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Noninvasive Assessment of Renal Fibrosis by Magnetic Resonance Imaging and Ultrasound Techniques

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Abstract

Renal fibrosis is a useful biomarker for diagnosis and guidance of therapeutic interventions of chronic kidney disease (CKD), a worldwide disease that affects more than 10% of the population and is one of the major causes of death. Currently, tissue biopsy is the gold standard for assessment of renal fibrosis. However, it is invasive, and prone to sampling error and observer variability, and may also result in complications. Recent advances in diagnostic imaging techniques, including magnetic resonance imaging (MRI) and ultrasonography, have shown promise for noninvasive assessment of renal fibrosis. These imaging techniques measure renal fibrosis by evaluating its impacts on the functional, mechanical, and molecular properties of the kidney, such as water mobility by diffusion MRI, tissue hypoxia by blood oxygenation level dependent MRI, renal stiffness by MR and ultrasound elastography, and macromolecule content by magnetization transfer imaging. Other MR techniques, such as T_1/T_2 mapping and susceptibility-weighted imaging have also been explored for measuring renal fibrosis. Promising findings have been reported in both preclinical and clinical studies using these techniques. Nevertheless, limited specificity, sensitivity, and practicality in these techniques may hinder their immediate application in clinical routine. In this review, we will introduce methodologies of these techniques, outline their applications in fibrosis imaging, and discuss their limitations and pitfalls.

Keywords

Renal Fibrosis; Renal Biopsy; Magnetic Resonance Imaging; Ultrasound

INTRODUCTION

Renal fibrogenesis is in fact a wound healing process gone astray after initial insults.^{1,2} Peritubular infiltration of inflammatory cells is initiated with an attempt to repair tissue damage. Yet, sustained injury leads to non-resolving inflammation, which triggers activation and expansion of myofibroblasts from multiple sources.³ These myofibroblasts produce copious extracellular matrix (ECM) components, including fibronectin and type I/III

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collagens,⁴ which may eventually evolve into fibrosis (Fig. 1). Such fibrotic process may affect all compartments of the kidney, leading to glomerulosclerosis, tubulointerstitial fibrosis, and arteriosclerosis.

Renal fibrosis is a common pathological feature in chronic kidney disease (CKD) and a major determinant of renal insufficiency. CKD is characterized by abnormalities in kidney structure or function for over three months with implications for health of an individual. Commonly accepted criteria for CKD include glomerular filtration rate (GFR) under 60 ml/min/1.73m² or kidney damage defined by structural or functional abnormalities other than decreased GFR, such as vascular obliteration, tubular atrophy, and kidney shrinkage.⁵ CKD afflicted 14.8% of the US adult general population in 2011–2014⁶ and its worldwide prevalence is estimated to be 8–16%.⁷ A large portion of CKD eventually progresses to end-stage renal failure, which requires dialysis or kidney transplantation. CKD has become a major public health issue, imposing enormous socioeconomic burdens to affected individuals.⁶ Therefore, early diagnosis of CKD is imperative for timely therapeutic interventions to halt disease deterioration.

Renal fibrosis serves as an important biomarker in the diagnosis of renal diseases, as it correlates well with renal function.^{8–9} Several clinical studies have also shown that renal fibrosis quantification can help predict outcome in renal transplants^{10–12} and native kidney diseases.^{13,14} Furthermore, since renal fibrosis can be easily detected and quantified in experimental models of CKD, it has been commonly used as endpoint for assessment of anti-fibrotic therapies.^{15–18} Overall, accurate detection and staging of renal fibrosis is essential for diagnosis of kidney disease, prognosis of disease progression, and guidance of therapeutic interventions.

Currently, the reference standard method to assess renal fibrosis is percutaneous renal biopsy followed by histopathological assessment such as Masson's trichrome or Sirius red staining.¹⁹ Although widely adopted in routine kidney evaluation, renal biopsy suffers from several limitations. First, the invasive tissue sampling may cause complications including bleeding, pain, gross hematuria, perinephric hematoma, arteriovenous fistulas, and even acute renal failure.²⁰ Therefore, repeated renal biopsy for disease follow-up may not be practical. Second, the sampled tissue only constitutes a small portion of the kidney and may not be representative, leading to unreliable diagnosis. Moreover, histopathological assessment of renal fibrosis may not be reliable. For example, Masson's trichrome staining has been shown to be insensitive to mild fibrosis.^{21,22}

Recent advances in diagnostic imaging techniques, including magnetic resonance imaging (MRI) and ultrasound elastography (UE) have shown promise for noninvasive assessment of renal fibrosis. These imaging techniques indirectly probe renal fibrosis by assessing its impact on kidney. Renal fibrosis is often accompanied by vascular obliteration, tubular atrophy, and kidney shrinkage (Fig. 1), which lead to a range of changes in functional, mechanical, and molecular properties of the kidney. For example, deposition and accumulation of the ECM and tubular atrophy restrict the mobility of water molecules, increases kidney stiffness, and elevates macromolecule content, which can be assessed by diffusion MRI, MR elastography (MRE) and UE, and magnetization transfer imaging (MTI),

respectively. Vascular rarefaction lowers renal perfusion and oxygen supply, leading to tissue hypoxia, which can be assessed using blood oxygenation-level-dependent (BOLD) MRI. Other MR techniques, such as T_1/T_2 mapping and susceptibility-weighted MRI, have also been explored as potentially useful biomarkers for renal fibrosis. Promising findings have been reported in both preclinical and clinical studies. Nevertheless, limited accuracy, specificity, and practicality of these techniques hinder their immediate clinical application. In this review, we will introduce these imaging techniques, outline their promising application for fibrosis imaging, and discuss potential limitations and pitfalls inherent in these techniques.

