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Current MRI Techniques for the Assessment of Renal Disease

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Abstract

Purpose of review—Over the past decade a variety of magnetic resonance imaging (MRI) methods have been developed and applied to many kidney diseases. These MRI techniques show great promise, enabling the noninvasive assessment of renal structure, function, and injury in individual subjects. This review will highlight current applications of functional MRI techniques for the assessment of renal disease and discuss future directions.

Recent findings—Many pathological (functional and structural) changes or factors in renal disease can be assessed by advanced MRI techniques. These include renal vascular structure and function (contrast-enhanced MRI, arterial spin labeling), tissue oxygenation (blood oxygen level-dependent MRI), renal tissue injury and fibrosis (diffusion or magnetization transfer imaging, MR elastography), renal metabolism (chemical exchange saturation transfer, spectroscopic imaging), nephron endowment (cationic-contrast imaging), sodium concentration (^{23}Na-MRI), and molecular events (targeted-contrast imaging).

Summary—Current advances in MRI techniques have enabled the non-invasive investigation of renal disease. Further development, evaluation, and application of the MRI techniques should facilitate better understanding and assessment of renal disease and the development of new imaging biomarkers, enabling the intensified treatment to high-risk populations and a more rapid interrogation of novel therapeutic agents and protocols.

Keywords

Magnetic Resonance Imaging; Kidney Imaging; Glomerular Imaging; Renal Function; Renal Disease

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Conflicts of interest

None

Introduction

Renal disease is a complex process that involves multiple stages, loss of physiological regulation, and interactions between the damaged cells and surrounding tissues. To understand disease pathogenesis and potential interventions, it is essential to develop methods that enable the study of renal disease in its natural environment and the repeated measurements during the course of the disease. In this context, non-invasive and quantitative imaging technologies provide a unique opportunity to investigate renal disease in living subjects over time. Magnetic resonance imaging (MRI) is a widespread technique that is able to provide excellent anatomical images with high contrast and an adequate image resolution. Further, functional magnetic resonance (MR) imaging techniques are increasingly performed to evaluate renal function and injury. These include perfusion, diffusion, and blood oxygenation level-dependent (BOLD) imaging [1–3]. Because functional, molecular and cellular changes precede anatomic changes, functional MR imaging enables the early detection of renal disease as well as improved understanding of disease pathogenesis that could facilitate the development of better treatment options and improve patient prognosis. Also, these techniques may compensate for the limitations of currently available tests of renal function. Thus, functional MR imaging may be effectively used for the assessment of renal disease. This review will highlight the current renal applications of functional MRI techniques and discuss about future work.

Assessment of Renal Perfusion and Oxygenation

Abnormalities in perfusion and oxygen delivery are associated with many renal diseases. Consequently, there exist numerous MRI methods to assess these physiological parameters. BOLD MRI has been explored extensively for characterizing blood oxygen delivery to the renal parenchyma [4, 5]. BOLD relies upon magnetic field variations between blood vessels and the surrounding tissue and is quantified using the transverse relaxivity rate (R_2*). The strength of these variations and their impact on R_2* depends upon the local blood oxygen saturation, vascular geometry, blood flow, hematocrit and blood volume. This complex dependency on several related, but physiologically distinct, parameters potentially confounds the interpretation of the BOLD signal at steady state and following pharmacological-induced changes [6]. Despite this complex biophysical basis BOLD MRI continues to show potential as a biomarker of renal function and hypoxia. Saad et al recently demonstrated that quantifying the percentage of R_2* values above a value of 30 sec^{-1}, across the whole kidney, provides a way to characterize fractional tissue hypoxia in patients with renal artery stenosis [7]. The fractional tissue hypoxia was found to be inversely correlated with blood flow, perfusion and GFR. Relying upon changes in the BOLD signal following hypercapnic or hyperoxic challenges, Milman validated the use of hemodynamic response imaging for characterizing vascular reactivity without the use of contrast agents [8]. As confirmed by Doppler US perfusion measurements, the vascular reactivity in acute kidney injury mice was significantly attenuated as compared to control mice. Hueper also showed the utility of BOLD in assessing vascular reactivity to nitric oxide inhibition in diabetic mouse kidneys [9]. Clinical validity and translation of BOLD techniques will continue to expand as its biophysical basis and limitations are better characterized. Similar

efforts in neuroimaging have led to quantitative BOLD (qBOLD) techniques that enable the quantification of steady-state local blood oxygen saturation [10, 11].

