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Recent Advances in Magnetic Resonance Imaging Assessment of Renal Fibrosis

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Abstract

Chronic kidney disease is a global public health problem. Renal fibrosis is a final common pathway leading to progressive loss of function in chronic kidney disease. The degree of renal fibrosis predicts the prognosis of chronic kidney disease. Recent studies have shown that bone marrow–derived fibroblasts contribute significantly to the development of renal fibrosis, which may yield novel therapeutic strategy for fibrotic kidney disease. Therefore, it is imperative to accurately assess the degree of renal fibrosis non-invasively to identify those patients who can benefit from anti-fibrotic therapy. In this review, we summarize recent advances in the assessment of renal fibrosis by magnetic resonance imaging.

Keywords

Chronic kidney disease; Fibrosis; Magnetic resonance imaging; Fibroblast; Extracellular matrix

INTRODUCTION

Chronic kidney disease (CKD) is a major cause of mortality and a serious global health challenge[1]. The prevalence of CKD continues to rise worldwide[2]. Therefore, new strategies for diagnosis and treatment of CKD are much needed to reduce its morbidity and mortality. Renal fibrosis is a pathological hallmark of CKD, which is manifested by extensive fibroblast activation. Activated fibroblasts produce a large amount of extracellular matrix (ECM) resulting in destruction of renal parenchyma and progressive loss of kidney function[3–5]. Clinical studies have shown that the degree of renal interstitial fibrosis strongly predicts the prognosis of CKD[6].

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Conflicts of interest

The authors have declared that no conflict of interest exists.

Traditionally, activated fibroblasts are thought to arise from resident fibroblasts[7, 8]. Recently, compelling evidence indicates that bone marrow-derived fibroblast precursors contribute significantly to the population of activated fibroblasts and the development of renal fibrosis[9–12]. Bone marrow-derived fibroblast precursors termed fibrocytes express hematopoietic markers such as CD45 and CD11b as well as mesenchymal markers such as platelet-derived growth factor receptor-β (PDGFR-β) and vimentin[13–15]. Recent studies have demonstrated that bone marrow–derived fibroblast precursors contribute substantially to pathogenesis of renal interstitial fibrosis[15–18].

Kidney biopsy is currently considered the gold standard for the evaluation of renal fibrosis. However, this invasive procedure has inherent complications such as pain or bleeding to major complications including death. Furthermore, kidney biopsy is limited by inevitable sampling error. Currently, there are no routine non-invasive assessments available for clinical diagnosis. Recent studies have shown that MRI may have clinical utility for non-invasive diagnosis of renal fibrosis.

Mechanisms of Renal Fibrosis

In response to kidney injury, multiple cell types in the circulation are recruited to the site of injury to participate in a wound healing response. A dysregulated wound healing process causes renal fibrosis, where extracellular matrix and fibroblasts replace normal renal parenchyma leading to kidney dysfunction. Fibrosis is a complex and progressive pathological process. This involves infiltration of mononuclear cells including monocytes and immune cells. The interaction and communication among these cell types are involved in the pathogenesis of fibrotic disorders[19, 20]. Because fibroblasts are the principal effector cells that mediate extracellular matrix production in the fibrotic kidney disease, their activation is regarded as an important event in the pathogenesis of renal fibrosis[21, 22]. The activated fibroblasts are traditionally thought to arise from resident fibroblasts within the kidney. Recent studies have shown that these activated fibroblasts may originate from bone marrow-derived fibroblast precursors[16, 23–27]. Using bone marrow transplantation of transgenic mice that express GFP driven by collagen α1(I) promoter, we have shown that bone marrow-derived hematopoietic fibroblasts migrate into the kidney, proliferate, and differentiate into myofibroblasts in an experimental model of obstructive nephropathy[16, 28].