DIFFUSION MRI

In a free medium, water molecules undergo random, microscopic movement due to thermal collisions. Such motion is termed Brownian motion, which was discovered by Robert Brown in 1827 and mathematically characterized by Einstein in 1905.²³ Diffusion of water molecules in a free medium is unrestricted and statistically follows a three-dimensional Gaussian distribution. By contrast, water motion in biological tissues is restricted by tissue components such as fibers, macromolecules, and to some extent cell membranes, and thus deviates from the Gaussian distribution. Thus, water diffusion pattern can reflect structural features and geometric organization of tissues. In fibrotic kidneys, deposition and accumulation of the ECM as well as tubular atrophy further restrict the mobility of water molecules. Thus, measurement of water molecule diffusion may infer the presence and extent of renal fibrosis.

In diffusion MRI, a pair of diffusion-sensitizing gradients with adjustable duration and separation are applied to impose diffusion-weighting in measured MR signals.²⁴ These two gradients generate diffusion weighting by modulating the phase of water protons and therefore measured MR signal. Specifically, the first gradient magnetically labels water protons by inducing a phase change based on their spatial location. Then a time interval is allowed for water molecules to diffuse away from their original position, before the second gradient with opposite polarity is applied in order to undo the accumulated phase for stationary water protons or impose net phase changes to those that have relocated in-between the two gradients. Thus, stationary protons maintain phase coherence, and diffusing protons fall out of phase, resulting in a signal loss. Such signal loss depends on not only diffusion but also the intensity and separation of the two gradients, termed the “b-value”. The observed diffusion-weighted MR signal within one voxel reflects integration of all microscopic displacement distributions of the water protons contained in this voxel. As a result, the measured diffusion differs from the physical diffusion coefficient and is called the apparent diffusion coefficient (ADC). Diffusion MRI typically measures water motion ranging from 1 to 17 μm .²⁵ Notably, microscopic motion of water protons in kidney includes a fast diffusion component due to microvascular perfusion, glomerular filtration, and tubular flow, and a slow diffusion component secondary to true water diffusion.²⁶ Whereas a low b-value imposes a larger contribution to the ADC of the fast diffusion component, a high b-value renders more weighting on the slow diffusion component. It is recommended that b-values over 200 sec/mm^2 should be used for quantification of the true water diffusion in the kidney.²⁷

DWI can be applied in several different manners.

Apparent Diffusion Coefficient

Principles—The ADC has been most widely used to characterize renal function and structures. The underlying assumption is that the measured MR signal and ADC follow a simple mono-exponential relationship. Thus, the ADC along one direction can theoretically be measured using as few as two images acquired at different b-values (Fig. 2). Nonetheless, more b-values may offer more robust and accurate measurement of ADC using a mono-exponential curve fitting. To eliminate the impact of diffusion anisotropy on ADC measurement, diffusion MRI is typically performed in three orthogonal directions, from which the averaged ADC is calculated.

Findings—A number of preclinical and clinical studies have reported lower renal ADC in dysfunctional renal transplants^{28–30} and native kidney diseases.^{31–39} Togao and colleagues first tested the utility of ADC in detecting renal fibrosis in a mouse model of unilateral ureteral obstruction (UUO).³³ The renal cortical ADC correlated with cellular density and α -smooth muscle actin expression, indicating the potential of ADC as a sensitive noninvasive biomarker of renal fibrosis. Similar findings were also observed in a rabbit model of UUO⁴⁰ and murine renal allograft.^{30,41} Recent clinical studies demonstrated a good correlation between renal ADC and histopathological fibrosis score,^{34,39,42} supporting the usefulness of ADC in assessment of human renal fibrosis.

It is not surprising that the decreased ADC in diseased kidneys or dysfunctional renal transplants has been widely reported. The ADC is influenced not only by true water diffusivity but also microvascular perfusion -induced water mobility has been reported to be an order magnitude larger than the true water diffusivity in human kidneys.²⁷ A fall renal perfusion and tubular flow in fibrotic kidneys^{43–45} may lead to decreased ADC. Interestingly, Boor et al. showed in rats with UUO that the cortical ADC decreased in vivo but increased at postmortem due to tubular dilation and expanded extracellular space, despite the presence of renal fibrosis.⁴⁶ It was concluded that in vivo ADC is unlikely a direct measure of renal fibrosis, but a measure of renal perfusion and filtration function. In order to separate the true water diffusion from pseudodiffusion induced by vascular perfusion and tubular flow, Le Bihan et al. proposed the intravoxel incoherent motion (IVIM) imaging.⁴⁷

