Functional MRI as a Tool for Evaluating Interstitial Fibrosis and Prognosis in Kidney Disease

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Keywords

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Abstract

Background: Kidney fibrosis is a key driver of progression of kidney diseases. Renal biopsies remain the gold-standard approach to specifically diagnose and stage renal fibrosis at present. However, there is a lack of multi-dimensional pictures showing renal function, histology, and imaging of the fibrotic kidney. **Summary:** Magnetic resonance imaging (MRI) strategies have been rapidly evolving during the past couple of decades, especially driven by advances in technology. Recently, several pioneer and remarkable studies demonstrated that advanced functional MRI (fMRI) tools could be useful for the evaluation of kidney fibrosis and progression, which provides more opportunities to benefit from the significant value of fMRI tools for clinical implementation. **Key Messages:** fMRI will be a novel approach to evaluate interstitial fibrosis and prognosis in kidney disease.

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Introduction

Chronic kidney disease (CKD) has turned into a major global public health problem that affects approximately 10% of the world's population, which causes millions of deaths each year and requires hundreds of thousands of people to use dialysis to stay alive [1, 2]. Previously known as kidney disease, CKD is a condition characterized by a gradual loss of kidney function. Kidney fibrosis, which is characterized by the excessive deposition of extracellular matrix (ECM), is a key driver of progression of CKD [3, 4].

Despite several limitations, at present, biopsies remain the gold-standard approach to specifically diagnose and stage renal fibrosis. Needle-based biopsies are invasive, bear the risk of sampling errors, are limited in terms of spatial information, and are not suitable for long-term monitoring of disease progression or therapy responses.

It is noticeable that magnetic resonance imaging (MRI) strategies have been rapidly evolving during the past couple of decades, especially driven by advances in technology. There are several advanced MRI tools, including functional MRI (fMRI) and molecular MRI. Functional imaging approaches, such as magnetic resonance elastog-

raphy (MRE) as well as diffusion-weighted and blood oxygen level-dependent (BOLD) MRI, have been proven useful for the diagnosis, staging, and treatment monitoring of renal function in CKD and allograft. However, fMRI has not routinely been used in the setting of kidney diseases. Traditional molecular MRI usually means using molecular-targeted probes to detect different biological processes in an organ. In a broad sense, advanced fMRI has the potential of including molecular imaging. In the future, traditional fMRI should be combined with molecular MRI to obtain anatomic, functional, and molecular information simultaneously, which is not possible from a single imaging session. At present, there are several studies, which are in progress or have been published, showing that fMRI and molecular MRI are noninvasive, useful tools for evaluating interstitial fibrosis and prognosis in kidney diseases. In this review, we describe recent data from fMRI and molecular MRI evaluating kidney fibrosis.

Evaluation of Native Kidney Fibrosis by fMRI

Key Pathophysiologic Disorders of the Fibrotic Kidney

It is well known that there are multiple key physical changes occurring in the fibrotic kidney. Firstly, accumulating evidence has demonstrated that progressive capillary loss occurs in parallel to kidney scarring, resulting in reduced blood flow and oxygen delivery to tubular epithelial cells of the kidney parenchyma, which can drive further fibrogenesis. Thus, capillary loss and hypoperfusion are not only key features of the fibrosing kidney, but also drivers of further fibrosis-associated injury [5, 6]. The second important point is that, as the nephron is scarred, the deposited ECM increases, which in turn increases kidney stiffness [5, 6]. Progressive ischemic tubular injury leads to tubular cell apoptosis, tubular atrophy, and dilation.

Evaluation of Kidney Fibrosis Based on a Combination of Histology and fMRI

To evaluate kidney fibrosis based on a combination of renal histology and multiparameter fMRI, in one of our recent unpublished works, we applied representative models of ECM-to-kidney cortex interstitial ratio and peritubular capillary (PTC) densities using intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI), MRE imaging, and estimated glomerular filtration rate (eGFR). In this pioneer study, CKD patients from G1 to G4, who received kidney biopsy for the diagnosis, were

studied. In the study, we found that kidney fibrosis could be quantitatively assessed by kidney interstitial ECM volume and density of PTCs as well as the relevant multiparameters of fMRI and eGFR. The ECM-to-kidney cortex interstitial ratio was calculated by an Aperio ScanScope system using Masson's trichrome slices. The kidney cortex microcirculation was quantitatively assessed by PTC densities using CD34 staining.

Firstly, we found that the densities of PTCs were in line with the DWI-fraction value and eGFR, which were both positively related with densities of PTCs. This result suggests that the lower the eGFR and DWI-fraction, the lower the PTC density will be, which also means more serious fibrosis in the kidney (Fig. 1).