The recruitment of circulating fibroblast precursors into the sites of injury is mediated by chemokines generated in the local microenvironment. The chemokine CXCL16 is induced in the kidney following obstructive injury[16, 29]. We have used CXCL16 knockout (KO) mice to study the functional role of CXCL16 in the pathogenesis of renal fibrosis. CXCL16 KO mice accumulate fewer bone marrow-derived fibroblast precursor and myofibroblast and displayed less extracellular matrix protein deposition in the obstructed kidneys[16]. These results indicate that CXCL16 promotes renal fibrosis by recruiting bone marrow-derived fibroblast precursors into the kidney in response to obstructive injury. We further examined the role of CXCL16 in angiotensin II (Ang II)-induced renal injury and fibrosis. Genetic deletion of CXCL16 protects the kidney from renal dysfunction, inhibits renal fibrosis, reduces proteinuria, suppresses bone marrow-derived fibroblast accumulation, myofibroblast formation, macrophage and T cell infiltration and pro-inflammatory cytokine expression

with no effect on Ang II-induced hypertension[30]. More recently, we have shown that CXCL16 plays a crucial role in the development of kidney fibrosis induced by DOCA/salt and renal artery stenosis[31, 32].

CXCR6 is the CXCL16 receptor. We have recently shown that both circulating fibroblast precursors and bone marrow-derived fibroblasts in the kidney express CXCR6[16, 28]. We further demonstrate that genetic disruption of CXCR6 reduces the recruitment of bone marrow-derived fibroblast precursors into the kidney and the development of renal fibrosis induced by ureteral obstruction, ischemia-reperfusion, and Ang II induced hypertension[28, 33].

The activation of bone marrow-derived fibroblasts is modulated by inflammatory cells in the local microenvironment. T cells play an important role in the development of renal fibrosis[34], which have been shown to promote fibrocyte activation[12]. Naïve $CD4^+$ T cells can differentiate into two major distinct phenotypes, Th1 and Th2 cells, which are characterized by specific patterns of cytokine expression[35]. Th2 cells release Th2 cytokines such as IL-4 and IL-13 to induce alternative activation of macrophage and promotes monocyte-to-fibroblast transition[35, 36]. Th1 cells generate Th1 cytokines such as IFN-γ and IL-12, which promote classical activation of macrophages and inhibit fibrocyte differentiation[35, 36]. However, the molecular signaling mechanisms by which Th2 cytokines stimulate bone marrow-derived fibroblast activation are not well-understood. We have recently shown that JAK3/STAT6 signaling stimulates bone marrow-derived fibroblast activation and extracellular matrix protein production[15]. Pharmacological inhibition of JAK3 with CP 690550 or genetic deletion of STAT6 suppresses myeloid fibroblast activation and inhibits development of renal fibrosis[15].

Adiponectin is a multifunctional cytokine that regulates metabolism and inflammation. Recent evidence indicates that adiponectin levels in the circulation are elevated in patients with CKD, and a high level of adiponectin is linked to increased mortality[37–41]. We have discovered that adiponectin is induced in the kidney following ischemia-reperfusion and obstructive injury[11]. Genetic disruption of adiponectin inhibits bone marrow-derived fibroblast accumulation and myofibroblast activation, which is associated with a reduction in the expression of profibrotic chemokines and cytokines and the production of extracellular matrix proteins in the injured kidneys following ureteral obstruction or ischemia-reperfusion. These results indicate that adiponectin promotes activation and maturation of myeloid fibroblasts and the development of renal fibrosis. Furthermore, we have shown for the first time that alternatively activated (M2) macrophages produce collagen I, suggesting a link between M2 macrophage polarization and myeloid fibroblast activation[11]. Consistent with this novel concept, adiponectin deficiency reduces the number of procollagen-expressing M2 macrophages in the kidney following ureteral obstruction or ischemia-reperfusion injury[11].

These studies demonstrate that bone marrow-derived fibroblasts contribute significantly to the development of renal fibrosis. The recruitment and activation of bone marrow-derived fibroblasts are mediated by the interactions between locally produced chemokines and

cytokines in the microenvironment. Therefore, targeting the signaling machinery of these chemokines and cytokines represents novel therapeutic strategy for fibrotic kidney disease.

Diagnosis of Renal Fibrosis

Kidney biopsy is the gold standard for the detection and diagnosis of renal fibrosis. However, there are several limitations of kidney biopsy including sampling error, intra- and inter-observer variability, and life-threatening complications[42]. Several biological molecules have been proposed as biomarkers for kidney fibrosis, but none of them have been validated and utilized clinically[43]. Recent advances in magnetic resonance imaging (MRI) techniques may allow accurate assessment and longitudinal evaluation of renal fibrosis. Two promising MRI techniques for assessing kidney fibrosis are diffusion-weighted MRI (DWI) and MR elastography (MRE). The use of gadolinium-containing MRI contrast agents in patients with advanced chronic kidney disease is associated with nephrogenic systemic fibrosis, which is mediated by bone marrow-derived fibrocytes[44, 45]. Fortunately, both DWI and MRE do not require gadolinium-containing MRI contrast agents for the assessment of renal fibrosis.

