Magnetic Resonance Imaging to Evaluate Kidney Structure, Function, and Pathology: Moving Toward Clinical Application

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Recent advances in multiparametric magnetic resonance imaging (MRI) allow multiple quantitative measures to assess kidney morphology, tissue microstructure, oxygenation, kidney blood flow, and perfusion to be collected in a single scan session. Animal and clinical studies have investigated the relationship between the different MRI measures and biological processes, although their interpretation can be complex due to variations in study design and generally small participant numbers. However, emerging themes include the apparent diffusion coefficient derived from diffusion-weighted imaging, T_1 and T_2 mapping parameters, and cortical perfusion being consistently associated with kidney damage and predicting kidney function decline. Blood oxygen level–dependent (BOLD) MRI has shown inconsistent associations with kidney damage markers but has been predictive of kidney function decline in several studies. Therefore, multiparametric MRI of the kidneys has the potential to address the limitations of existing diagnostic methods to provide a noninvasive, noncontrast, and radiation-free method to assess whole kidney structure and function. Barriers to be overcome to facilitate widespread clinical application include improved understanding of biological factors that impact MRI measures, development of a larger evidence base for clinical utility, standardization of MRI protocols, automation of data analysis, determining optimal combination of MRI measures, and health economic evaluation.

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Magnetic resonance imaging (MRI) provides a powerful, radiation-free method to image human tissues. The importance of this discovery to clinical medicine was recognized by the joint award of the Nobel Prize in Physiology or Medicine to Sir Peter Mansfield and Paul Lauterbur in 2003. Early development focused on qualitative anatomical imaging, and MRI is now integral in clinical care for a wide range of conditions. Moreover, recent developments in MRI have made it possible to derive quantitative MRI parameters to assess blood flow and tissue perfusion as well as tissue properties that change in the setting of inflammation and fibrosis; this is termed multiparametric MRI (mpMRI).[1]

Application of mpMRI to the kidneys has great potential to assist in the assessment and management of kidney diseases. At present, clinicians rely largely on biochemical measures of glomerular filtration rate (GFR) and proteinuria as well as kidney biopsy to diagnose and monitor disease. However, GFR is limited by the fact that it may not change during early nephron loss due to compensatory hyperfiltration by remaining glomeruli. Proteinuria is a nonspecific marker of glomerular filtration barrier dysfunction, and kidney biopsy is invasive, associated with a risk of severe complications and interpretation limited by potential sampling error. Multiparametric MRI has the potential to address these limitations to provide a noninvasive, radiation-free method to assess whole kidney morphology, function, and microstructure.

In this Perspective we seek to supplement other reviews of kidney MRI[2,3] by providing an overview of MRI parameters used to assess the kidneys, a review early clinical studies, and a discussion of future developments required to overcome the remaining barriers to clinical application.

Multiparametric Kidney MRI: Measures and Parameters They Assess

Multiparametric MRI generates multiple measures of kidney structure and function. Here we provide a brief overview of the most commonly used non-contrast-based MRI measures that show the greatest promise for clinical application, with additional technical details and more advanced MRI measures provided in Table 1.

Kidney Morphology

Kidney length and volume can be measured with anatomical MR images, typically T_2-weighted scans to measure total kidney volume (TKV)[4,5] and T_1-weighted scans for segmentation of the cortex and medulla.[5] TKV is a key prognostic measure in persons with autosomal dominant polycystic kidney disease (ADPKD) but may also be important in monitoring of chronic kidney disease (CKD) progression. In ADPKD, the increase in TKV occurs at an earlier stage than the decline in estimated GFR (eGFR),[6,7] and TKV by MRI has been approved by the European Medicines Agency (2015) and the US Food and Drug Administration (2016) as a prognostic enrichment biomarker to identify patients at increased risk of disease progression Fig. 1.

Tissue Microstructure

Tubular atrophy and interstitial fibrosis are important determinants of CKD prognosis.[8] Diffusion-weighted

imaging (DWI) and relaxometry mapping (T_1 and T_2), are MRI methods that have been most frequently applied to characterize such tubulointerstitial pathology Fig. 1.

