Diffusion Tensor Imaging – A New Biomarker for Evaluation of Renal Function: Preliminary Results and Literature Review

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Abstract

Introduction and objectives. Renal function is monitored using clinical and imaging methods; however, an early assessment of renal damage is currently achievable by biopsy only. Diffusion Tensor Imaging (DTI) is a method that measures the rate of diffusion along different directions. In the kidney nephrons run radially to the renal pelvis, so diffusion along these structures is expected. The aim of this study is to describe DTI as a tool for evaluation of renal microarchitecture.

Materials and Methods. Ten healthy patients were analyzed in this study. For DTI, a free-breathing coronal plane echo-planar imaging (EPI) sequence was performed. Different regions of interest (ROI) were placed and fractional anisotropy (FA) values were measured and compared between cortex and medulla. Finally, tractography was performed with visual display of renal fibers bundles.

Results. FA values were significantly different between renal cortex and renal pyramids, with values in medulla the highest (median value of 0.5) suggesting tightly packed fibers, compatible with normal histologic configuration. Tractography revealed bundles of renal tracts in the pyramids with a strictly exterior to interior orientation.

Conclusions. FA values obtained by DTI represent a new biomarker that expresses normal architecture of renal tract bundles in the pyramids. Early renal damage is manifested by edema and disruption of renal tracts which can only be assessed by biopsy. However, this kind of damage can be detected by a decrease of fractional anysotropy values measured by DTI, and also visually shown as fewer tracts displayed by tractography. The application of this method is straightforward with short acquisition time. Therefore, the applications of DTI in renal disease are vast, from congenital obstructed uropathy to renal allografts evaluation.

Key-words: renal function, end stage renal disease, kidney transplant, Diffusion Tensor Imaging, DTI

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Introduction

Renal disease is a vast group of kidney disorders and is highly prevalent among children and adults, being a worldwide health problem. Without treatment, the natural history is towards progressive and irreversible unilateral or bilateral kidney malfunction, with, in some cases end stage renal disease (ESRD) and necessity for permanent dialysis or renal transplantation.

The etiology is diverse, consisting of immunological, mechanical (obstruction), metabolic and toxic, to number a few. But, regardless the cause of renal injury, the histological hallmark of ESRD is fibrosis affecting each compartment: glomerulosclerosis, vascular sclerosis and tubulointerstitial fibrosis.[1,2] Usually kidney disease is monitored by clinical and laboratory parameters. However, the kidneys are characterized by a huge functional reserve. Therefore, usual parameters may be normal even in advanced injury, which in many cases can be detected only by invasive biopsy.[3]

Normal kidney histology consists of the renal cortex and medulla. In the cortex, glomeruli, renal tubules and microvessels are arranged in a dense, unsystematized architecture, whereas in the pyramids, loops of Henle, collector ducts and blood vessels are tightly packed in clusters with a radially orientation from the base of the pyramids to the papilla.[4] This histologic configuration can be observed macroscopically by morphologic imaging studies (ultrasound, computed tomography or MRI) that show a clear contrast between the two zones – cortex and medulla. When fibrosis occurs, this architecture is distorted, with fewer parallel longitudinal tracts in the pyramids and loss of normal cortico-medullary differentiation.[2]

Diffusion weighted imaging (DWI) is a non-invasive imaging tool that is sensitive to Brownian motion of water molecules and its restriction in particular.[5] This technique has widespread applications, from detecting brain ischemia to tumor analysis. Diffusion tensor imaging (DTI) is an advanced application of DWI, helpful to determine the direction of diffusion and its anisotropic nature, most often used in characterization of nervous tracts.[6] Fractional anisotropy (FA) is a coefficient measured by DTI which reflects the degree of the histological organization in the tissue. If water is restricted to diffuse only in certain directions, than the FA will be high. Reversely, if water moves freely in any direction, than the FA will be low. The particular architecture of the kidney histology, makes it amenable to DTI analysis. Therefore, the purpose of this paper is to analyze and present the DTI findings in normal kidneys and to highlight the utility of this technique in clinical practice, making a review of the literature.

Materials and Methods

We included ten patients (five males and five women, aged from 30 to 64 years, mean age 50.8 years) that were examined by abdominal MRI for non-renal pathology. All patients had no history of renal disease, with normal serum creatinine levels and a minimum estimated glomerular filtration rate of 50 mL/min/1.73 m^2. Informed consent was given by all patients in the study.

All examinations were performed on a 1.5 Tesla Siemens Aera machine (Siemens Medical Systems, Erlangen, Germany) using a spine and a body phased array coils.

