Characteristics of Blood Oxygen Level-Dependent and Diffusion-Weighted Magnetic Resonance Imaging in Tubulointerstitial Nephritis: an initial experience

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Abstract

Diffusion weighted (DW) and blood oxygen level-dependent (BOLD) magnetic resonance (MR) imaging are basic classical sequences of functional MR (fMR) in clinical application, but the exploration in the field of non-transplanted kidney disease is limited.

Objects

To analyze the characteristics of global apparent diffusion coefficient (ADC) values and renal oxygenation status by $R_2^*$ values using DW and BOLD imaging in patients with acute, chronic tubulointerstitial nephritis (ATIN, CTIN) and healthy control.

Methods

Four biopsy-proven ATIN, thirteen clinical CTIN patients in stage 2-5 of chronic kidney disease and four controls were enrolled. They underwent fMR imaging with a 3.0-T MR scanner. A multiple gradient-echo sequence was used to acquire 12 T2*-weighted images for calculation of $R_2^*$ map. DW imaging was acquired by combining a single-shot spin-echo echo planar imaging pulse sequence and the additional motion probing gradient pulses along the x, y, z-axes. We used two different $b$ value groups: 0 and 200 s/mm² as well as 0 and 800 s/mm². For ATIN patients, DW and BOLD MR were performed at the time of renal biopsy (T0) and the third month (T3). Serum creatinine levels at the T3 and sixth month (T6) were regarded as indicators of long-term renal prognosis. Pathological changes such as tubular injury, tissue edema, severity of interstitial inflammation or fibrosis were assessed semi-quantitatively. Activity index (AI) and chronic index (CI) were calculated. Correlation analysis were conducted within MR parameters, pathological and clinical indexes.

Results

In ATIN kidneys, ADCs were significantly lower than control, and showed an obvious remission through three months (both $b$ values, $p<0.05$). Both cortical $R_2^*$ values ($CR_2^*$) and medullary $R_2^*$ values ($MR_2^*$) were decreased, the difference was significant in the change of $MR_2^*$. A rapid recovery of $MR_2^*$ was also observed at T3. There was no relationship between fMR parameters and histopathological indexes (whether compared separately or as AI and CI). $MR_2^*$ had a close relationship with eGFR ($R=0.682, P=0.001$). The change of ADCs ($\Delta$ADC) when $b$ value was 0,200 s/mm² ($R=0.956, P=0.044$) and 0, 800 sec/mm² ($R=0.968, P=0.032$) were inversely correlated to ADCs, $\Delta$MR$_2^*$ ($R=0.979, P=0.021$) and pathological CI ($R=0.977, P=0.023$). Renal long-term prognosis analysis among candidate predictive markers showed no relationship with time-point ADC or $R_2^*$ values, but $\Delta$MR$_2^*$ had a significant correlation to Scr levels at T3 ($R=0.959, P=0.041$) and T6 ($R=0.98, P=0.02$). That was, the lower the ADC value ($b$ was 0, 200 sec/mm²), the greater the increase of ADC and $MR_2^*$ in the next three months, then the subsequent Scr level would be lower. In CTIN group, a low level of $MR_2^*$ was observed while $CR_2^*$ remained unchanged.

Conclusions

Direct evidence of global ADCs and renal oxygenation were got in TIN patients for the first time. $MR_2^*$ served as a promising marker reflecting eGFR. A lower ADC value when $b$ was 0, 200 sec/mm² was a predictive marker to reversible acute injury. The "pseudo normalization" of $CR_2^*$ in CTIN might be the result of the aggravation of renal ischemic changes, contributing to the progression of CKD.

Background

Functional magnetic resonance (fMR) imaging has recently grown to be a useful tool to evaluate real-time renal function[1]. The functional MR sequences mainly include blood oxygen level-dependent (BOLD), diffusion-weighted (DW) imaging, arterial labeling perfusion (ASL) and dynamic contrast-enhanced imaging (DCI). They provide information about diffusion, perfusion, and oxygenation of kidneys besides morphological parameters. These novel techniques serve as promising markers helping to further understand pathophysiology of acute kidney injury (AKI) and chronic kidney disease (CKD)[2-6]. Functional MR is also recommended for early differentiation diagnosis of renal dysfunction after kidney transplantation[7-8]. Researches with fMR were still exploratory in animal models of AKI and some human observational studies[9-11], in human studies of CKD trying to compare MR parameters with renal pathological index[3,9]. It can be seen that the characteristics of fMR in non-transplantation human kidney diseases by contrast, were poorly understood yet.