Intravoxel Incoherent Motion Imaging

Principles—While the true water diffusion is passive and indicative of tissue microstructure, vascular and tubular flows are pseudorandom and biased by organization of the capillary network and renal tubules. By acquiring multiple diffusion-weighted images at a range of b-values, both true diffusivity (D_t) and pseudodiffusivity (D_p) as well as the pseudodiffusion fraction f_p can be quantified using the IVIM model, which describes the measured MR signal using a bi-exponential equation.⁴⁷ The IVIM-measured pseudodiffusivity D_p (Fig. 2c) is more than one order of magnitude larger than the true diffusivity D_t , which is typically lower than the ADC.²⁷

Findings—Similar to ADC, IVIM imaging detected decreased diffusion as well as lower perfusion in native kidney diseases^{48–55} and dysfunctional renal allografts.^{56–58} However, by yielding a larger number of renal physiological parameters, IVIM imaging offers new insights into renal pathophysiology. Studies demonstrated IVIM-measured diffusion coefficients had higher accuracy compared with ADC in discriminating renal lesions and that f_p could provide information regarding lesion vascularity,^{59,60} although others suggested that IVIM could not provide more information in the evaluation of renal dysfunction.⁴⁹

The capability of IVIM in measuring renal fibrosis has been demonstrated in both preclinical and clinical studies. In animal models of UUO, IVIM-measured parameters as well as ADC correlated well with renal fibrosis.^{40,61,62} In a swine model of renal artery stenosis (RAS), Ebrahimi et al. showed that IVIM-derived parameters could not only detect subtle functional and structural changes in stenotic kidneys, but also serve as markers for tubular injury.³⁸ The IVIM imaging also provided insights into the underlying reasons for alterations in the ADC. Hennedige et al. found in murine UUO that reduction in ADC observed in renal fibrosis was attributable not only to reduced D_t but also a decrease in vascularity as assessed by f_p .⁶² One clinical study by Mao et al reported significant negative correlations between the IVIM-measured renal parameters and histopathological fibrosis score in patients with CKD.⁶³ Taken together, IVIM imaging has shown great potential in assessment of renal fibrosis by showing hints of true water diffusion as well as tissue perfusion and vascularity.

Diffusion Tensor Imaging

Principles—Preferential diffusion in certain directions in biological tissues or diffusion anisotropy reflects tissue microstructure. An advanced diffusion MR technique, diffusion tensor imaging (DTI), offers the opportunity for investigating the spatial preference of diffusion. DTI requires diffusion measurements performed along a minimum of six directions,⁶⁴ from which the mean diffusivity and fractional anisotropy (FA) can be assessed. Here, the mean diffusivity is equivalent to the ADC from conventional DWI and FA is an index for the amount of diffusion asymmetry within a voxel. By assigning colors to voxels based on a combination of anisotropy and direction, a principal diffusion direction map can be generated to offer direct visualization of renal tissue microstructures.^{27,65}

Findings—Application of DTI in the kidney has revealed higher FA in the renal medulla than the relatively isotopically-structured cortex.^{66–69} This has been attributed to both the anisotropically oriented tubules and tubular flow in the renal medulla.^{27,65} Since tubular flow is associated with the filtration function of the kidney, several studies have demonstrated a good correlation between medullary FA and eGFR.^{68–71} In fibrotic kidneys, the diffuse interstitial fibrosis as well as tubular atrophy, cell infiltration, and glomerular scarring may also alter water diffusion and correlate well with renal FA in both animal models^{72,73} and humans.^{36,69,74,75}

Diffusion Kurtosis Imaging

As mentioned before, tissue components such as fibers and macromolecules restrict water diffusion, which follows a non-Gaussian distribution. The degree deviation from the Gaussian distribution (“kurtosis”) reflects the microstructural complexity of tissue. Diffusion

kurtosis imaging (DKI) is an emerging MR technique^{76,77}, which is a natural extension of DTI, exception that relatively larger b-values ($>1000 \text{ s/mm}^2$) are needed for robust measurement.⁷⁷ In addition to the mean diffusivity and FA, DKI also measures metrics related to diffusion kurtosis, providing complementary information about tissue complexity and heterogeneity. Application of DKI in the human brain has yielded encouraging results in ischemic stroke,^{78,79} Alzheimer's disease,⁸⁰ and aging.⁸¹ Its feasibility has also been demonstrated in healthy human kidneys, which show higher kurtosis in the renal cortex than medulla.⁸² The utility of DKI in measurement of renal fibrosis has not been reported. Given that accumulation of ECM in fibrotic kidneys imposes additional obstacles to water diffusion and thus increases diffusion kurtosis, DKI may be useful in measuring renal fibrosis, which warrants future investigation.