Diffusion weighted magnetic resonance imaging (DWI) is an imaging technique that utilizes the diffusion of water molecules to generate contrast in MR images[46]. This technique allows non-invasively mapping the water movement in biological tissues in vivo. The commonly-used parameter to quantify DWI is apparent diffusion coefficient (ADC) value. ADC is calculated by filtering signaling intensities (SIs) from a series of DWI with different diffusion weightings (b values).

DWI has been used to evaluate renal fibrosis in patients with chronic kidney disease. In a clinical study, Inoue et al. used DWI to detect renal fibrosis in vivo in 142 patients with varying degree of kidney dysfunction[47]. Healthy volunteers were recruited as controls. ADC values were significantly lower than healthy controls. Kidney biopsy was performed in a subset of CKD patients and kidney sections were the degree of renal fibrosis was evaluated morphologically by Masson's trichrome staining. The percentage of fibrotic area relative to the cross-section area in the kidney biopsy significantly correlated with reduced ADC values. This study indicates that DWI may have clinical utility to evaluate renal fibrosis non-invasively. In another study, Zhao et al. examined the utility of DWI for evaluation of renal fibrosis in patients with CKD[48]. Forty CKD patients and 30 healthy volunteers participated in the study. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine (SCr) using the CKD-EPI equation. Kidney biopsies were performed in 25 CKD patients. ADC values were considerably lower in patients with CKD than those of healthy controls. Furthermore, cortical ADC values inversely correlated with SCr, urinary protein, histopathological fibrosis score and positively correlated with eGFR. These results further support the potential usefulness of DWI for assessment of renal fibrosis in CKD patients. One limitation of the study is that CKD-EPI equation may not be accurate in estimating eGFR when the kidney function is relatively normal. Frutehrmore, the applicability of the DWI for evaluation of kidney fibrosis could be challenging because of artifacts caused by respiratory motion and image distortion.

Recently, a new technique termed Readout Segmentation Of Long Variable Echo-trains (RESOLVE) has been developed to reduce distortion of DWI[49]. The RESOLVE technique is

based on a segmentation of k-space into several shots along the readout direction to shorten the echo spacing leading to a reduction in imaging distortion. [K-space refers to the storage area where MRI image data is held before it is converted into an image. Segmentation of k-space is the acquisition of data in multi-line segments. Echo spacing is the distance in time between the echoes in multiple echo sequences. A short echo space produces compact sequence timing and less image artifact]. Using this novel strategy, Friedli et al. have reported that there was a moderate negative correlation between absolute cortical ADC values and interstitial fibrosis as assessed by Masson's trichrome staining, but not by Sirius red staining in kidney allograft recipients[50]. Furthermore, ΔADC, defined as the difference between cortical ADC values and medullary ADC values, improved the correlation with eGFR and the degree of renal fibrosis assessed by Masson's trichrome staining and by Sirius red staining. Therefore, DWI with RESOLVE sequence allows the differentiation of cortex and medulla to calculate ΔADC, which decreases inter-patient variability with improved correlation to histopathological assessment of renal interstitial fibrosis. Further studies are needed to validate applicability of this technique in assessment of renal fibrosis in vivo.

Magnetic Resonance Elastography (MRE) is a novel MRI-based technique that can directly visualize propagation of shear waves in the tissue. MRE of the liver has emerged the most accurate non-invasive technique for detection and staging of hepatic fibrosis independent of body mass index (BMI) and etiology of chronic liver disease[51]. Lee et al. evaluated the applicability of MRE in the detection of renal fibrosis in kidney transplant recipients. Two patients had moderate degree of renal fibrosis. Six patients had mild degree of renal fibrosis. The calculated tissue stiffness was higher in patients with moderate renal fibrosis than those with mild renal fibrosis, which did not reach statistical significance. This study indicates the MRE may have potential to detect and stage renal fibrosis. Further studies are needed to validate the utility of MRE as a non-invasive tool to assess renal fibrosis.

In summary, recent advances in MRI techniques allow novel non-invasive detection and assessment of renal fibrosis. Further studies are needed to validate the utility of these techniques for accurate assessment and longitudinal follow up of renal fibrosis.

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