DW and BOLD from magnetic resonance imaging are early used techniques. The apparent diffusion coefficient (ADC) calculated from DW images was influenced by both pure diffusion and perfusion-dependent diffusion at a low $b$ value. The value was observed to decrease associated with severity of renal dysfunction and degree of renal fibrosis after AKI[12]. But in another CKD rat model, ADC values could not reflect degree of kidney fibrosis[10]. BOLD MR imaging was demonstrated to effectively detect changes in intra-renal oxygenation by measuring the $R_2^*$ levels of the renal cortex and medulla[9]. Li et al. observed the immediate increase in $R_2^*$ in the renal inner stripe of the outer medulla after the injection of contrast agent, which suggesting existence of tissue hypoxia probably induced by hypoperfusion[13], that BOLD served as an earliest biomarker of contrast induced AKI. In diabetes patients, it was found that $R_2^*$ value was decreased after single dose of furosemide
injection as a result of increased oxygen consumption of tubular Na-K transporter working. While in another report, Renal BOLD-MRI was found not reflecting renal function CKD [14]. Furthermore, intra-renal change of oxygenation contributes to progression of chronic kidney disease[15]. This shows that both ADC and $R_2^*$ value might be influenced by intra-renal perfusion, tubular injury, interstitial inflammation or fibrosis, all these pathological changes that resulting in the change of water diffusion capacity and tissue oxygen consumption.

The pathogenesis of tubulointerstitial disease lies in damage of tubules, changes of inflammation, edema or subsequent fibrosis involving corresponding interstitial regions, and following regulation of intra-renal microcirculation, while glomeruli are initially intact[16]. Besides, tubulointerstitial changes subsequent to kinds of glomerular diseases also play a key role of disease progress. This is a perfect disease model for initial study of functional MR characteristics. The aim of this study was to observe the characteristics of BOLD and DW magnetic resonance imaging both in patients with acute and chronic tubulointerstitial nephropathy (TIN).

**Methods**

**Patients**

Patients with acute tubulointerstitial nephritis (ATIN) matched 1: 2: 1 with chronic tubulointerstitial nephritis (CTIN) and healthy control were enrolled in this study from Jan 2008 to Jan 2009. ATIN patients were included if they (a) were adults diagnosed with biopsy-proven ATIN, (b) were capable to undergo fMR examination three days within percutaneous renal biopsy, (c) had no signs of other kidney diseases both clinically and pathologically. CTIN patients were selected from our specialty clinic for all-cause tubulointerstitial nephritis (TIN) diseases. Patients were included if they (a) were adults clinically diagnosed with CTIN, (b) clinically had no signs of other kidney diseases, and been followed up for more than one year, (c) with a stable serum creatinine level at CKD stage 2-5 [17]and well-controlled hemoglobin level in the recent three months. Healthy volunteers were recruited if they (a) were adults with no history of renal or cardiac diseases, and (b) had normal serum creatinine concentrations one week before MR scanning. Patients with renal malignancy, malformation, and history of partial nephrectomy were excluded from the study. For ATIN patents, serum creatinine (Scr) and hemoglobin were routinely performed for six months (T6). BOLD and DW imaging were performed at the time of renal biopsy(T0) and the third month after supportive therapy(T3).

This prospective study was in compliance with the declaration of Helsinki, and approved by the Human Ethics Committee of Peking University First Hospital. All subjects provided written informed consent and were compatible with MR scanning.

**MR imaging**

All patients underwent MR imaging with a 3.0-T MR scanner (General Electric Medical Systems, Milwaukee, WI, USA). A multiple gradient-echo (mGRE) sequence was used to acquire 12 T2*-weighted images for calculation of $R_2^*$ map. The parameters of sequence were as follows: TR/TE/Flip angle/BW/matrix/ thickness/gap=100ms/6.7-32.1ms(12echoes)/45°/31.3kHz/128×96/5mm/1mm.NEX=1, and five to 6 axial slices were acquired within one breath hold 24 seconds. DW imaging was acquired by combining a single-shot spin-echo (SE) echo planar imaging (EPI) pulse sequence and the additional motion probing gradient (MPG) pulses along the x, y, z-axes. The parameters were as follows: TR/TE/BW/matrix = 2300ms/56.1ms/250kHz/128×128. NEX=2, and the slice position was identical to the BOLD imaging by the “copy” function embedded in the MR scanner, which were scanned within 18 seconds. We used two different b value group:0 and 200s/mm² as well as 0 and 800 s/mm². Axial images were acquired for both BOLD and DW images.