Dynamic contrast enhanced (DCE) MRI may also be used to characterize renal perfusion and vascular properties. Two classes of contrast agents have been leveraged for such studies; iron-oxide nanoparticles that are considered to be primarily intravascular and Gadolinium-based small molecular weight agents that are freely filtered. Iron-oxide agents can introduce magnetic field variations around blood vessels and alter R_2* values. As with BOLD contrast, the magnitude of the R_2* change reflects the local blood volume and blood vessel geometry. Alternatively, Gd-based contrast agents are typically used to alter a tissue's longitudinal relaxation rate (R_1), an effect that is more straightforward as the signal change depends primarily on the local contrast agent concentration. Rapid imaging (on the order of a second) may be used to track the passage of a contrast agent through the kidney. With proper kinetic analysis renal blood flow, glomerular filtration rate, total or capillary renal blood volume (or the volume of distribution) and plasma and tubular mean transit times may be assessed with these MR imaging [12–15]. Intravascular iron-oxide agents can also be used to dynamically assess vascular changes following pharmacologic interventions [16] or assess the patency and architecture of the vasculature following renal transplants [17]. In the context of cancer imaging, iron-oxide or Gadolinium agents are also used to quantify (map) the mean vessel size and vascular architecture [18, 19]. This technique could be adapted for renal vessel characterization and may provide another readout of renal vascular pathology. Other than DCE-MRI, arterial spin labeling (ASL) may also be used to assess renal perfusion [1, 2].

Assessment of Renal Injury and Fibrosis

Diffusion-weighted imaging (DWI) is a MR modality that detects the movement of water molecules in tissues [20, 21]. DWI quantifies bulk water movement, such as that found in the blood microcirculation and Brownian motion of water molecules within tissues, and senses changes in water diffusion due to renal injury. The apparent diffusion coefficient (ADC) is used as a quantitative parameter of DWI. Diffusion tensor imaging (DTI) is a more comprehensive method that evaluates the directionality of water mobility (fractional anisotrophy, FA) as well as its magnitude (ADC) [20, 21]. Further, intravoxel incoherent motion (IVIM) is another advanced diffusion imaging approach that differentiates between water motion due to perfusion and diffusion [20, 21]. A body of literature demonstrates that a reduction in ADC or FA correlates with decreased renal function in many renal diseases in human and animals, including chronic kidney disease (CKD) [22, 23], acute kidney injury (AKI) [9, 24], and renal transplantation [25, 26]. Further, recent studies show that renal ADC values correlate with histological measures of fibrosis in patients with CKD and experimental renal disease [22, 27–29]. Also, IVIM imaging was recently applied to characterize changes in renal perfusion, tubular flow, and tissue diffusion that are associated with renal structural damage [30, 31]. The data suggested that renal perfusion is reduced earlier and affected more than molecular diffusion during renal disease progression. Thus, diffusion MRI is a promising MRI technique to assess renal disease. More recently, an approach termed diffusion temporal spectroscopy has been specifically developed to detect microstructural variations at both subcellular and supracellular levels [32]. Although its

utility in renal disease remains to be elucidated, its enhanced sensitivity to intracellular features, such as the nucleus, suggests that this technique may enable finer assessments of renal disease and provide unique insights into renal pathology.