Diffusion MRI: Limitations and Pitfalls

Although diffusion MRI has shown great potential for assessment of renal fibrosis, it has some limitations that warrant attention in clinical application. Diffusion MRI is prone to artifacts associated with imperfect gradient hardware, eddy currents, patient motion etc. Readers may refer to the exquisite review article by Le Bihan et al. for details.⁸³ Importantly, most commonly observed artifacts are geometric distortion and susceptibility artifacts. To reduce respiratory motion artifact, diffusion MRI typically employs single-shot echo-planar imaging for image acquisition. Nevertheless, the acquired images have low spatial resolution and are subject to in-plane geometric distortions caused by the off-resonance water protons present at the bowel and tissue interface. To alleviate these issues, Friedli et al. proposed a novel sequence named “readout segmentation of long variable echo-trains” to improve image resolution and reduce distortions, which nevertheless needs respiratory gating and longer acquisition time.⁸⁴

Another major limitation of diffusion MRI is its poor specificity to underlying pathological changes in diseased kidneys. The IVIM model can separate true water diffusion from fast diffusion components, yet requiring multiple diffusion-weighted images at various b-values, more sophisticated image analysis, and high signal-to-noise ratio.⁸⁵ However, substantial variability in D_t , D_p , and f_p has been reported since the pseudodiffusion may consist of a fast component by perfusion and a slow component by tubular flow,^{65,86} for which Sophie et al. proposed to use a triexponential model in diffusion analysis to individually account for these two pseudodiffusion components.⁸⁷ Ebrahimi et al. also proposed a triexponential model to account for tissue adiposity.⁵⁰ Although such models may provide additional information about kidney function and structure, curve fitting may be more prone to error and their physiological indications remain to be investigated.

Diffusion MRI has undergone several technical advancements and is now widely recognized as a powerful tool for imaging renal microstructure and function. Other MR techniques may be combined with diffusion MRI to improve its specificity and complement evaluation of kidney function and structure.⁸⁸ Additional technical developments should minimize its susceptibility to artifacts commonly seen in body imaging. Moreover, standardization and optimization of image acquisition and postprocessing are also required to enhance its reproducibility across sites.⁸⁹

BLOOD OXYGENATION LEVEL DEPENDENT MRI

Principles

Chronic hypoxia has been recognized as the final common pathway to end-stage renal failure,^{90,91} and tissue oxygenation has been used to infer the degree of interstitial fibrosis. BOLD-MRI allows noninvasive assessment of tissue oxygenation by an intrinsic tissue MR parameter, i.e., the effective transverse relaxation time T_2^* . The paramagnetic effect of deoxyhemoglobin shortens T_2^* , providing an opportunity for indirect measurement of tissue oxygenation level using BOLD-MRI. A multi-echo gradient echo sequence is typically used to collect multiple images with a range of echo times, from which T_2^* maps can be achieved by pixel-wise mono-exponential fitting (Fig. 3a). The reciprocal of T_2^* , or the effective transverse relaxation rate R_2^* is preferred by some investigators to index tissue hypoxia. A lower T_2^* (or higher R_2^*) refers to greater concentration of deoxyhemoglobin, and hence greater tissue hypoxia. A representative R_2^* map of a normal kidney is shown in Fig. 3b. The renal medulla often shows a larger R_2^* than the cortex, which is in line with the fact that medulla operates habitually on the brink of anoxia.⁹²

Findings

BOLD-MRI was firstly developed by Ogawa et al. in 1990 for assessment of brain neuronal activity.⁹³ In 1996, Prasad et al. applied this technique in human kidney and demonstrated the capability of BOLD-MRI in monitoring changes in intrarenal oxygenation in response to stimuli that induced diuresis.⁹⁴ They found shortened medullary T_2^* after administration of the loop diuretic furosemide as well as water loading, consistent with the improved medullary oxygen tension after diuresis.⁹⁵ The ability of BOLD-MRI to noninvasively assess renal oxygenation has also been proven in kidneys with acute kidney injury (AKI)^{96–99} or after diuresis.^{100–102}

Despite the consensus that BOLD-MRI is sensitive to changes in tissue oxygenation in response to AKI or diuresis, its application in CKD has generated controversies. Although a few studies found decreased T_2^* in CKD patients,^{34,103,104} the majority reported unaltered or even increased T_2^* .^{105–110} Contrarily, a recent multicenter study by Prasad et al. showed slightly decreased cortical T_2^* and increased medullary T_2^* in patients with advanced CKD.¹¹¹ Such discrepancy may be attributed to different severity or etiology of CKD, or to dependence of tissue T_2^* on many factors other than deoxyhemoglobin, such as renal perfusion, vascular volume, presence of inflammatory cells and edema, and hydration status.¹¹² Changes in these factors may offset the effect of deoxyhemoglobin in decreasing T_2^* . Importantly, since deoxyhemoglobin is intravascular, BOLD-MRI assesses intravascular rather than extravascular oxygenation. Although under healthy conditions blood and tissue oxygenation are considered to be at equilibrium, microvascular obliteration in fibrotic kidneys limits the access of deoxyhemoglobin to the tissue. Thus, T_2^* measured in fibrotic tissue may not change compared to healthy and well-oxygenated tissue. In recognition of this, some researchers proposed mathematical models to distinguish these factors from hypoxia so as to quantify tissue oxygen tension using BOLD-MRI in normal kidneys.^{113,114} However, whether these methods are applicable in diseased kidneys remains to be investigated.