Both $R_2^*$ map and apparent diffusion coefficient ADC map were generated on an AW 4.2 workstation (General Electric Medical Systems, Milwaukee, WI, USA) using “Functool” software. The reader was blinded to the subject's clinical information. At least 8 regions of interest (ROIs), each area of which was at least 10 pixels, were carefully placed on the cortex and medulla on the corresponding anatomical template separately (using image of TE=32.1ms as a template), the measured slices covered most part of the kidney. Because of the poor resolution of the images, particularly in severe renal impairment patients, it was not possible to reliably discriminate between the cortex and the medulla, which meant that the ROIs could not be reliably placed. Hence it was only possible to calculate global ADCs for each kidney. The ROIs were manually delineated in the parenchyma of the kidneys. Both $R_2^*$ and ADC values were read out on the corresponding $R_2^*$ and ADC map [Fig 2-3]. The cortical and medullary $R_2^*$ as well as global ADC of kidney were calculated separately for each side.

**Pathology**

Renal tissues from four ATIN patients were handled routinely by Haemotoxylin-Eosin, Masson's trichrome, periodic acid-Schiff, and periodic acid-silver methenamine staining for light microscopy examination. The tissue core was often obtained at depths of about 1 cm. The histopathological indexes included tubular injuries (tubular epithelial cells atrophy, vacuolar degeneration, brush border shedding, necrosis and tubulitis) and interstitial changes (edema, inflammation and fibrosis). Area and degree of tubular brush border shedding, atrophy and interstitial change were semiquantitatively assessed as scores 1, 2, 3 and 4 corresponding to not, mild, moderate and severe changes by two difference pathologists referring to a modification of the Banff Working Classification[20-21]. They were also blind to the clinical data. The activity index
was the total of the scores for tubular injuries, interstitial edema, and inflammatory infiltration. The chronicity index was the total of the scores for tubular atrophy and interstitial fibrosis.

Statistical analysis

Statistical analyses were performed using the software SPSS Version 20.0 (IBM Corp., Armonk, NY). Data were presented as the median and range. Differences between groups were analyzed by the non-parametric Kruskal-Wallis test. Correlations were assessed according to the Pearson test for parametric data and the Spearman test for non-parametric data. The correlations between serum creatinine, eGFR levels and the fMR parameters (kidney volume, ADC value and R\textsubscript{2}\textsuperscript{*} value) of all kidneys were determined. The correlations between pathological indexes and fMR parameters were also analyzed. A P-value less than 0.05 was defined as statistically significant.

Results

Clinical and pathological characteristics

There were altogether 20 individuals recruited for this study, including 5 ATIN patients, 15 CTIN patients, and 5 healthy control. Four patients were excluded from the study because the quality of their fMR images was poor to be used (Fig 1. flow chart). Four patients with ATIN, thirteen patients with CTIN, and five healthy control were finally enrolled. The demographic and clinical data of the subjects are summarized in table 1. The ATIN patients were 43.8±19.4 years old, with an averaged 52.0±13.3 years old of CTIN patients. All the ATIN patients experienced acute kidney injury (AKI) defined using the Kidney Disease: Improving Global Outcomes (KDIGO)[20-21] criteria and consensus report of the Acute Disease Quality Initiative 16 Work group. There were two patients in AKI stage 1, two in AKI stage 2 and one in AKI stage 3. Renal pathology revealed that in ATIN kidneys, the glomeruli were relatively intact. Focal or diffuse tubular injuries, and diffuse interstitial edema and mononuclear cells infiltration were predominant pathological findings (Fig 4). The activity index was averaged 12.8±3.3, with the chronicity index 3.5±0.6. The Scr level was 112~401 μmol/l (217.4±126.4 μmol/l, eGFR 37.4±31.5 ml/min/1.73m\textsuperscript{2}) at the time of renal biopsy, and gradually declined to normal level after short-term steroids administration during the following three months, the eGFR was averaged 65.5±29.0 ml/min, 74.4±41.1 ml/min at the third (T3) and sixth month (T6). The hemoglobin of ATIN patients was 99.0±13.4 g/L initially, and corrected to 129.0±13.2 g/L.