DWI[9] provides a measure of water molecule movement, which is quantified by the apparent diffusion coefficient (ADC). The diffusion of water molecules is hindered when the interstitial space is narrowed by fibrosis, thus the progression of CKD is reflected by lower ADC values[10] and a reduced corticomedullary difference in ADC,[11] whereas kidney inflammation increases ADC. An extension to DWI is diffusion tensor imaging (DTI),[12] which characterizes the directionality of water diffusion in terms of the fractional anisotropy (taking a value of 0 to 1, where 0 represents random motion in all directions) to provide information on kidney microstructure. DTI is particularly sensitive to the tubules, collecting ducts, and blood vessels in the medulla in which water preferentially moves in 1 direction, leading to higher fractional anisotropy values in the medulla compared with the cortex in healthy kidneys. Medullary fractional anisotropy has been shown to be reduced in patients with CKD categories G2-4.[12]

T_1 and T_2 mapping[13] of tissue measures the longitudinal and transverse relaxation times, respectively, which are determined by how rapidly protons re-equilibrate their spins after being excited by a radiofrequency pulse. Increased T_1 has been shown to associate with fibrosis (due to association of collagen with supersaturated hydrogel) or inflammation (interstitial edema, cellular swelling).[14] Tissue T_2 mapping increases in response to inflammation and tends to decrease with severe fibrosis.

Kidney Oxygenation

Hypoxia has been implicated as a key factor in tissue damage during acute kidney injury (AKI) and CKD.[15,16] Blood oxygen level-dependent (BOLD) MRI provides an indication of tissue oxygenation. It uses the fact that deoxyhemoglobin is strongly paramagnetic whereas oxyhemoglobin is not, which acts to shorten the transverse relaxation time constant (T_2*) or increase R_2*, which is expressed as ($1/T_2$*) thereby reducing the signal from tissues Fig. 2. Higher R_2* (or lower T_2*) thus indicates lower tissue oxygenation (Po_2). Due to the position on the oxygen dissociation curve (partial pressure of oxygen in the medulla is 10-20 mm Hg compared with 40 mm Hg in the cortex), the medulla is more sensitive to changes in oxygenation than the cortex, where most of the hemoglobin is oxygenated.

A large number of studies have been published on BOLD-MRI in kidney disease, as summarized in a comprehensive review.[17] Some have reported a reduction in oxygenation in CKD compared with healthy controls, but others have found no differences.[18] These divergent results may reflect factors other than oxygenation that can affect the BOLD-MRI signal, including technical factors, analysis method, or patient clinical factors including hydration status, age, hematocrit, dietary sodium, pH, or body temperature.[17,19] Technical advances to unravel these links are underway.[20]

Kidney Blood Flow and Tissue Perfusion

Changes in arterial flow and in tissue perfusion at the capillary level contribute to the pathogenesis of kidney diseases and may provide insights into efficacy of therapies.

Phase contrast (PC-MRI) provides a method to determine blood flow in the renal artery,[21] and has been shown to correlate well with alternative measures of kidney blood flow.[22] Arterial spin labeling (ASL) provides an alternative to methods that involve exogenous contrast agents to measure kidney perfusion by using the radiofrequency magnetic labeling of protons in the water within arterial blood that act as a diffusible tracer. Tissue perfusion is determined by subtracting images in which arterial blood is not labeled from those in which labeling has been applied; by collecting images across a range of times after labeling of the blood and normalizing the images to fully recovered magnetization, perfusion can be estimated by fitting the data to a model Fig. 2. Animal studies have shown ASL can detect changes in kidney perfusion associated with induced ischemia, and perfusion correlates with histological damage and kidney function.[23]

The majority of human kidney mpMRI is performed on 1.5 and 3 Tesla MR scanners, although studies have shown the benefits of 3 Tesla for signal-to-noise ratio, examination time, and spatial resolution. In 2018, the COST Action PARENCHIMA initiated a drive toward standardization in kidney MRI,[24] with a focus on the most common kidney MRI techniques of T_1 and T_2 mapping,[13] PC-MRI,[25] ASL,[25] DWI,[26] and BOLD.[27]

Clinical Studies

The number of clinical studies employing kidney MRI is increasing rapidly, but their interpretation is complex due to the variation in number and type of MRI measures used. Moreover, it is important to note that lack of correlation between an MRI measure and a clinical variable (eg, GFR) is not necessarily interpreted as a lack of value. For example, a change in pathophysiology may occur independently of GFR but could be detected by MRI. Cross-sectional comparisons against histology are important, but heterogeneity of kidney disease may affect comparisons between a small core of biopsy tissue with a whole-organ quantitative MRI measure. Longitudinal studies will help determine the prognostic value of various MRI measures and establish the rates at which MRI measures change over time to inform their use for monitoring. We will focus on applications of kidney MRI in CKD, AKI, and kidney transplant (Fig 3), acknowledging the wider uses of MRI, for example, in kidney cancer, ADPKD, and hepatorenal syndrome.