The utility of BOLD-MRI has been investigated in a number of studies. For example, in a rabbit model of UUO, Woo et al.⁴⁰ and Zha et al.¹¹⁵ found that T_2^* correlated well with the percentage of renal fibrosis in the kidney. In folic acid-induced murine AKI, Jiang et al. observed a good correlation between R_2^* and renal fibrosis in the renal cortex, but not in the medulla.⁹⁹ Inoue et al. also detected a significant correlation between renal T_2^* and fibrosis area in CKD patients without diabetes, but not in patients with diabetic nephropathy or AKI.³⁴

Taken together, the usefulness of baseline T_2^* or R_2^* in assessment of tissue hypoxia and renal fibrosis is limited as a result of its low specificity and dependence on a wide range of tissue factors. Nevertheless, furosemide-induced increase in T_2^* has been shown to be compromised in RAS,^{106,116} and CKD,¹⁰⁹ indicating altered oxygen-dependent solute transport. Therefore, future studies are warranted to investigate the usefulness of furosemide-enhanced BOLD-MRI in measuring renal fibrosis.

MAGNETIC RESONANCE ELASTOGRAPHY

Principles

The accumulation of ECM during development of renal fibrosis typically hardens affected organs.¹¹⁷ Therefore, tissue stiffness has been used as a biomarker for fibrosis. MRE noninvasively measures tissue stiffness by visualizing the propagation of shear waves in the tissue. Mechanical vibrations are applied to the target organ at frequencies ranging from 40 to 200 Hz¹¹⁸ using a pneumatic driver placed against the body (Fig. 4a). These vibrational acoustic waves generate shear waves propagating in the tissue, which can be imaged using a phase contrast sequence. The wave propagation speed is dependent on organ stiffness, i.e., stiffer tissue faster propagating waves with longer wavelength. Finally, tissue stiffness map or am (Fig. 4b) can be extracted by processing the wave images.¹¹⁹

Findings

MRE was originally developed for liver imaging¹²⁰ and is now a gold standard technique for diagnosis and staging of liver fibrosis.^{121–123} Recently, an increasing number of studies have been exploring its application in the kidney. A pilot study by Shah et al. demonstrated the feasibility of MRE in detecting increased renal shear stiffness in rats with ethylene glycol-induced nephrocalcinosis but preserved renal function and mild interstitial fibrosis.¹²⁴ Korsmo et al. used MRE in a swine model of RAS,¹²⁵ and found a significant correlation between MRE-measured tissue stiffness and renal medullary fibrosis. The same group has also recently demonstrated the capability of MRE in monitoring changes in medullary stiffness in response to treatment in the swine ischemic kidney.¹²⁶

A limited number of studies have reported the utility of MRE in human kidneys. Rouviere et al. demonstrated a good reproducibility of kidney MRE in young healthy adults,¹²⁷ whereas in renal allografts. Lee et al. showed that patients with moderate interstitial fibrosis had only slightly higher kidney stiffness than patients with mild interstitial fibrosis.¹²⁸ In a single patient, MRE-measured kidney stiffness was predictive of the development of fibrosis in the kidney allograft.¹²⁹ With a larger cohort of patients, Kirpalani et al. reported a good

association between whole-kidney stiffness and biopsy-derived Banff fibrosis as well as eGFR.¹³⁰

Taken together, these promising findings indicate that kidney stiffness may serve as a good biomarker of renal fibrosis. Nevertheless, high blood flow and heterogeneous tissue texture may confound MRE in detecting renal fibrosis. For example, failure of MRE in measuring renal fibrosis in the renal cortex of pigs with RAS has been attributed to the reduced cortical turgor due to decreased renal blood flow.^{125,131} The anisotropic structure of renal tissue has also been shown to influence tissue stiffness.¹³² Therefore, caution needs to be exercised when interpreting the MRE-measured tissue stiffness as these hemodynamic and structural factors may mask the presence of fibrosis.

MAGNETIZATION TRANSFER IMAGING

Principles

Fibrotic kidneys usually undergo tubular atrophy and progressive accumulation of ECM components, composed mainly of fibronectin and collagen type I, III, and IV,⁴ which elevate macromolecule content, and may serve as an imaging target for renal fibrosis. Magnetization transfer (MT) is the physical process by which protons in macromolecules (the bound pool) cross relax with those in free water molecules (the free pool). Macromolecule protons are invisible in the MR signal due to their extremely short T_2 ($<1\text{ms}$).¹³³ By saturating the bound pool with off-resonance MT pulses, the measured MR signal from the free pool also drops due to the MT between these two pools. Therefore, MTI can be used to assess the macromolecule content in biological tissues. In MTI, only two sets of images need to be acquired, images at baseline without application of MT pulses and MT-weighted images. The percent signal decrease in the MT-weighted images is the MT ratio (MTR), which is considered indicative of the macromolecule content.