First, a single shot coronal-oblique T2 HASTE sequence covering only the kidneys was acquired for anatomic details. For the DTI sequence, we adapted a spin echo echo-planar diffusion technique to achieve the best signal to noise ratio, for the best resolution. It was planned in a slightly oblique coronal plane parallel to the long axis of the kidneys, with a field of view of 278 mm, a FOV phase of 100% and a slice thickness of 5 mm, which allowed us to image both kidneys, and still get a fair voxel size. According to Chuck et al[7], best image quality for DTI on 1.5 T is achieved with a b value of 300 to 500 sec/mm^2. So, we used a baseline b value of 50 sec/mm^2, with a maximum of 400 sec/mm^2. The diffusion pathways in the kidney are limited, mostly peripheral, so the number of directions in which the water diffusion is measured doesn't need to be high. Most researchers agree on application of the diffusion gradient in 6 directions.[8,9] Other parameters used were TR/TE = 1500/115 ms, echo train length 144, and bandwidth of 1500 Hz. We chose to perform the sequence in free breathing mode, although, form some patients the quality was not exceptional secondary to breathing distortion. The acquisition time was ~60 seconds. Trace DWI, ADC, and FA images were reconstructed inline by the acquisition station. The images were reviewed on a dedicated viewing program (RadiAnt DICOM viewer 3.0.2, Medixant) in which hand-drawn regions of interest (ROI) were placed in renal cortex and medulla respectively. Three ROIs were measured in different places for every region, and the mean value was noted. Next, the acquired data sets were transferred to a specialized software – Neuro 4D (Siemens Healthcare) and tractography was performed by seed-point method with a FA threshold of 0.2 and an maximum angle of

30 degrees. Statistical analysis was performed in SPSS v 20. Because of the low number of cases, we performed non-parametric tests. For median comparisons of numerical values Wilkoxon Signed Rank test was used and to study correlations, we performed Spearman's rho non-parametric correlations with scatter plots for visual estimations.

Results

By visually inspecting the FA images (fig. 1) it was clearly seen a net differentiation between the renal cortex and the medulla. The cortex has low, homogenous signal, whereas the pyramids are markedly hyperintense.

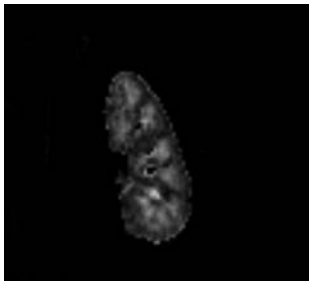

Figure 1.
FA image with cortico-medullary differentiation.

When measured, the FA values in the cortex had a median of 0.19 (interquartile range 0.05), and for the pyramids, the FA values were much higher with a median of 0,50 (IQR 0,14). When analyzed, these values were significantly different ($p<0,005$, fig. 2).

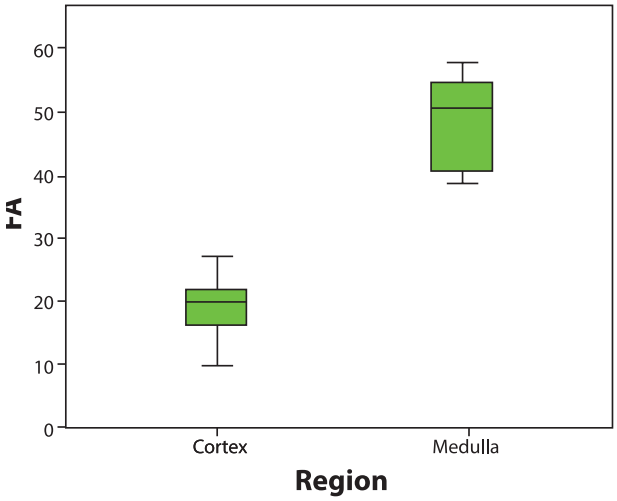

Figure 2. Box-plot graph showing differences between cortex and medulla FA values.

Tractography images (fig. 3) show the pyramids as a funnel shaped structure composed of tightly packed tracts running radially from the cortex to the papilla.

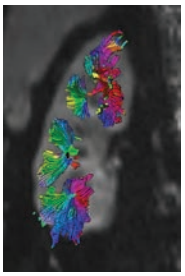

Figure 3.
Kidney tractography with colors delineating direction: red left-right, green cranio-caudal, blue anterior-posterior.

Although not statistically significant, we found a descending trend for FA values with the decrease in eGFR (fig. 4).

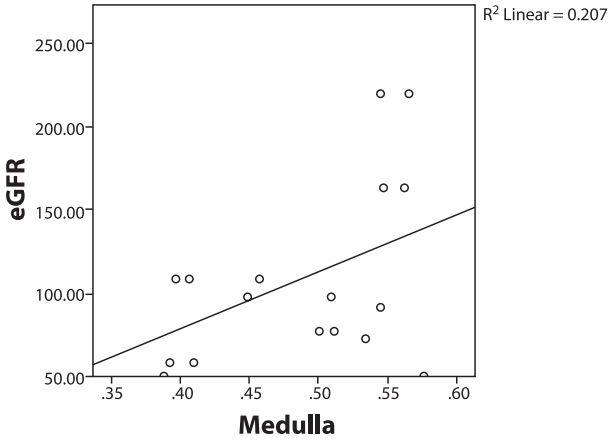

Figure 4. Relationship between FA values and eGFR.