Secondly, the cortex interstitial ECM volume was in line with the natural logarithm of the MRE value and eGFR, which were both negatively associated with matrix volume. The data indicated that the MRE value and eGFR were both negatively associated with ECM volume. This result suggests that the lower the MRE value and eGFR, the higher the cortex interstitial ECM volume will be, which means more serious fibrosis in the kidney (Fig. 2).

From these data, the multi-dimensional pictures, including histology features, MRI, and eGFR, were delineated. Once the patients' fMRI and eGFR have been obtained, their fibrosis situation can be calculated. This study not only provided histological evidence to support that fMRI can effectively evaluate fibrosis in the kidney; moreover, these findings depict kidney fibrosis based on a combination of histology, imaging, and eGFR, which has significant value for clinical implementation.

In this study, 2 advanced fMRI tools were used: IVIM-DWI and MRE. In biologic tissues, the IVIM of water molecules includes both diffusion of water and microcirculation of blood in the capillary network (perfusion). Different from conventional DWI, IVIM-DWI using a biexponential fit model can separately estimate the tissue capillary perfusion. Specifically, biexponential fitting can be performed to obtain the pseudo-perfusion apparent diffusion coefficient, which is mainly determined by the much faster microcirculation and perfusion. The perfusion fraction represents the fractional volume of capillary blood flowing in each voxel [7]. In 2011, Inoue et al. [8] reported on the noninvasive evaluation of kidney fibrosis and eGFR by using DWI-MRI in CKD and acute kidney injury patients. Mao et al. [9, 10] performed IVIM-MRI on CKD patients to assess functional and pathological alterations. Recently, Feng et al. [11] and Deng et al. [12] utilized IVIM-DWI to evaluate early renal function

Fig. 1. Representative images of IHC staining and DWI scanning show kidney fibrosis. Representative images show peritubular capillaries and IVIM-DWI. As kidney function decreased, the CD34-positive capillary densities decreased (**a1**, **a2**, and **a3**; original magnification $\times 400$). IVIM-DWI values were generated from DWI-fraction and DWI-standard ADC scanning; the relevant colored images are displayed as DWI-fraction (**b1**, **b2**, and **b3**) and DWI-standard ADC (**c1**, **c2**, and **c3**), showing that both values of these tools went down as kidney function decreased. IHC, immunohistochemistry; ADC, apparent diffusion coefficient.

Fig. 2. Representative images of histology and MRE scanning show kidney fibrosis. Representative images of histology show fibrosis and kidney stiffness. As kidney function decreases from CKD G1 to G4, the Masson slides show extracellular matrix volume increase (**a1**, **a2**, **a3**, and **b1**, **b2**, **b3**; original magnification $\times 100$). Kidney stiffness was generated from MRE scanning. The colored images relevant to stiffness (**c1**, **c2**, and **c3**) show that the stiffness value (red color) went down as kidney function decreased.

changes in type 2 diabetic patients and found that the IVIM parametric values are more sensitive than the albumin-to-creatinine ratio in detecting early-stage kidney changes. MRE combines imaging with the assessment of acoustic waves for the quantitative determination of viscoelastic properties of tissues based on their response to external mechanical vibration [13]. Rouvière

et al. [14] firstly showed MRE feasibility and reproducibility in healthy adults. MRE is already a well-established technique for liver fibrosis imaging, having been shown to accurately reflect biopsy-derived liver fibrosis measurements [15-17]. Up to date, there are 3 high-quality studies to evaluate MRE in human kidney allografts [18-20].

Evaluation of Transplanted Kidney Fibrosis by fMRI

Evaluation of Transplanted Kidney Fibrosis by fMRI and Histopathology

Similar to native kidneys, interstitial fibrosis is also a universal histologic finding in progressive kidney parenchymal lesions in transplanted kidneys. Another recently published work from our center showed that fMRI measures highly correlate with histologic findings and degree of interstitial fibrosis [21, 22]. A total of 103 kidney transplant recipients who underwent a for-cause biopsy and 20 kidney transplant patients with stable kidney allograft function and a normal biopsy were included.

Apparent diffusion coefficient from DWI correlated with interstitial fibrosis. Additionally, decreased arterial spin labeling (ASL) was accompanied by PTC density reductions. BOLD imaging demonstrated cortical hypoxia with increasing interstitial fibrosis. This study demonstrated that fMRI measurements were strongly correlated with kidney allograft interstitial fibrosis. Therefore, the authors suggest that this noninvasive modality could serve as a tool to assess chronic allograft injury. This study is a step toward incorporating fMRI into clinical care. In the way it has been applied and proposed, an fMRI would be very useful as a prognostic tool, considering its ability to provide information about the degree of fibrosis.