Findings

The MTR map has been widely used to characterize microstructural disruptions in the brain,^{134, 135} lungs,¹³⁶ intestines,¹³⁷ and rectal cancer.¹³⁸ Recent studies have explored its utility in animal models of kidney diseases. In mice with UUO, Wang *et al.* observed a significant paradoxical decrease in MTR due to urine accumulation.¹³⁹ In murine polycystic kidney disease, Kline *et al.* found that the MTR correlated well with both cystic and fibrotic changes.¹⁴⁰ In a murine model of RAS, Jiang *et al.* found that the MTR map showed a good spatial concordance with renal fibrosis by Masson's trichrome and Sirius red staining (Fig. 5a). The measured renal MTR also correlated significantly with fibrosis by histology as well as hydroxyproline content (Fig. 5b). The ability of MTI to monitor the progression of renal fibrosis was also demonstrated.¹⁴¹ The same group later demonstrated that MTR detected renal fibrosis in a mouse model of folic acid-induced AKI at 16.4 T⁹⁹ and a swine model of RAS at a clinical field strength of 3.0 T.¹⁴²

Although the MTR has been shown to be a promising biomarker for detection of renal fibrosis, it is intrinsically semi-quantitative and may be influenced by a complex combination of scan and tissue specific parameters, and may not be reproducible across

sites.^{143,144} To address this limitation, quantitative MT (qMT) techniques have been developed to offer more quantitative measurement of the macromolecule content in biological tissues based on mathematical models of the MT process.^{143,145,146} The extracted parameter is the pool size ratio (PSR), i.e., the ratio of the bound pool to the free pool, which is a more direct and quantitative measurement of the macromolecule content. Preliminary application of qMT by Wang et al. showed that PSR could detect the decreased cortical macromolecule content due to urine retention in mice with UUO.¹⁴⁷ They later demonstrated in a mouse model of diabetic nephropathy that the PSR can reliably detect cortical fibrosis.¹⁴⁸

Taken together, both the MTR and PSR reflect the macromolecule content in kidneys and are useful indices of renal fibrosis. Although the PSR provides more quantitative measurement of the macromolecule content, the measurement of MTR is easier and more clinically feasible. Notably, MTI may have a potential advantage over other MRI techniques in measuring renal fibrosis. By targeting at the presence of macromolecules, it may be less influenced by altered renal hemodynamics than other MRI techniques including DWI and MRE. Nevertheless, further studies are needed to test this relationship. So far, the ability of MTI in measuring renal fibrosis has only been demonstrated in animal models of kidney diseases, and the promising results warrants further studies to test its utility in patients.

OTHER MRI TECHNIQUES

T₁/T₂ mapping and susceptibility weighted imaging have also been explored for measuring renal fibrosis. T₁ and T₂ are the spin-lattice and spin-spin relaxation time, respectively. T₁ and T₂ are dependent on tissue composition and provide differential tissue contrast in anatomical MRI. Pathological changes like inflammation, edema, and fibrosis, may induce changes in these two relaxation times. In patients with decreased GFR, loss of corticomedullary differentiation on T₁-weighted MR images has been attributed primarily to an increased T₁ relaxation time of the cortex.¹⁴⁹ Increased T₁ and T₂ in mouse models of native kidney diseases and allograft rejection have been found to correlate well with renal fibrosis as well as inflammation.^{30,41} Despite these promising findings, the sensitivity and specificity of T₁ and T₂ mapping are low and their utility in detecting renal fibrosis remains to be tested in patients.

Magnetic susceptibility is a measure of the extent to which a substance becomes magnetized in an external magnetic field. Susceptibility-weighted imaging (SWI) can be used to characterize tissue components based on differences in their susceptibilities. Renal fibrosis alters tissue components and susceptibility, which offers an opportunity for fibrosis imaging using SWI. The ability of SWI in noninvasive measurement of renal fibrosis has been shown in a rabbit model of UUO.^{150,151} By incorporating sophisticated mathematical analysis, quantitative susceptibility mapping can be used to extract susceptibility maps from susceptibility-weighted images. Xie et al. demonstrated a good sensitivity of high-resolution quantitative susceptibility mapping in detecting renal fibrosis in fixed kidneys of mice deficient for angiotensin receptor type-1.¹⁵² The performance of this technique on fibrosis imaging in vivo or in patients remains to be investigated.

A common issue associated with many MRI techniques is their low specificity to renal fibrosis, as they indirectly assess renal fibrosis by evaluating its impact on tissue properties. By contrast, molecular MRI using gadolinium-based contrast agents that can specifically bind to molecules involved in fibrogenesis may show high specificity for renal fibrosis. Such contrast media allow accurate measurement of hepatic,^{153–156} pulmonary,^{155,157} and cancerous¹⁵⁸ fibrosis. Clearly, the ability of molecular MRI of renal fibrosis warrants future investigation

ULTRASOUND ELASTOGRAPHY

Like MRE, UE is used for detecting renal fibrosis by assessing tissue stiffness. UE techniques that have been used for renal fibrosis assessment can be classified into two categories based on the measured physical quantity, i.e., strain elastography (SE) and shear wave elastography (SWE). In SE, a strain map is generated by measuring the tissue displacement caused by external compression. Therefore, SE is only useful in renal allografts that are close to the body surface, but not in native kidneys located deeper in the body. A few studies have reported decreased elasticity or strain in fibrotic renal transplants. Orlicchio et al. reported an inverse correlation between SE-derived elasticity and the degree of fibrosis in patients with renal allografts.¹⁵⁹ Gao et al. showed that corticomedullary strain outperformed Doppler parameters and duration of transplantation in assessment of renal allograft cortical interstitial fibrosis as well as tubular atrophy.¹⁶⁰ The same group also reported that two SE-derived parameters, the normalized cortical strain¹⁶¹ and corticomedullary strain ratio,¹⁶² decreased in fibrotic renal allografts and could be used as a reliable biomarker of renal fibrosis.