Renal fibrosis is a hallmark of progressive renal disease; therefore, its assessment is critical for the evaluation of renal disease, including prediction of prognosis and follow-up after therapy. Other than DWI, the following MRI techniques have been used for interrogating renal fibrosis. First, magnetization transfer (MT) imaging is an approach that is sensitive to large immobile macromolecules distributed within tissue and could provide a means to evaluate the pathological events that are accompanied by changes in macromolecular components, such as apoptosis and fibrosis [33]. MT imaging utilizes off-resonance radiofrequency pulses to saturate macromolecular protons and the acquisition of the free water proton signal at a time sufficient for proton exchange between the two proton pools. The decrease in the water signal following exchange indirectly provides information on the macromolecules. MT has been shown to detect intestinal or pancreatic fibrosis [34–36] and apoptotic cell death [37]. Further, we have recently shown that progressive renal injury (cell death, urine retention, and fibrosis) in ureteral obstructed mouse kidneys may be assessed by MT imaging [38]. Thus, MT imaging has the potential to quantitatively assess renal fibrosis. Second, Korsmo et al. has recently demonstrated that renal medullary fibrosis caused by renal artery stenosis can be characterized by MR elastography (MRE) in swine [39]. MRE is an emerging MRI modality that can noninvasively quantify and visualize tissue elasticity. In this study, MRE-determined medullary stiffness correlated with the degree of fibrosis in stenotic kidneys, as determined by histology. Further, a recent study by Xie et al. successfully detected, ex vivo, small (~50 μm) renal lesions of inflammation and fibrosis in type 1 angiotensin receptor deficient mice using quantitative susceptibility mapping (QSM) [40]. This approach is highly sensitive to changes in diamagnetic material composition within tissue which may be altered by changes in protein, lipid and mineral content. Thus, advances in MR methodology may enable the non-invasive assessment of renal fibrosis in future. To this end, it would be important to evaluate the sensitivity and reproducibility of these approaches (e.g. what size of fibrosis can be detected?) and precision in detecting fibrosis, including its ability in differentiating from other pathological events.

Assessment of Renal Metabolism

MR spectroscopic imaging (MRSI) enables the characterization of certain metabolites within tissue. Hyperpolarization of ^{13}C-labeled molecules remarkably enhances its sensitivity and allows noninvasive investigation of dynamic metabolic processes of the substrates. Using a hyperpolarized [1-^{13}C]pyruvate, Laustsen et al. has shown that reduction of inspired oxygen increases renal lactate and alanine formation in diabetic mice, while this effect is not observed in non-diabetic controls [41, 42], indicating that reduced oxygen availability alters renal energy metabolism in diabetes. Further, Keshari et al. has assessed the oxidative stress in diabetic mouse kidneys using a hyperpolarized [1-^{13}C] dehydroascorbate (DHA), a new endogenous redox sensor, and shown that redox capacity is decreased in diabetic kidneys prior to histological evidence of nephropathy and that angiotensin converting enzyme inhibition restores the renal redox status in diabetic mice [43]. Further, Clatworthy et al. has assessed renal fumarate metabolism in folic acid-induced

AKI mice using this technique and shown that renal production of [1,4-$^{13}C_2$]malate, a fumarate metabolite, is increased in early phase of AKI [44]. Given the fact that fumarate uptake is limited in viable cells but increased in necrotic cells, they proposed that MRSI of hyperpolarized [1,4-$^{13}C_2$] fumarate may be used for detecting early tubular necrosis. Thus, recent reports demonstrated the potential utility of MRSI in assessing metabolic changes in renal disease.

