kidneys resulting from fusiform dilations of the collecting tubules [1]. There are currently no available disease-modifying therapies for ARPKD, and treatment is directed at management of CKD complications [2, 3]. Several novel therapies have shown promise in ARPKD animal models [4–6], and an early-stage clinical trial is now underway in children (NCT03096080). However, a major limitation for implementing clinical trials of new therapies is the absence of sensitive measures of ARPKD progression.

ARPKD progression is most often measured clinically using serum creatinine to estimate glomerular filtration rate (GFR). However, due to compensatory hyperfiltration, GFR may not decline until there is significant cyst progression. Commonly used imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) can show anatomic changes associated with ARPKD, such as enlarged kidneys with

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microcysts. However, standard anatomic protocols do not provide quantitative measures of disease progression. MRI-based volumetric measures have been utilized successfully as a surrogate endpoint to measure autosomal dominant PKD (ADPKD) kidney disease progression and response to therapy [7–9]. These basic volume assessments, unfortunately, are not applicable to ARPKD, as kidney size often stabilizes or decreases over time despite worsening cystic disease [10]. Newer quantitative noninvasive, noncontrast, imaging assessments are therefore required as biomarkers to measure progression of ARPKD.

Histologically, healthy kidneys have their nephrons well organized within the renal parenchyma and follow a radial arrangement [11]. In ARPKD, as the disease progresses, there is displacement of coherent renal tubule orientation [12]. These microstructural alterations can be quantified using MRI-based diffusion tensor imaging (DTI) [11]. DTI measures the Brownian motion of water molecules, which can be used to quantitatively assess the microstructures and morphologies of different tissues in the body, including kidney, bone, and brain [13–16]. DTI is based on the application of diffusion gradients in different directions in space, enabling the evaluation of the movement of water molecules in three dimensions, and whether there is a dominant direction to diffusion restriction. In conjunction with DTI, fiber tracking is based on the dominant direction of water movement in each voxel. The orientation and length of fiber tracts may be measured according to the dominant direction of water movement in each voxel [13]. DTI provides quantitative parameters including fractional anisotropy (FA), apparent diffusion coefficient (ADC), track length, and track volume, and also allows one to generate tractography-based maps. FA reflects the dominance of one particular water movement direction in a voxel, and is measured from 0 to 1. ADC is related to the magnitude of water molecule diffusion distance, and measures the directionally averaged diffusivity.

DTI-MRI has been utilized for over a decade to measure tissue damage in other organs (such as the brain), but its application in kidney disease is more recent [17]. The fiber tracking algorithm can be used to track a fiber along its whole length. The tracking works on the principle that the center of one voxel must be within a certain defined angle of the direction of the adjacent voxel and vice versa [18]. Tractography is a useful tool for measuring deficits in track lengths in patients with progressive disease, and its estimation of track length is increasingly accurate in neurodegenerative disease. In kidneys, we assume FA is related to the water molecule transport in the collecting tubules; we hope to use this measure in patients with kidney damage [19].

The objective of this study was to explore DTI-MRI as a quantitative biomarker for kidney disease severity in ARPKD. We compared DTI of the kidneys and its derived metrics (ADC, FA, mean track length, and volume) to detect differences in the kidney parenchyma between normal age-matched healthy controls and children with ARPKD. We also explored whether these measures differed based on kidney disease severity within the ARPKD group.

Methods

Participants

In this prospective, cross-sectional pilot study conducted between October 2014 and May 2018, ARPKD participants ≤ 21 years were recruited from the nephrology practice at our institution. The diagnosis of ARPKD was based on standard clinical criteria including characteristic findings of enlarged echogenic kidneys with poor corticomedullary differentiation and heterogeneous liver echotexture on standard ultrasound. Although genetic testing is not mandatory to establish a diagnosis of ARPKD and was not performed as part of this study, 4 of the 6 participants had previously had confirmatory genetic testing. Children who had undergone kidney transplantation and those on dialysis were not eligible for the study. A reference population of healthy control children with no personal history of hypertension, obesity, hematologic or rheumatologic disease, and no family history of kidney or liver disease, was recruited from our primary care practices. Participants with contraindication to MRI or inability to tolerate unsedated MRI were excluded. The Institutional Review Board approved this study (IRB 14-10785), and informed consent was obtained from all participants/guardians.