Thirteen patients with CTIN were from our out-patient specialty for tubulointerstitial nephritis under integrative supportive therapy for CKD. The renal function was stable the recent three months before MR imaging. Patients were in CKD stage 2~5 non-dialysis, whose eGFRs were averaged 34.7±21.9 ml/min (Scr 102~526 μmol/l). Renal anemia of CTIN patients had already been corrected to 126.8±16.8 g/L, which was matchable with healthy control.

Functional MR imaging features

In control kidneys (Fig 5), the outline was smooth and there was clear differentiation between renal cortex and medulla on T1-weighted SE and IR sequence. The averaged volume of kidneys was (137.8±26.6)×10\textsuperscript{3} mm\textsuperscript{3}. Global ADC values of DW imaging was 3.54±0.25 and 2.24±0.19 respectively when \textit{b} value was 0, 200 or 0, 800 sec/mm\textsuperscript{2}. Cortical R\textsubscript{2}\textsuperscript{*} value calculated from BOLD MR imaging was 19.4±1.9 Hz, that was obviously lower than medulla [(31.9±4.1) vs. (19.4±1.9) Hz, p<0.05].

In ATIN patients, swollen kidneys were observed (Fig 6). The volume was (176.8±82.8)×10\textsuperscript{3} mm\textsuperscript{3}. ADC values obtained in DW imaging both when \textit{b} value 0, 200 sec/mm\textsuperscript{2} and 0, 800 sec/mm\textsuperscript{2} were used, were all found to have significant decreases as 23.5%, 19.2% respectively than control group when \textit{b} value was 0, 200, and 0, 800 sec/mm\textsuperscript{2} (Table 1). And obvious rising of decreased ADC values were observed following improvement of renal function to achieve a 48.1%, 80.9% recovery at the third month but still lower than control (see Table 1). Both cortical and medullary R\textsubscript{2}\textsuperscript{*} values of ATIN kidneys were also lower than controls at the time of renal biopsy, the differences was significant in MR\textsubscript{2}\textsuperscript{*} values as 23.8% (difference in CR\textsubscript{2}\textsuperscript{*} values was 9.3%). The medullary R\textsubscript{2}\textsuperscript{*} values firstly went back to a level similar as control, while the cortical R\textsubscript{2}\textsuperscript{*} values remained low. For CTIN patients (Fig 7), extremely shrink kidneys with irregular outlines were found (fig 2). The volume was 89.0±23.0×10\textsuperscript{3} mm\textsuperscript{3}. Both ADC values when \textit{b} value 0, 200 sec/mm\textsuperscript{2} and \textit{b} value 0, 800sec/mm\textsuperscript{2} were similar as healthy control. In R\textsubscript{2}\textsuperscript{*} map, medullary R\textsubscript{2}\textsuperscript{*} value of CTIN kidneys was averaged 28.0±5.0 Hz, which was lower than control but the difference was not statistically significant.