Chemical exchange saturation transfer (CEST) is an advanced MRI technique with wide application potential due to its ability to examine complex molecular contributions [45]. The CEST contrast mechanism indirectly detects the exchangeable solute protons resonating at frequencies different from bulk water. These solute protons are selectively saturated with low bandwidth RF irradiation, and the saturation is transferred to bulk water protons via chemical exchange, resulting in an attenuation of the measured water proton signal. Thus, CEST-MRI displays solute/water proton interactions that resonate at specific spectral frequencies, and is capable of detecting low-concentration metabolites. This technique has been applied to map the concentration of glucose, glycogen, glycosaminoglycan (GAG), amide protein, and pH in disease organs [46]. Using this technique, Longo et al. has evaluated renal pH levels in a mouse model of AKI and demonstrated that AKI causes a robust increase in renal pH values [47]. Further, we recently applied this technique to the characterization of murine diabetic nephropathy (DN) and found that hydroxyl (−OH) group metabolites that peak at 1.2 ppm are increased in db/db eNOS −/− kidneys that show progressive DN (Figure 1), suggesting increased glucose and glycogen depositions in these kidneys. Thus, this technique may be used for assessing renal metabolites.

Growing evidence demonstrates that renal accumulation of lipids, including triglyceride, cholesterol and fatty acid, greatly contributes to the pathogenesis of renal disease, especially in diabetic nephropathy [48]. This finding indicates that non-invasive assessment of renal lipid deposition is required to evaluate renal disease. In this context, MRI and spectroscopic imaging is of great interest as they have the capacity to detect and assess lipid depositions in tissue [49, 50]. Peng et al. applied chemical shift-selective imaging to evaluate lipid deposition in db/db mouse kidneys and showed higher lipid levels in these kidneys [51, 52]. In addition, Wagner et al. demonstrated that perivascular renal sinus fat may associate with microalbuminuria in humans [53]. Although further investigations are required, these findings suggest that MRI assessment of renal or peri-renal fat deposition may be useful for evaluating the risk or status of renal disease.

Assessment of Glomerular Number

Total glomerular number, which closely associates with nephron number, varies widely between individuals in normal populations. This is of clinical importance as low glomerular number is associated with the development of hypertension and CKD [54]. Further, experimental studies show that reduction of glomerular number (e.g. nephrectomy, hypoplastic kidney) predisposes to more severe renal injury in animals. Thus, glomerular number predicts the risk of CKD and affects outcome of renal disease. Noninvasive measures of glomerular numbers could permit the targeted and intensified treatment to high-risk patient populations. To this end, a MRI-based technique has recently been developed

[55, 56]. Bennett et al have demonstrated that intravenously administered cationized ferritin (CF) binds to anionic proteoglycans in the glomerular basement membrane and surface glycocalyx of the glomerular endothelium [57]. Its glomerular accumulation can be detected as a black dot with T_2- and T_2*-weighted imaging [55, 56]. Using three-dimensional ex vivo imaging, glomerular number and size in CF-perfused rat kidneys were measured and found to agree with those obtained using histological methods [58, 59]. Further, a potential utility of CF-MRI in assessing glomerular barrier function and pathology that may alter the pattern of CF accumulation in glomerulus (e.g. glomerular hypertrophy, segmental or global glomerulosclerosis) was also discussed [56, 57, 60]. Although several technical challenges remain to make *in vivo* detection of CF practical, including the relaxivity of CF and differentiating background from blood, these studies clearly demonstrate the potential utility of MRI in assessing glomerular number, function, and pathology. In this context, it is noteworthy that Qian et al. has recently shown that individual rat glomeruli can be identified as hyper intensive (high blood flow) regions by MRI *in vivo*, when MRI's sensitivity is enhanced with an implantable Wireless Amplified NMR Detector (WAND)[61]. In this study, the authors also demonstrated that WAND enables the detection of CF-labeled glomeruli *in vivo*. In addition, this study showed that Mn^{2+}-mediated contrast enhancement can be used to separate renal tubules from glomeruli. Although the sensitivity, reproducibility, precision, and variability of these approaches in detecting glomerular number in living subjects remain to be evaluated, MRI may be used for the assessment of glomerular number.