Laboratory measurements were performed only in children with ARPKD. Estimated glomerular filtration rate (eGFR) was calculated, from tests performed in the same visit, based on serum creatinine using the bedside CKD in Children (CKiD) Study equation for children < 18 years old [20], and the CKD-EPI equation in adults ≥ 18 years old [21].

Imaging

DTI-MRI of the kidney was obtained using a fat-suppressed spin-echo echo-planar sequence (TR/TE 2600-3900/64-74 ms) on a 3T MR scanner (Sykra, Siemens, USA). A slice thickness of 4 mm, a matrix size of 128 × 96 and a bandwidth of 1698 Hz/pixel were used. We applied the diffusion gradients in 20 noncollinear directions with $b = 400$ s/mm^2 in addition to a $b = 0$ s/mm^2. Images were obtained for each sequence without respiratory triggering in a scan time of approximately 4 min. We used selective fat suppression with spectral adiabatic inversion recovery and standard shimming was performed through the preimaging with the Siemens'

diffusion sequence. For all subjects, a parallel imaging acceleration factor of 2 was used.

Imaging post-processing

Diffusion Toolkit version 0.6.4.1 and TrackVis version 0.6.0.1 were used for analysis and segmentation [16]. Fiber tractography is a 3D reconstruction technique to access renal tracts using data collected by DTI. Fibers were reconstructed using a deterministic fiber tracking algorithm with a minimum FA threshold of 0.10 and a maximum turning angle of 55° between two adjacent voxels based on published parameters for renal tractography [4]. TrackVis was used to manually draw regions of interest (ROI) covering the entire volume of the renal parenchyma, excluding the collecting system. ADC and FA values were calculated for each whole-kidney ROI, then the ADC and FA values for left and right kidneys were averaged to calculate the mean ADC and FA values for each participant. Fiber-tracking data were used to calculate the mean length and volume of the tracks, with mean track length and track volume again calculated from the average of the left and right kidneys. Tract length refers to the distance in millimeters between two end points where the tracking can no longer follow the direction of diffusivity to neighboring voxels within the angle threshold set by the image reconstruction. Track volume refers to the volume of parenchymal tissues included in the segmentation.

The fiber tracks obtained from the ROIs (Fig. 1) were qualitatively analyzed for the presence of any artifacts, direction of tracks, and differences in FA values within the renal parenchyma. The assessment was done using tractography maps: (1) a standard color-coded reconstruction to visualize the orientation of tracks where blue tracks represented diffusion in the craniocaudal direction, green tracks represented diffusion in the anterio-posterior direction, and red tracks showed diffusion in the transverse direction; (2) a scalar FA map with minimum and maximum FA thresholds of 0.1 and 0.6, respectively; and (3) total track length information for each kidney in each group of participants.

Statistical analysis

Statistical analyses were performed using MedCalc version 18.2 (MedCalc Software, Ostend, Belgium) and Stata 13.1 (StataCorp LP, College Station, TX). Participant characteristics were reported as number (percentage), means and standard deviations (SD), and ranges as appropriate. Differences between ARPKD and control groups were calculated using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for binary variables. Statistical significance was accepted at $p < 0.05$.

Results

14 healthy controls and 8 ARPKD participants underwent MRI. Of these, 6 controls' and 2 ARPKD participants' DTI data had artifacts and could not be used. Clinical and demographic characteristics of the 8 controls and 6 ARPKD participants included in this study are shown in Table 1. Healthy controls and ARPKD participants were of similar ages (mean age 12.9 vs. 13.8 years; $p = 0.9$), and there was a lower proportion of males in the control group compared to the ARPKD group (13% vs. 83% males, $p = 0.03$). ARPKD participants had relatively well-preserved kidney function, with mean eGFR of 81 ± 17 mL/min/1.73 m^2.