Chronic Kidney Disease

CKD is common but of heterogeneous etiology, and it progresses at a variable rate through multiple mechanisms

Table 1. Quantitative Noncontrast Kidney MRI Techniques With Descriptive Outline, Pathophysiological Process That Can Be Measured, Associated MRI Biomarker, and Advantages and Pitfalls of Each Technique

MRI Measure	Descriptive Outline	Pathophysiology	Biomarker	Advantages	Pitfalls
Morphometry					
Volumetry[a]	TKV measured from T_2-weighted or mDixon scans. Cortex and medulla volume measured from T_1-weighted scan.	Kidney volume and its change over time is key in ADPKD. Kidney volume may also be important in CKD progression, AKI, diabetic nephropathy, renal transplants, and renal artery stenosis.	TKV (mL), cortex volume (mL) and thickness (mm), and medulla volume (mL).	Single breath-hold scan which can easily be collected across multisite and multivendor studies.	Manual segmentation time-consuming and prone to investigator error. Thus, automatic segmentation using deep learning is preferred, but these are sequence specific and require training and validation.
Tissue Composition					
Diffusion-weighted imaging (DWI)[a]	DWI acquires data at a range of b-values to measure water molecular motion in tissue and quantify in terms of the ADC. Using an increased number of low b-values, molecular diffusion (D), pseudo diffusion (tubular/vascular flow, D*), and perfusion fraction (F) are measured using the IVIM model.	DWI measures the free diffusion of water molecules in the kidney microstructure. This may be restricted, for instance, due to kidney fibrosis, cellular infiltration (inflammatory or tumorous) or edema, and changes in kidney perfusion and in water handling in the tubular compartment.	ADC (mm^2/s), molecular diffusion (D) (mm^2/s), pseudo diffusion (D*) (mm^2/s), perfusion fraction (F) (%).	DWI can be collected on all major MR vendor platforms. Provides information on both diffusion and perfusion.	Images are susceptible to artifacts especially at higher spatial resolution and high b-values due to a longer echo time. Since DWI collects data at multiple b-values, acquisitions are sensitive to respiratory motion which needs correcting through triggering and/or realignment. In DWI, the range of b-values defines which diffusion components (perfusion [D*,F] or molecular diffusion D) dominate the ADC value. IVIM requires relatively long acquisition times. Pseudo diffusion and perfusion fraction parameters have large coefficient of variation compared to ADC.
Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI)	Applies diffusion-sensitizing gradients along a number of prespecified directions to assesses the directionality of diffusion. This is quantified by the FA parameter and MD.	Any changes in the microstructure that lead to a change in the preferred direction of water diffusion are detected. This can occur due to tubular dilatation, tubular obstruction, or a loss in the organization of medullary tubules that can occur in CKD.	FA where 0 is complete isotropic diffusion and 1 is complete anisotropy, MD in mm^2/s.	Allows assessment of the degree of diffusion and thus organization of tissue structure and its loss.	Requires the acquisition of more images than basic DWI, leading to long acquisition times to collect data with sufficient SNR. Nonstandard methods for collecting multiple directions with respiratory triggering across MR vendors.

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Table 1 (Cont'd). Quantitative Noncontrast Kidney MRI Techniques With Descriptive Outline, Pathophysiological Process That Can Be Measured, Associated MRI Biomarker, and Advantages and Pitfalls of Each Technique