Further analysis disclosed that neither ADC values nor R\textsubscript{2}\textsuperscript{*} values, was correlated to histopathological indexes including tubular injuries (tubular epithelial cells atrophy, vacuolar degeneration, brush border shedding, necrosis and tubulitis) and interstitial changes (edema, inflammation and fibrosis) when compared separately. We also found no relationship within ADC values, R\textsubscript{2}\textsuperscript{*} values, Al and CI. It seems that ADC and R\textsubscript{2}\textsuperscript{*} values changed along with that of renal function (Table 1) in ATIN kidneys, while close relationship was only identified in MR\textsubscript{2}\textsuperscript{*} values with eGFR (R=0.682, P=0.001), the situation was similar whether for CTIN patients (R=0.615, P=0.025) or all TIN patients (R=0.956, P=0.044). Both ADC values were inversely correlated to the change of ADC values (ΔADC, the change of ADC value over the following three months) when \textit{b} value
was $0.200\text{ sec/mm}^2$ ($R=0.956, P=0.044$) and $0.800\text{ sec/mm}^2$ ($R=0.968, P=0.032$). The change of medullary $R_2^*$ values ($\Delta R_2^*$, the change of $MR_2^*$ value over the following three months) was found to have close relationship with $\Delta ADC$ when $b$ was $0, 200\text{ sec/mm}^2$ ($R=0.979, P=0.021$) which was regarded as a marker mainly affected by blood perfusion, inversely with pathological CI ($R=-0.977, P=0.023$). Renal long-term prognosis analysis among candidate predictive markers showed that no relationship was found with time-point ADC or $R_2^*$ values, but $\Delta MR_2^*$ had a significant correlation to Scr levels at the third ($R=-0.959, P=0.041$) and sixth month ($R=0.98, P=0.02$). In other words, the lower the ADC value ($b$ was $0, 200\text{ sec/mm}^2$), the greater the increase of ADC in the next three months, the greater the increase of $MR_2^*$, then the subsequent Scr level would be lower.

in ATIN kidneys, a significant reduction of medullary $R_2^*$ value and ratio of $MR_2^*$ to $CR_2^*$ were detected. The rapid and reversible change of the medullary $R_2^*$ values suggested that the tubular injury is mainly caused by ischemic factors.

Although both $CR_2^*$ and $MR_2^*$ were decreased than those of healthy control at ATIN, their changes after treatment were varied, with further decline of $CR_2^*$ in two patients; in the CTIN group, only a low level of $MR_2^*$ was observed while $CR_2^*$ could remain at the normal level, suggesting that there might be a delayed recovery of AKD injury and the “pseudo normalization” of $CR_2^*$ caused by oxygen adaptation changes during CKD.

**Discussion**

In this study, we assessed kidneys of ATIN presenting acute kidney injury and CTIN kidneys of stable renal function with DW and BOLD MR imaging. The correlation of functional MR parameters with critical pathological and clinical factors indicate the potential significance of these novel techniques as noninvasive methods, contributing to diagnosis, long-term prognosis assessment and further understanding of kidney diseases.

Diffusion-weighted MR imaging yields the ADC value as an index reflecting microenvironment of diffusing water molecules. It is considered as a simple marker reflecting tissue microstructure. In case of renal dysfunction, tubular injuries lead to reduced water reabsorption process resulting in decreased diffusion[22]. Factors involving microcapillary perfusion, status of tissue edema and fibrosis also theoretically contribute to ADC. Boor et al.[10] observed ADC values in unilateral ureteral obstruction rat model, and found that renal ADCs postmortem dropped almost 75% off than baseline in vivo, suggested the leading role of perfusion contributing to ADC value especially when $b$ value $<200\text{ sec/mm}^3$. Oppositely when $b$ level was higher than $400\text{ sec/mm}^3$, ADC value declined only 25%, because the value was mostly generated from the effect of diffusion. Xu et al.[23] reported that ADC values of impaired kidneys (when $b$ was 500) were significantly lower in a linear but positive correlation with eGFR in patients mainly with renal arterial stenosis. In the current study, we revealed similar level of the global ADC values in CTIN patients as control. While there were obviously decreased but reversible changes of ADC values when $b$ is $0, 200$ and $0, 800\text{ sec/mm}^2$ in patients with ATIN, when compared with control. Presumably this indicated that there was redistribution of intra-renal micro-circulation in the background of interstitial inflammation leading to reduced blood perfusion, and decreased water diffusion because of tubular injuries, thus ADC in both low and higher $b$ values declined. The delayed recovery of ADC (especially when $b$ was $0, 200\text{ sec/mm}^2$) also meant that kidney injury was still in the process of repair or left behind chronicity. After that, the kidney was likely to undergo adaptive changes continually, and when it finally reached a stable CKD stage, as data shown in CTIN patients, ADC could approach normal level. It is concluded from the current study that ADC may serve as a promising marker reflecting reversible acute injury, but not sensitive for interstitial fibrosis.