Representative tractography maps of healthy control and ARPKD participants are shown in Fig. 1, demonstrating disruption of coherent renal fiber orientation in ARPKD. There was no significant difference in ADC

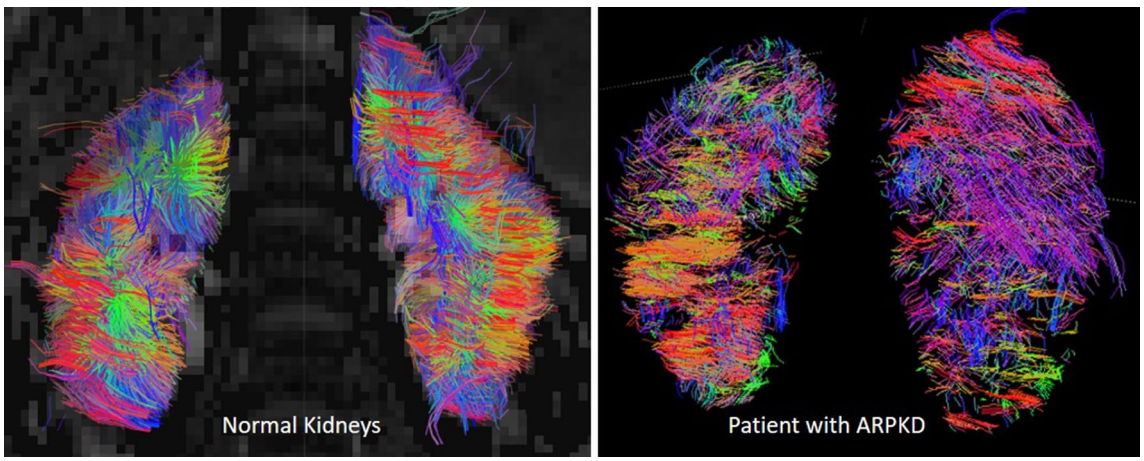

Fig. 1 Representative DTI tracks generated from **a** control versus **b** patient with ARPKD

Table 1 Participants' characteristics

Characteristic	Controls $n=8$	ARPKD $n=6$	p value
Age			0.9
Mean ± SD, years	12.9 ± 4.0	13.8 ± 6.0	
Range, years	8.3-20.0	8.5-21.0	
Males, n (%)	1 (13%)	5 (83%)	0.03
eGFR*, mean ± SD, mL/min/1.73 m^2	–	81 ± 16.7	n/a

*Estimated glomerular filtration rate calculated based on serum creatinine using the bedside CKD in Children (CKiD) Study equation for children < 18 years old [20], and the CKD-EPI equation in adults ≥ 18 years old [21]. Laboratory measurements performed only in ARPKD participants

longer in healthy controls compared to ARPKD participants (16.73 ± 3.43 vs. 11.61 ± 1.29 mm, $p=0.005$) (Fig. 2b). Mean track volume was significantly lower in healthy controls compared to ARPKD participants (165.70 ± 39.87 vs. 355.39 ± 223.24 cm^3, $p=0.005$) (Fig. 2c) (Table 2).

The six participants with ARPKD had an eGFR of ranging from 61.0 to 106.9 mL/min/1.73 m^2. To explore whether ARPKD kidney disease severity was associated with DTI parameters, we divided the ARPKD participants into two groups based on eGFR. We compared FA values, track lengths, and track volumes between ARPKD participants with higher eGFR (≥ 80 mL/min/1.73 m^2, $n=3$) versus lower eGFR (< 80 mL/min/1.73 m^2, $n=3$).