Discussions

Renal imaging has recently experienced a shift in the way its role should be considered. Until now, MR-urography (MRU) was a mainly morphological tool to assess renal disease, but advanced techniques have opened a new front of functional and physiological evaluation of the kidneys.[10,11] Functional MR techniques are increasingly becoming of clinical value with the main purpose to differentiate various pathologic entities that cannot be outlined by morphological studies.[12] The main task of these new techniques is to introduce new bio-markers for renal function in a non-invasive way, without the use of radiation and in certain cases, even without renal contrast. Blood oxygen level-dependent (BOLD), arterial spin-labeling (ASL) imaging and DWI with DTI are already under intense research to make them clinically available.[13,14]

The specific renal histological architecture, with tubes filled with fluid arranged in an organized and relatively simple manner makes it amenable to DTI analysis. DWI works by detecting motion of water molecules by applying a field gradient of strength and duration

encoded by a parameter called b-value. Water diffusion is not uniform in most of the human tissues. Cell membranes, fibers and intracellular environment make the water molecules diffuse along certain paths. This is called anisotropy of water diffusion.[6] The measure of anisotropy is the fractional anisotropy described originally by Basser and Pierpaoli.[15] FA can be measured by applying the diffusion gradient multiple times in several possible directions of diffusion. The more complicated the diffusion pathways are (like in the brain), the higher the number of directions should be measured. In the kidney, the renal tubes are organized in bundles with radial orientation, from the renal cortex to the papilla. Therefore, the number of diffusion directions is limited, so the gradient should be applied in fewer directions.

Because the water flows in an organized manner in the medulla compared to the cortex, the FA value in the pyramids must be higher. Our results are concordant with the theory and restate the value of DTI to detect in a non-invasive way the histological features of the kidney.

DTI in the kidney was first used by Reis in 2001.[16] Since then, the feasibility of the method was demonstrated by multiple studies on 1.5 and 3 T. [5,17,18] They all revealed different values of FA between renal cortex and medulla with pyramids FA values ranging from 0.35[18] to 0.45[17]. Also, Jaimes et al[19] described the technique in children, finding no change of FA values with age. The variability in FA values observed in previous studies and also in our results (median of 0.50) reflects the fact that researchers used different machines, with different techniques and states the need for technique standardization and equivalence between vendors, hardware and software.

Diffusion metrics can also vary in normal individuals with changing diuretic challenges. Sigmund et al[20] found that diffusion variables are significantly sensitive to flow alterations after administration of Furosemide and suggested that vascular flow, tubular dilatation, water reabsorption and intratubular flow are responsible for DWI contrast.

Applications of DTI were studied by multiple groups in various clinical applications: chronic renal disease[21], acute kidney injury[22], diabetes[23,24], polycystic kidney disease[25] or renal masses[26]. One of the most studied areas was evaluation of transplanted kidneys. Lanzman et al. showed that medullary FA significantly correlated with eGFR and also that it was significantly lower in patients whose renal function did not recover compared to those with stable allograft function at six months.[27] A similar correlation between FA and eGFR is found in our study also, but without statistical significance, most likely because low number of cases and no patients with severe renal disease included. In the same topic of transplantation, Hueper also revealed correlation between FA and eGFR and showed significant differences of FA values between transplanted patients and normal controls. Also, tractography was different, with fewer tracts visualized in transplanted kidneys, which indicate microstructural changes.[28] In a different study, the same group reported correlation between early detected low FA values with fibrosis development on long-term follow-up.[29] Lu et al. studied DTI in diabetes and found that changes in medullary DTI assessments may serve as indicators of early diabetic nephropathy.[24] Feng[30] and Liu[31] compared FA values with pathology and found a negative correlation between FA and the glomerulosclerosis and tubulo-interstitial injury. The value of DTI was also demonstrated in children and adolescents, managing to make a clear distinction between normal patients and children with altered renal function.[8]

The change in FA values in renal disease has been attributed to low filtration rate and low water transport[16]; also, inflammation, edema, necrosis and fibrosis narrow spaces between tubules and water diffusion is reduced.[9]

DTI application in abdominal imaging might be prone to distortion secondary to breathing motion. Seif et al showed that respiratory triggering in native kidneys might be slightly advantageous over non-triggering. However, the differences are relatively low.[32]

Moreover, it makes it a useful method in evaluation of conditions that affect a single kidney such as obstructive uropathy, as single kidney renal function can be assessed only by scintigraphy.

Conclusions

FA values measured by DTI can be used as a biomarker reflecting renal function and renal microstructure. The method is easy to perform, has a short acquisition time and is completely non-invasive with no radiation exposure and without any need of intravenous contrast medium administration. Its applications can be diverse, being able to detect early structural and functional renal changes.

However, multicentric studies where all major vendors of MRI hardware and software should be involved must be performed in order to standardize and calibrate the method.

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