Molecular Imaging

Specific molecular events may also be assessed by MRI using the targeted superparamagnetic iron-oxide (SPIO) contrast agents. Akhtar et al. conjugated a VCAM-1 monoclonal antibody to the 1-μm iron-oxide microparticles and visualized and defined three-dimentional distribution of VCAM-1 expression in ischemia-reperfusion rat kidney injury [62]. Sargsyan et al. conjugated a recombinant protein that contains the C3d binding region of complement-receptor-2 (CR2) to the 70-nm SPIO and monitored renal C3 deposition (cortex, outer medulla, inner medulla) in the MRL/lpr model of lupus nephritis [63–65]. Note: SPIO can also be used to track the cell infiltration (e.g. SPIO-labeled macrophages) or to assess macrophage accumulation in renal tissue [65].

Others

Renal sodium concentration gradient along the corticomedullary axis demonstrates renal fluid and iron homeostasis. Therefore, quantitative sodium (^{23}Na) MR imaging that senses the changes in corticomedullary sodium gradients may be useful for assessing renal fluid homoeostasis, tissue viability, and renal function [66, 67]. Further, recent studies demonstrated the potential utility of ^{23}Na MR imaging of skin or muscle in assessing the risk of developing hypertension and CKD [68, 69].

Conclusion

Renal MR imaging clearly demonstrates the capability and potential for non-invasive evaluation and characterization of the renal status in individual subjects (Table 1),

complementing the physiological and pathological information obtained by conventional tests. The application of these MRI techniques should improve our understanding and assessment of pathological processes of renal disease, hasten the development of new imaging biomarkers, and enable the intensified treatment and clinical trials to high-risk patient populations.

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Key points

- Recent advances in MRI techniques have enabled us to assess the pathological (functional and structural) changes in renal disease at molecular and cellular levels.
- Various pathological changes and factors in renal disease can be assessed by MRI, including renal perfusion, oxygenation, injury, fibrosis, metabolism, nephron endowment, and molecular expression (Table 1).
- The application of these MRI techniques should improve our understanding and assessment of renal disease, hasten the development of new imaging biomarkers, and enable the intensified treatment to high-risk patient populations.

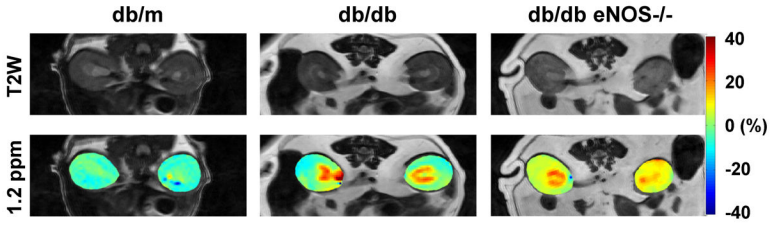

Figure 1. CEST MR imaging of diabetic mice

Sixteen week-old db/m, db/db, and db/db eNOS−/− mice were subjected to the CEST MR imaging. Renal MTRasym maps (at 1.2 ppm RF offset) were created by asymmetric analysis of CEST spectra. Upper panels show the corresponding T2-weighted (T2W) images. Red color area indicates large renal vessels. Note: The CEST contrast at 1.2 ppm RF offset is increased in db/db eNOS −/− kidneys.

Table 1

Current MRI Techniques and its Utility in Renal Disease

MRI Technique	Readout
BOLD	Oxygen delivery, Vascular reactivity
qBOLD	Local oxygen saturation
DCE	Perfusion
	Glomerular filtration
	Blood volume
	Vessel size
	Vascular reactivity
ASL	Perfusion
DWI, DTI	Perfusion, Tissue injury, Fibrosis
IVIM	Perfusion
MT	Cell death, Urine retention, Fibrosis
MRE	Fibrosis
MRSI	Metabolism
CEST	Metabolites, pH
CF-MRI	Glomerular number and size
	Glomerular barrier function
	Glomerular lesion
Targeted SPIO	Molecular imaging
^{23}Na-MRI	Fluid homeostasis
	Renal function and injury