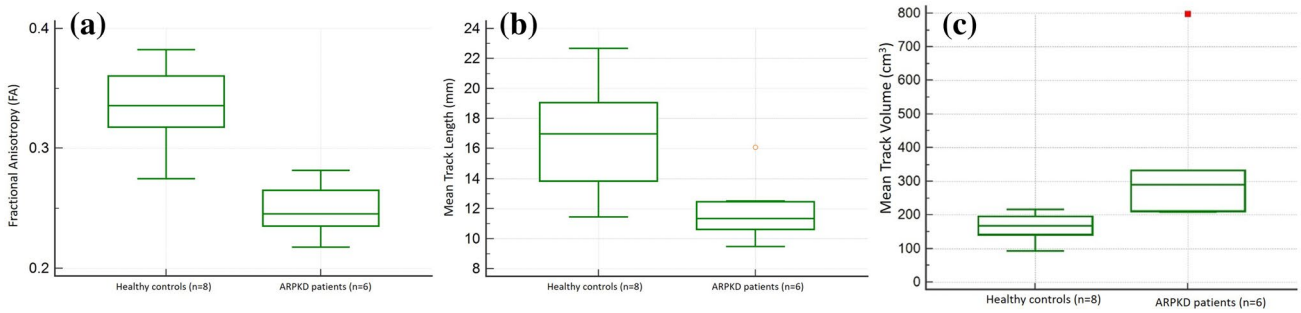

Fig. 2 Box and whisker plot of **a** mean FA ($p<0.001$), **b** track length ($p=0.005$), and **c** track volume ($p=0.003$) in controls versus patients with ARPKD. Horizontal lines within boxes represent medians, and vertical lines and whiskers represent the lowest and highest observations within 1.5 interquartile ranges of lower and upper quartiles, respectively. The data points with the circles are values that fall outside the 1.5 interquartile range but within 3 interquartile range

Table 2 Kidney DTI parameters in healthy controls and ARPKD participants

DTI parameter (mean ± SD)	Controls $n=8$	ARPKD $n=6$	p value
Mean ADC (mm^2/s)	$2.02 \pm 0.16 \times 10^{-3}$	$2.07 \pm 0.26 \times 10^{-3}$	0.7
Mean FA	0.33 ± 0.03	0.25 ± 0.02	0.002
Mean track length (mm)	16.73 ± 3.43	11.61 ± 1.29	0.005
Mean track volume (cm^3)	165.70 ± 39.87	355.38 ± 223.24	0.005

Table 3 Kidney DTI parameters in ARPKD patients with higher versus lower eGFR values

DTI parameter (mean ± SD)	ARPKD (eGFR ≥ 80 mL/min/1.73 m^2) $n=3$	ARPKD (eGFR < 80 mL/min/1.73 m^2) $n=3$	p value
Mean FA	0.24 ± 0.02	0.25 ± 0.02	0.8
Mean track length (mm)	11.11 ± 0.81	12.13 ± 1.13	0.3
Mean track volume (cm^3)	264.08 ± 338.84	446.69 ± 310.84	0.5

between healthy controls and ARPKD participants (ADC 2.02 ± 0.16 vs. $2.07 \pm 0.26 \times 10^{-3}$ mm^2/s, $p=0.7$). Mean FA for healthy controls was significantly higher than that of ARPKD participants (0.33 ± 0.03 vs. 0.25 ± 0.02, $p=0.002$) (Fig. 2a). Mean track length was significantly

In this small-population sample, we were not able to detect any statistically significant differences in any of the DTI parameters between ARPKD participants with higher versus lower eGFR (Table 3) (Fig. 3).

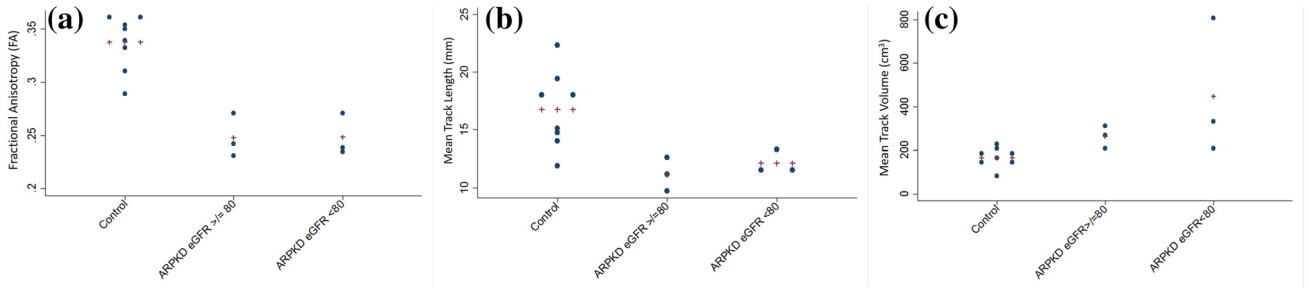

Fig. 3 Dot plot of **a** mean FA in controls versus mild ARPKD versus moderate ARPKD, **b** track length in controls versus mild ARPKD versus moderate ARPKD, and **c** track volume in controls versus mild ARPKD versus moderate ARPKD. The individual dots represent the individual subject data and plus sign represent the mean of the datasets in the column