SWE assesses tissue elasticity by measuring ultrasound-generated shear wave velocity (SWV) to calculate tissue stiffness, which is proportional to the square of the SWV. SWE techniques include transient elastography, acoustic radiation force impulse, and supersonic shear imaging. Unlike SE, SWE does not require external compression and can therefore be used in both allografts and native kidneys. In CKD, most studies have reported decreased SWV^{163–165}, associated with impaired renal function.^{163,165} One study also demonstrated a good correlation between SWE-measured SWV and renal fibrosis.¹⁶⁴ On the other hand, Samir et al. found increased renal stiffness in CKD patients¹⁶⁶ and Wang et al. showed that SWE-estimated stiffness did not predict CKD stage or correlate with renal fibrosis.¹⁶⁷ Possibly, different levels of renal fibrosis or hemodynamics might contribute to these discrepancies.

In renal transplants, controversy also arises with regard to the utility of SWE in assessing renal fibrosis. Some studies showed that SWE-measured parenchymal stiffness or SWV correlated well with renal fibrosis by histology,^{168–170} whereas others showed that SWE was not useful in distinguishing grafts with different grades of fibrosis.^{171–173} Notably, Grenier et al. reported that SWE-measured renal cortical stiffness showed no correlation with semi-quantitative Banff score or the level of interstitial fibrosis, but instead correlated well with total Banff scores of chronic lesions and of all elementary lesions.¹⁷² Therefore, the reference standard may affect these comparisons.

The conflicting results about the usefulness of UE in measuring renal fibrosis are not surprising. Intrarenal stiffness can be influenced by a spectrum of factors other than renal fibrosis, including tissue perfusion, tubular or interstitial pressure, and tissue anisotropy.¹³² Notably, accumulating evidence is showing that SWE-measured renal stiffness is significantly decreased by a reduction in renal perfusion, which may mask the presence of renal fibrosis.^{174,175} This is consistent with recent findings using MRE.¹²⁵ The effect of renal perfusion is more pronounced in the renal cortex than in the medulla, since 90% of renal blood flow goes to the cortex.¹⁷⁶ This may explain the observation by Early et al. that renal stiffness was not reflective of cortical fibrosis but moderately associated with medullary fibrosis.¹⁷⁷ Possibly, SWE-measured renal stiffness may be more useful at a late stage of allograft failure, when severe fibrosis is present.¹⁷⁸

OTHER METHODS

Besides MRI and ultrasonography, other imaging modalities, including computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), have also shown promise for imaging of renal fibrosis. For example, Zhu et al. developed gold nanoparticles conjugated to an anti-collagen- I antibody as a CT imaging contrast for evaluation of renal fibrosis, and demonstrated its efficacy in murine kidneys with unilateral RAS.¹⁷⁹ PET^{180,181} and SPECT¹⁸² ligands that target fibrogenesis have also been developed and shown useful for assessment of hepatic,¹⁸² pulmonary,¹⁸⁰ and cardiac¹⁸¹ fibrosis, supporting future investigation of their use of renal fibrosis.

CONCLUSIONS

The last two decades saw great advancement in MRI and ultrasound imaging technologies for noninvasive assessment of renal fibrosis. The versatility of MRI offers the opportunity for probing renal fibrosis by measuring its influences on tissue structural and functional properties. The relatively easy access and low cost of ultrasonography has also generated interest in investigating the utility of ultrasound elastography in measuring renal fibrosis in recent years. Implementation of these techniques has produced promising findings, which need to be validated in future large-cohort, multi-center randomized trials. For this, standardization of imaging techniques among centers and across different platforms is necessary for reliable comparison. Translational studies are also critical for validation of emerging imaging techniques in measuring human renal fibrosis. Technical challenges may arise when adopting imaging protocols to different clinical systems, for which nephrologists and MR scientists should collaborate and devote intensive research efforts.