MRI Measure	Descriptive Outline	Pathophysiology	Biomarker	Advantages	Pitfalls
T_1 mapping[a]	T_1 is a tissue-specific relaxation time that can distinguish microstructural tissue composition. Absolute T_1 relaxation times are calculated using MOLLI, IR-EPI, or bFFE methods and are field strength dependent.	Changes in the molecular environment, for example, water content, fibrosis (due to the association of collagen with supersaturated hydrogel), and inflammation (interstitial edema, cellular swelling).	T_1 in ms for whole kidney, cortex, medulla, and CMD.	High SNR, high sensitivity to detect disease progression due to low coefficient of variation and large absolute change.	Quantification across vendors and sites must be validated using phantom measures. MOLLI T_1 measures can be sensitive to other factors such as B0 field effects, and care must be taken to use a lower flip angle to avoid errors due to field effects.
$T_{1\rho}$ mapping	Measures T_1 relaxation time in the rotating frame. This provides a measure of the decay of magnetization in the transverse plane in the presence of a spin-lock pulse that is applied parallel to the magnetization vector.	$T_{1\rho}$ is sensitive to low-frequency interactions between macromolecules and bulk water. There has been significant interest in application of $T_{1\rho}$ for measurement of collagen deposition in fibrotic tissue. $T_{1\rho}$ has consistently shown an increase in the presence of fibrosis.	$T_{1\rho}$ in ms.	$T_{1\rho}$ is sensitive to collagen deposition in fibrosis.	Not a standard sequence. Further research in this field is needed, including additional optimization of the performance of $T_{1\rho}$ for fibrosis imaging as well as reduction in acquisition times.
T_2 mapping[a]	Provides quantification of T_2 as a tissue-specific relaxation time parameter. Changes with tissue water content.	Changes in the molecular environment. T_2 is assumed to be more sensitive to the effects of edema and/or inflammation. Limited published data in human kidney disease to date.	T_2 in ms for whole kidney, cortex, medulla, CMD.	High SNR and high sensitivity to change in water content.	Quantification across vendors and sites must be validated using phantom measure and take into account B_1 field effects.

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MRI Measure	Descriptive Outline	Pathophysiology	Biomarker	Advantages	Pitfalls
Magnetization transfer imaging (MTI)	Probes the tissue macromolecule content based on the exchange of the magnetization between the 2 tissue proton pools: an unbound "free" water pool, which contributes to the bulk of the MR signal, and a restricted water pool "bound" to local tissue macromolecules. The frequency spectrum of the bound pool is broader than the free water pool. MTI applies an off-resonance RF pulse to selectively saturate bound protons. Magnetization exchange between the 2 pools reduces longitudinal magnetization of the free pool and the MR signal intensity. The magnitude of this effect depends on the bound pool fraction.	The fraction of large macromolecules or immobilized cell membranes in tissue has been shown to correlate with fibrosis. Higher MTR values indicate greater availability of bound tissue macromolecules (eg, collagen) to exchange magnetization with mobile water macromolecules.	MTR (%) is computed from 2 images with MT pulses ON and OFF. Bound pool fraction (%) is computed if a fully quantitative approach is used by varying the RF saturation offset and power and using a multicompartmental model.	The bound pool fraction has been shown to have utility in assessing renal fibrosis.	A fully quantitative MTI sequence that spans a range of frequency of saturation is not routinely available on MR scanners to implement. Estimation of the bound pool fraction requires complex multicompartmental modeling and has therefore mostly been limited to small-scale methodological studies.
Quantitative susceptibility mapping (QSM)	Uses phase images to provide information of magnetic susceptibility of the tissue by solving the ill-posed inverse problem.	Sensitive to molecular content, cellular arrangement, and tissue microstructure. It has been demonstrated to be sensitive to inflammation and fibrosis.	Susceptibility (ppm).	Has potential diagnostic value to study inflammation and fibrosis.	Optimization of the multiecho 3D gradient echo sequence is needed to reduce the scan time to an achievable breath-hold. Further work is required on analysis pipelines for QSM in the body.
Magnetic resonance elastography (MRE)	Uses external mechanical vibration to quantify organ stiffness on MRI.	Sensitive to renal stiffness driven by inflammation and fibrosis; for example, through the replacement of compliant cells with rigid matrix and cross-linking of matrix fibrils.	Kidney stiffness (kPa).	MRE-derived stiffness has been shown to associated strongly with microvascular inflammation.	Requires extra hardware in the form of a pneumatic driver, and software for spin-echo EPI MRE. Not routinely available in the clinical setting.