As we have known, the $R_2^*$ value of BOLD MR imaging has been regarded as a factor reflecting tissue oxygenation[24]. The renal medulla is vulnerable to hypoxia because of low oxygen delivery due to low vascular density in medulla, arterial-venous shunting, and high oxygen consumption for active transcellular transport of sodium and chloride in loop of Henle. Therefore, it is not difficult to understand that oxygen consumption and $R_2^*$ values decrease due to renal tubulointerstitial injury. If the injury is mainly related to direct toxicity, it only shows the decrease of cortical $R_2^*$[25]. However, if the mechanism of renal tubular injury is also involved in ischemic factors, such as renal ischemia with redistribution of blood flow during acute inflammation, renal artery stenosis, diabetic microangiopathy, acute rejection of graft-kidney[26] and aristolochic acid nephropathy, then the $R_2^*$ of both cortex and medulla will change. The change of medullary $R_2^*$ would happen earlier and more significant. In our study, we verified that medullary $R_2^*$ was closely correlated to eGFR for all the patients, that it can be regarded as an important marker to reflect renal dysfunction. The change of $CR_2^*$ was mild, it is because acute ischemia compromises oxygen delivery while oxygen consumption by the reabsorption is maintained. The reduction of $MR_2^*$ to $CR_2^*$ ratio was detected in ATIN, suggested that the tubular injury was mainly caused by ischemic factors. The delayed recovery of $CR_2^*$ value is due to the increase of tissue oxygenation due to the improvement of blood perfusion, so the change of $CR_2^*$ was not significant. It is interesting that cortical $R_2^*$ was normalized in CTIN kidneys opposite to the persistent low medullary $R_2^*$. And this “pseudo normalization” of $CR_2^*$ by supportive change in CTIN may be the result of the aggravation of renal ischemic changes, and contributes to the progression of CKD.

DW MR imaging and BOLD imaging are the basic classical sequences of functional nuclear magnetic resonance in clinical application, but the exploration in the field of non-transplanted kidney disease is still limited. From the results of this study, we consider that DW combined with
BOLD imaging may be helpful to judge AKD, especially the emergence of AKD on the basis of the original CKD in case of not applicable to kidney biopsy, as a non-invasive diagnostic method that can be tried. However, the response of DW MR to renal interstitial fibrosis is insensitive, because the result of patients with stage CKD3-5 showed no difference from those of normal. But the joint examination using the basic scanning sequence is one of the feasible ways that can be popularized and applied to clinic in the future.

The limitation of our study was the disability to get direct information of intra-renal perfusion, despite that DW and BOLD imaging were nowadays the most frequently used functional MR imaging techniques in human diseases. Combination of these data could indirectly to some extent reflect tissue edema, inflammation, fibrosis and even be relevant to organ dysfunction. Microcirculation might also be roughly assessed, but could not be determined histologically by routine methods. More and special multi-sequence should be researched and developed in the future in order to further understand the mechanism of diseases[27-28]. The limitation of functional MR sequence scanning also lies in the influence of respiration on the scanning image quality. For critically ill patients, the poor respiratory cooperation in the intensive care unit is a problem that restricts the clinical application of fMR.

This is an initial observational study and we produced direct evidence of intra-renal oxygenation and got global values of ADC in acute and chronic TIN patients for the first time. Short-time reduced R$_2^*$ values of both cortical and medullary accompanying with reduced ADC values were observed in ATIN kidneys. On the contrary, there was obvious but persistent change of tissue oxygenation in CTIN kidneys. Long-term observation deserves close attention.

**Abbreviations**

MR: magnetic resonance; fMR: functional MR; DW: diffuse weighted; BOLD: Blood oxygen level-dependent; ADC: global apparent diffusion coefficient; ATIN: acute tubulointerstitial nephritis; CTIN: chronic tubulointerstitial nephritis; CR$_2^*$: cortical R$_2^*$ values; MR$_2^*$: medullary R$_2^*$ values

**Declarations**

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**Authors’ Contributions**

TS and LY contributed to patient diagnosis, management and clinical data analysis. XY, RW and XW contributed to analysis of functional MR imaging data and provided relating images. TS and XY wrote manuscript drafting, contributed to data analysis, interpretation and intellectual content of critical importance to the work described. LY and XW interpretation and intellectual content of critical importance to the work and revised the manuscript. All authors had the opportunity to revise the manuscript.

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**Availability of data and materials**

The patient was regularly followed up and the clinical data is traceable. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

Not Applicable.