While standardization of imaging protocols for large-scale clinical validation is important, endeavors are also needed to develop innovative and cutting-edge imaging technologies to improve diagnostic accuracy. Although promising results have been widely reported for some MRI techniques, some conflicting findings argue against their reliability for measuring renal fibrosis. This may be attributed to the multi-factorial and dynamic process of fibrosis development, and the intrinsic low sensitivity and specificity of these imaging techniques. An important consideration for renal fibrosis imaging is the sensitivity of the technique. The

goal of imaging fibrosis early is to identify patients at a relatively early stage of CKD or allograft dysfunction, with moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)-¹⁸³ who are prone to lose GFR rapidly.⁹ Therefore, imaging modalities should preferably be capable of detecting at least 25% of cortical fibrosis. The ability to detect milder forms of fibrosis may afford an advantage by detecting earlier disease instigation and progression, so that timely interventions can be implemented to halt CKD progression or transplant failure, for example by control of blood pressure and reduction of proteinuria¹⁸⁴, or alleviating rejection-associated inflammation.¹⁸⁵ Future research may aim at resolving these issues in order to improve the performance of these imaging techniques in fibrosis assessment. Technical advancement is still needed to minimize imaging artifacts and optimize protocols. Another promising direction is the implementation of multi-parametric imaging techniques for more informative and integrated understanding of renal fibrosis. Furthermore, development of molecular imaging contrast agents that are highly specific to fibrotic biomarkers may also improve the diagnostic accuracy.

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Abbreviations:

CKD	chronic kidney disease
MRI	magnetic resonance imaging
GFR	glomerular filtration rate
ECM	extracellular matrix
MRE	magnetic resonance elastography
UE	ultrasound elastography
MTI	magnetization transfer imaging
BOLD	blood oxygenation level dependent
ADC	apparent diffusion coefficient
UUO	unilateral ureteral obstruction
IVIM	intravoxel incoherent motion
RAS	renal artery stenosis
DTI	diffusion tensor imaging
FA	fractional anisotropy

DKI	diffusion kurtosis imaging
AKI	acute kidney injury
MT	magnetization transfer
MTR	magnetization transfer ratio
qMT	quantitative magnetization transfer
PSR	pool size ratio
SWI	susceptibility-weighted imaging
SE	strain elastography
SWE	shear wave elastography
SWV	shear wave velocity

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Figure 1. Renal fibrosis and associated kidney injury.

Renal fibrogenesis is essentially a failed wound healing process, featured by infiltration of inflammatory cells in an attempt to repair tissue damage. Yet, sustained injury leads to non-resolving inflammation, which triggers the activation and expansion of myofibroblasts from multiple sources. These myofibroblasts generate a large amount of extracellular matrix (ECM) components, including fibronectin and type I/III collagens, which may eventually evolve into fibrosis. Renal fibrosis is often accompanied by vascular obliteration, tubular atrophy, and kidney shrinkage, which induce a variety of changes in functional, mechanical, and molecular properties of the kidney. Vascular rarefaction lowers renal perfusion and oxygen supply, leading to tissue hypoxia. Deposition and accumulation of the ECM and tubular atrophy restrict the mobility of water molecules, and increase kidney stiffness and macromolecule content.

Figure 2. Diffusion magnetic resonance imaging of one kidney of a healthy 68-year-old female subject with unilateral atherosclerotic renal artery stenosis.

(a) A baseline image with $b=0 \text{ sec/mm}^2$. (b) The apparent diffusion coefficient map by mono-exponential fitting of diffusion weighted images acquired with b -values of 0 and 600 sec/mm^2 . Compared to the right contralateral kidney, the measured apparent diffusion coefficient was lower in both the cortex (2.7 vs. 2.3 $\mu\text{m}^2/\text{ms}$) and medulla (2.3 vs. 2.0 $\mu\text{m}^2/\text{ms}$) of the left stenotic kidney, suggesting renal fibrosis. Courtesy of Dr. Stephen C Textor.

Figure 3. Blood oxygenation level dependent magnetic resonance imaging for measurement of renal hypoxia.

(a) Representative cortical and medullary mono-exponential fittings of the MR signal acquired at 12 different echo times from 3.5 to 60 ms using a multi-echo gradient echo sequence. Fitted time constant is T_2^* , whose reciprocal is R_2^* , an index of tissue hypoxia.

(b) Representative R_2^* map of a normal kidney. Increasing R_2^* indicates a higher concentration of deoxyhemoglobin or more tissue hypoxia. The renal medulla shows a larger R_2^* than the cortex, which is in line with the fact that medulla operates habitually on the brink of anoxia.

Figure 4. Magnetic resonance elastography for assessment of kidney stiffness.

Representative T₁-weighted anatomical image (a) and the corresponding kidney elastogram (b) of a healthy 32-year-old male subject. Kidney stiffness was measured using a spin-echo echo-planar imaging sequence with motion sensitizing gradients and flow compensation. Shear waves with 120 Hz vibrations were transmitted to the kidneys by placing two passive pneumatic drivers under each kidney on the posterior of the body. Elastograms were generated by post-processing wave images using a multi-model direct inversion algorithm.

Figure 5. Magnetization transfer imaging of renal fibrosis in mouse kidneys with renal artery stenosis.

(a) Representative trichrome and Sirius red-stained kidney sections and corresponding MTR map of one stenotic mouse kidney. The MTR map showed a good spatial concordance with renal fibrosis by Masson's trichrome and Sirius red staining. (b) Spearman's correlations between the measured renal MTR and percentage of renal fibrosis by histology as well as hydroxyproline content. The good spatial and quantitative correlations between MTR and histochemical analysis indicate that magnetization transfer imaging provides reliable measurement of renal fibrosis in murine kidneys with renal artery stenosis. Figure reproduced from Jiang et al.¹⁴¹ with permission.