In this study, besides IVIM-DWI, 2 advanced tools were used, ASL and BOLD. ASL uses blood as an endogenous contrast agent, assesses inflowing blood to kidney tissue, and serves as a surrogate for tissue microvascular perfusion [7]. BOLD imaging detects altered deoxyhemoglobin levels and serves as a surrogate marker of tissue oxygenation. It correlates with inactive functional tissue, such as in fibrosis, because less cellular activity requires less oxygen to maintain function. However, BOLD cannot distinguish the changes in oxygenation caused by perfusion alterations from those attributed to oxygen consumption alterations [7].

Assessing Kidney Allograft Fibrosis by MRE

There is literature from the field of transplantation showing that MRE was used to assess fibrosis in kidney allografts [18]. In this study, the authors performed MRE scanning on a 3.0-T MRI scanner. Each patient had serial eGFR measurements after the MRE scan for a follow-up period of up to 1 year. Although there were only 16 patients who underwent MRE and biopsy, the most significant results from the study were that the kidney stiffness,

which was evaluated by MRE, was associated with a great eGFR decline. In this study, patients who had lower MRE readings at baseline and higher eGFR (>45 mL/min/1.73 m²) at baseline would have stable renal function in the next 2 years. However, patients who had higher MRE readings at baseline and lower eGFR (<45 mL/min/1.73 m²) would have deteriorated GFR in the next 2 years. This result suggests that we can use MRE reading to predict eGFR loss in clinical practice.

Evaluation of Kidney Fibrosis by Molecular MRI

Molecular MRI is also an advanced MRI tool to detect and evaluate organ lesions. There has been remarkable progress in a study recently. Sun et al. [23] used an elastin-specific imaging agent (ESMA) to noninvasively analyze kidney fibrosis. Firstly, the authors showed that elastin was hardly expressed in healthy mouse, rat, and human kidneys, whereas it was overexpressed in cortical, medullar, and perivascular regions in progressive CKD. Similar results were seen in vivo using 3 mouse models of kidney fibrosis.

Secondly, the data showed the ability of ESMA to noninvasively capture disease progression and therapy effects. They monitored fibrosis development in the adenine-induced nephropathy mouse model over 21 days. Crystal-induced nephropathies are recognized as a major pathogenic mechanism in progressive kidney diseases with fibrosis development. For the kidney fibrosis model, imatinib, which is a receptor tyrosine kinase inhibitor, was used for treatment from day 7 to 21, when fibrosis was already established. Data showed that imatinib significantly reduced renal fibrosis and renal elastin expression. More interesting, signal intensities obtained with molecular imaging using ESMA were significantly lower in imatinib-treated mice than those obtained in control mice. The most meaningful result from this study was that elastin imaging allowed for repetitive and reproducible assessment of renal fibrosis, and it enabled longitudinal monitoring of therapeutic interventions, accurately capturing antifibrotic therapy effects.

The Future of fMRI in Kidney Disease

As it was mentioned above, CKD is a condition characterized by a gradual loss of kidney function. At present, eGFR and albumin-to-creatinine ratio are the main factors which have been used to stage kidney diseases. However, the gap between fibrosis lesions and disease stages

still exists. Taken together, from the recent meaningful data cited above, comprehensive fMRI not only allows a noninvasive detection of fibrosis in the kidney, but also shows promise in longitudinally monitoring kidney injury. Further research is needed in the field, but the introduction of fMRI in kidney diseases to evaluate fibrosis could help provide more comprehensive and individualized care for our patients. Further evaluation requires multi-center studies to assess MRI measures across all CKD stages and in larger numbers to identify the optimal MRI measures, as well as longitudinal studies to assess the prognostic value of fMRI.

Conclusion

The development of fMRI in clinical medicine will open more opportunities for patients and clinicians. Evaluation of kidney fibrosis by imaging, histology, and renal function will be very useful for assessing kidney disease stages and prognosis. However, several challenges have to be faced. Although there are only a few pioneer studies, it is not only important to expand noninvasive and repeatable methods, but also to combine artificial intelligence with fMRI as a prognostic tool, considering its ability to provide information about the degree of fibrosis. This will be the future to provide more comprehensive and individualized care for CKD patients.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the idea, conceptual advice, and framework of the manuscript. J.Z. wrote the manuscript; L.J.Z. reviewed and revised the manuscript.

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