**Consent for Publication**

Written informed consent was obtained from the patients for publication and any accompanying images.

**Competing interests**

No one of the Authors has a financial and non-financial competing interest.
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### Tables

#### Table 1. Laboratory and fMR data of ATIN and CTIN kidneys

| Age | Scr (μmol/l) | eGFR (ml/min) | Hb (g/L) | Cortical R$_2^*$ (Hz) | Medullary R$_2^*$ (Hz) | ADC value $b$ value 800 | ADC value $b$ value 200 | Volume (cm$^3$) |
|-----|--------------|---------------|----------|----------------------|-----------------------|-------------------------|--------------------------|----------------|
| Control | 50.3±10.0 | 60~83 | 84~110 | 135.2±5.2 | 19.4±1.9 | 31.9±4.1 | 2.30±0.28 | 3.54±0.25 | 137.8±26.0 |
| ATIN T0 | 43.8±19.4 | 112~401 (217.4±126.4) | 9.9~82.8 (37.4±31.5) | 99.0±13.4 | 17.6±1.3 | 24.3±2.1 # | 1.76±0.12 # | 2.86±0.19 # | 176.8±82.8 |
| T3 | 88~121 (103.3±15.8) | 66.6±31.2 | 129.0±13.2 | 18.3±2.2 | 32.4±6.6 | 2.02±0.04 * | 3.41±0.10 * | 154.2±7.0 |
| T6 | 76~118 (97.5±21.0) | 74.4±41.1 | 134.8±8.6 | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| CTIN | 52.0±13.3 | 102~526 (240.2±146.0) | 5.1~79.8 (34.7±21.9) | 126.8±16.8 | 19.0±2.2 | 28.0±5.0 * | 2.20±0.20 | 3.46±0.43 | 89.0±23.0 * |
| eGFR<45 | | | | | | | 2.23±0.21 | 3.14±0.30 * |
| eGFR>45 | | | | | | | 2.15±0.19 | 3.66±0.37 |

Note: # when compared between T0 and control, the difference is significant P<0.05.

* when compared between T0 and T3, the difference is significant P<0.05.

no significant difference was found between T3 and control

^ when compared with control, the difference is significant P<0.05.

※ when compared with group eGFR>45 ml/min, the difference is significant P<0.05.
Figures

ATIN 5  CTIN 15  Healthy 5  Recruited 1: 3: 1

Excluded, because of poor MR images quality
◆ ATIN 1, CTIN 2, Healthy 1

÷ ATIN 4
÷ CTIN 13
÷ Healthy 4

Figure 1
the flow chart of the study.

Figure 2
A: DWI image. B: the corresponding ADC diagram. The method of manual placement of ROI is used to draw the outline of the kidney on the anatomical map with (DWI).

Figure 3
The method of manually placing ROI on the anatomical template is to place at least three ROI, in the cortical medulla and read the corresponding R2* value on the corresponding R2* diagram.

Pathological pictures of ATIN and normal kidney (all HE staining). A: example 1, magnification 100x. B: case 2, magnification x400. C: case 3, magnification x200. From A to C, ATIN showed exfoliated brush margin of renal tubules, dilated lumen, diffuse edema of renal interstitium, multifocal or diffuse (C) lymphoid and monocytes infiltration and eosinophils infiltration. There were no obvious pathological changes in glomeruli and arterioles. Figure D shows normal kidney, magnification x100: glomeruli and tubules are normal.

MRI diagram of normal kidney. In the picture, A1 to A4 are T1WI, T2WI, DWI and R2*, respectively. It can be seen that the demarcation of the epithelium and medulla on T1WI, T2WI and R2* maps is clear (3 points).
Figure 6

ATIN kidney MRI diagram. In the picture, B1 to B4 are T1WI and T2WI DWI and R2* pictures, respectively. It can be seen that the corticomedulla boundary between T1WI and T2WI is OK (2 points). Compared with normal, the cortical area of R2* map is slightly irregular.

Figure 7

CTIN kidney MRI diagram. In the figure, C1 to C4 are T1WI and T2WI Magol DWI and R2* pictures, respectively. The epithelial medulla boundary of T1WI and T2WI could only be seen faintly (1 point). Compared with normal and ATIN, the epithelial medulla of R2* was obviously irregular.