Discussion

ARPKD, characterized by diffuse corticomedullary microcysts resulting from fusiform dilatation of the collecting tubules, morbidity, and mortality is significant: only 70% of ARPKD children survive the neonatal period, and 40% progress to end-stage renal disease (ESRD) by age 15 [17]. Unfortunately, one of the major roadblock for implementing clinical trials in ARPKD patients is the absence of sensitive measures of disease progression [17]. Moreover, the microscopic nature of the cysts means that they cannot be quantified using routine anatomic MRI methods. In this study, we demonstrated that DTI-MRI is able to quantitate microstructural changes in ARPKD kidneys. We found that children and young adults with ARPKD had significantly lower kidney FA values than healthy controls, consistent with loss of normal coherent renal fiber orientation in ARPKD participants. Mean track length was significantly shorter in ARPKD participants compared to healthy controls, despite having much high renal track volumes, consistent with disruption of intact tubular tracks in ARPKD. These findings indicate that DTI may be a promising imaging biomarker to quantitate microstructural changes related to kidney disease progression in ARPKD. Validation of DTI measures and translation of these techniques to ARPDK patients is a key component in the further development of quantitative assessments of ARPKD kidney disease.

Published studies in adults have demonstrated that microstructural kidney changes detected using DTI correlate with functional parameters in a variety of conditions such as chronic parenchymal diseases, diabetic nephropathy, glomerulonephritis, and renal masses [22–24]. However, to the best of our knowledge, there are no prior studies of DTI in pediatric patients with ARPKD. In a study by Hueper et al., those authors found that FA values change before changes in ADC because the latter one is mainly influenced by perfusion, whereas the FA is related to the water molecule transport in the collecting tubules [19]. These studies suggested that DTI-derived FA could be a more appropriate technique for functionally evaluating the kidney compared to ADC derived from DWI. Our study shows that it is possible to measure FA and track length using DTI in children and young adults. The significance of this finding of our pilot study is that FA has the potential to be used now as a sensitive imaging-based biomarker to stage and monitor kidney disease in children, especially in patients with ARPKD.

Our study has a few limitations—mainly those of the small sample size and the unequal gender distribution. However, even with a small sample, the magnitude of differences in DTI parameters between control and ARPKD groups was large enough to show a statistically significant difference. We were, however, unable to detect differences in DTI parameters within the ARPKD group based on level of kidney function—a larger sample size would be needed to achieve adequate power to detect whether DTI parameters correlate with disease severity. Although best efforts were made to recruit matched controls, out of 14 controls, 6 datasets were lost due to artifacts, and so data from 8 controls were included in the study. The larger number of male ARPKD patients is purely by chance based on our patient population—ARPKD affects males and females equally, it was just by random selection that we had more males in the age range that was eligible for MRI. Because we included patients already diagnosed with ARPKD, it was not possible to determine how many FA changes are present, if any, in the preclinical stages of the disease compared to later stages. However, it is interesting to note that the significant alterations in DTI parameters are present even in ARPKD participants with relatively preserved kidney function. Given that this was a cross-sectional study, we were not able to determine how DTI parameters change as the disease progresses. In an ongoing longitudinal study, we plan to perform repeat DTI-MRI yearly in ARPKD participants to determine if DTI can quantitate progression of disease at the individual patient level. Future research efforts will also focus on further optimization of DTI sequences, and the recruitment of larger ARPKD samples that includes patients across the spectrum of disease severity. In this study, repeatability of

DTI in the kidney was not assessed and needs assessment in future studies if DTI of the kidney is to be relied as a biomarker.

Conclusions

DTI of the kidneys shows significantly lower FA values and mean track length in children and young adults with ARPKD compared to normal subjects. Our pilot study shows DTI of the kidney offers a novel approach for detecting renal disease based on changes in diffusion anisotropy.

Funding This work was partly funded by NIH grant number 5K23DK109203 (National Institutes of Health/NIDDK), PI: Erum Hartung.

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