



# Magnetic resonance imaging to assess fibrosis in chronic kidney disease

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## Abstract

Chronic kidney disease (**CKD**) is a major public health problem. Accumulating evidence suggests that a key contributor to the progression of nearly all forms of CKD is fibrosis. Multiple physical changes occur in the fibrotic kidney, such as 1) reduced capillary density, 2) dilated and atrophic tubules, 3) increased interstitial extracellular matrix, and 4) hypoxia. Although meaningful in the initial diagnostic assessment, renal biopsy remains an imperfect test for fibrosis measurement. The limitation is not only by its invasiveness, but also, for its sampling bias. Recent advances in imaging technology have raised the exciting possibility of using magnetic resonance imaging (**MRI**) for the study of tissue oxygen levels, microcirculation abnormality, tubular loss and the “kidney stiffening”. These new MRI-based techniques may provide potential noninvasive and accurate measurements for fibrosis in CKD.

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## Introduction

CKD is a major public health problem in both developed and developing countries. Many clinical conditions, such as glomerulonephritis and diabetes nephropathy (**DN**) have been the predominant causes of CKD, which result in end-stage renal disease. For example, China has a large population and a high prevalence of CKD. The number of patients with CKD in China is estimated to be approximately 119.5 million [1]. A cross sectional survey of a nationally representative sample of Chinese adults demonstrated that the prevalence of CKD with an overall prevalence of 10.8% [2]. In 2015, the percentage with CKD related to diabetes and glomerulonephritis were 1.10% and 0.75% in hospitalized patients, respectively [3]. In the general population, the percentage with CKD related to DN and glomerulonephritis were 1.23% and 0.91%, respectively [3]. The prevalence of CKD was about 13.8% and 10.2% in the USA and European countries respectively [1]. Once renal fibrosis, a major pathological hallmark of CKD, reaches a certain threshold, CKD progression becomes

irreversible and independent of the initial cause. Accumulating evidence has also suggested that CKD aggravates renal hypoxia, which is a key player, and in turn, the renal hypoxia accelerates fibrosis and CKD progression. In progressive CKD, dysregulated angiogenesis plays an important role in persisting capillary loss and hypoxia [4,5]. Recently, because of MRI development, several advanced techniques might be used to detect physiological changes in fibrosis, and also perform measurements of the fibrosis burden in CKD. MRI has its special advantages, including non-invasive, accurate, repeatable, and being able to possibly assess functional activity.

### Multiple physical changes in fibrosis kidney.

Renal biopsies usually are performed routinely in the nephrology units of most large hospitals and have provided histological evidence to support the diagnosis and make prognostic decisions. Also, histological pictures show most changes in the kidney as it scars, which include dilated atrophic tubules, re-



duced capillary density, increased in-terstitial extracellular matrix. Beyond these observational lesions, the microcirculation may be changed by extracellular matrix. Fibrils may compress and obliterate surrounding capillaries, and the oxygen diffusion distance to tubular cells is increased and blood flow is reduced. Furthermore, progressive ischemic tubular injury leads to more tubular cell apoptosis [6,7]. Oxygen is necessary for about all kinds of cell biology functions. Thus, cellular response against hypoxia is precisely controlled. Some transcriptional factors, like hypoxia-inducible factors play a central role in the hypoxia condition and may be associated with fibrosis [4,5]. Presently, a kidney biopsy is the gold standard for renal fibrosis assessment, although this is fraught with limitation. First, renal biopsy is associated with bleeding risk and some patients refuse to receive this procedure for this reason. Second, because biopsy samples are only about 2mm in diameter, there are usually 10-20 glomeruli for analysis, which may be much less than 0.01% of one kidney. Thus, renal biopsy diagnosis is subject to sampling bias. New, noninvasive methods that can safely, and accurately, assess kidney fibrotic burden repeatedly are needed for clinical and research activities.

### Advanced MRI techniques in CKD

Here we are going to discuss advanced MRI methods. Conventional MRI has been in-adequate to image fibrosis, and to measure the organ physiological changes.

Studies reported in the literature indicate that gadolinium-enhanced MRI might be used for cardiac fibrosis imaging. Unfortunately, these techniques are hard to perform in patients with significant renal dysfunction kidney because of the risk of gadolinium toxicity [8]. We will introduce several advanced functional MRI techniques, which have been applying in kidney diseases (**Table 1**).

#### Diffusion-weighted MRI (DWI)

Diffusion MRI is a non-contrast technique that images both directional water motion such as blood and urine flow, and also random motion of intra- and extracellular water. During scaring of the kidney, there is decreasing peritubular capillaries density, tubular loss, increasing fibrosis and aggravating extracellular matrix. All those histological changes have a similar effectin that water molecular motion is decreased. A study has showed that DWI-ADC was decreasing in CKD kidney with fibrosis [9].

#### Arterial Spin Labeling (ASL)

ASL doesn't need contrast agent either, which is a combination of radio frequency and magnetic gradient pulses to tag inflowing blood. ASL images can provide the information on the volume of tagged blood that flows into the imaged slices [10].

#### Blood Oxygenation Level-Dependent MRI

With reductions in blood flow, oxygen delivery is reduced, which can lead to local changes in blood and tissue oxygenation. As we have suggested above, hypoxia has strong relationship with fibrosis. BOLD depends on the difference in magnetic properties between oxy and deoxyhemoglobin. Several studies have examined whether BOLD MRI could be used to non-invasively detect hypoxia in CKD, and build up the relationship between T2\* signal with the degree of fibrosis [11,12]. However, confidence in conclusions based on data derived from BOLD measurements will require continuing advances and technical refinements for future use.

### Magnetic Resonance Elastography (MRE)

In CKD, by replacing soft healthy tis-sue with stiff extracellular matrix, the changes of tissue stiffness could be imaged by MRE. In MRE scanning, a gentle acoustic vibrational wave is applied on the skin overlying the kidney. The images at a frequency matched to those of the generated vibrational wave, thus capturing the small displacements in the vibrating organ. Recently, not only in native kidney in CKD, but also in renal transplantation, MRE has been used to detect the increase in kidney stiffness to provide a measurement of renal fibrosis [13-16]. More than this, recent study has showed that, the MRE signal may help to predict kidney allografts outcome in transplanted allograft [16].

### Summary

Fibrosis is playing a key role in CKD progression. Accompany with fibrosis, the kidney undergoes several physical changes. It is because of its invasive and biases from renal biopsy, thus a noninvasive, integrate, and repeatable methods are needed by physicians. Using advanced MRI techniques it may become possible to determine and measure these physiological and pathological changes and thus measure the role of fibrosis in the kidney and its effects in the progression of CKD.

### Table

Imaging technique	Key points of description
DWI	Noninvasive measurement for the entire both kidneys. Can estimate microvascular blood flow, perfusion, and overall microstructural of kidneys.
ASL	Noninvasive measurement for microvascular perfusion, especially for ischemia-reperfusion injury.
BOLD	Noninvasive measurement for blood oxygenation level and tissue pO <sub>2</sub> .
MRE	Noninvasive measurement for entire both kidney stiffness. Validated as a successful assessment of fibrosis in live and renal allograft.

**Table 1:** Utility in CKD for fibrosis assessment.

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