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MRI Measure	Descriptive Outline	Pathophysiology	Biomarker	Advantages	Pitfalls
Hemodynamics					
Phase contrast (PC) MRI[a]	Measurement of RBF in arteries and veins. Flow sensitized using bipolar gradients to modulate the phase of spins that flow with a uniform velocity in the direction parallel to the gradients. Global perfusion of the kidney can be estimated by dividing total RBF to the kidney by TKV.	Increased renal resistance to flow due to downstream microvascular obstruction, large-vessel arterial disease, or changes in systemic hemodynamics.	RBF (flux) (mL/s), renal artery velocity (cm/s), renal artery area (cm), global perfusion (mL/100 g/min).	RBF measurements can be collected on all major MR vendor platforms. PC-MRI has been technically validated both using flow phantoms and in vivo, showing good correlation with gold standard methods of RBF measurement.	The orientation of the measurement slice must be perpendicular to the vessel direction, which can be difficult to plan in the renal arteries. For this a good survey image, such as an angiography scan, should be collected to ensure that the plane is positioned correctly and before any bifurcations of the artery.
Arterial spin labeling (ASL)	A subtraction technique where arterial blood water is labeled (inverted) before imaging. Difference signals are determined by subtracting imaging data with and without labeling.	Cortical perfusion can be affected by a number of pathophysiological processes in acute and chronic renal disease.	Cortex and medulla perfusion (mL/100 g/min).	Provides noncontrast measure of perfusion of the kidney.	Renal ASL is not standardly available on all MR vendor platforms.
Oxygenation					
Blood oxygenation level dependent (BOLD)[a]	Deoxyhemoglobin is paramagnetic and shortens the transverse relaxation constant T_2* (ms), which is the inverse of the relaxation rate R_2* (1/s). Besides oxygenation, R_2* is also influenced by changes in hematocrit and tissue water content.	Changes in kidney oxygenation or changes in the microstructure of the capillary bed. Other factors such as hydration status, dietary sodium, and susceptibility effects also alter R_2*.	T_2* in ms or R_2* ($1/T_2$*). Typically assumed to represent measures of renal oxygenation.	BOLD measurements can be collected on all major MR vendor platforms.	Scanner-related and other nonrenal factors influence the BOLD signal. This can hamper the comparison of absolute R_2* values across sites. BOLD cannot distinguish between alterations in renal oxygen supply and alterations in renal oxygen consumption.

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MRI Measure	Descriptive Outline	Pathophysiology	Biomarker	Advantages	Pitfalls
T_2 relaxation under spin tagging (TRUST)	Spin tagging of blood, similar to ASL, is used to separate the signals from venous blood from surrounding tissues. This is collected at a range of T_2-weighted echo times. By measuring R_2 from venous blood signal the venous oxygenation (saturation) can be calculated.	Measures quantitatively blood oxygen saturation fraction.	Global oxygenation, renal venous saturation (%).	In contrast to BOLD, TRUST data are not influenced by scanner-related factors and edema effects.	A novel sequence more often used in the brain which is only available at limited research sites. TRUST is influenced by hematocrit. Validation studies are mainly from the central nervous system where oxygenation of the sagittal sinus is measured.

Abbreviations: ADC, apparent diffusion coefficient; ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; ASL, arterial spin labeling; bFFE, balanced fast field echo; CKD, chronic kidney injury; CMD, corticomedullary difference; 3D, 3-dimensional; EPI, echo-planar imaging; FA, fractional anisotropy; IR-EPI, inversion-recovery echo-planar imaging; IVIM, intravoxel incoherent motion; MD, mean diffusivity; MOLLI, modified Look-Locker inversion recovery; MR, magnetic resonance; MRI, magnetic resonance imaging; MTR, magnetization transfer ratio; RBF, renal blood flow; RF, radiofrequency; SNR, signal-to-noise ratio; TKV, total kidney volume.
[a]Current most established methods.

ncluding disease-specific injury, glomerular hemodynamic abnormalities, inflammation, and fibrosis. Despite progress in developing risk-stratification methods, more detailed individualized characterization is required to realize the goal of personalized medicine. This is particularly relevant with drug therapies that specifically address glomerular hyperfiltration[28] and kidney fibrosis,[28] with multiple anti-inflammatory therapies also in development. Multiparametric MRI has potential to characterize the dominant mechanism of injury in an individual with CKD to inform the choice of the optimal renoprotective approach and to monitor response to therapy.

To assess the relative importance of different MRI parameters, several cross-sectional studies have sought to evaluate multiple MRI parameters (summarized in Table 2). Direct comparison of studies is challenging, but the most consistent associations with CKD are with T_1 and ADC measures as well as cortical perfusion. In 2 studies, MRI parameters were combined in a multivariable approach. In one study, a model including T_1, ADC, and eGFR predicted interstitial fibrosis with good discrimination (area under the curve [AUC], 0.905 for ≥50% interstitial fibrosis).[29] In the other, a model including cortical perfusion and cortical T_1 predicted eGFR ($R = 0.87$) and log urinary protein-creatinine ratio (UPCR) ($R = 0.58$), and a model including T_1 and ADC predicted log UPCR ($R = 0.61$).[10]

Prospective studies include the evaluation of BOLD-MRI in 112 participants with CKD, 47 with hypertension without CKD, and 24 healthy controls. In a multivariable analysis, eGFR slope over 3 years was independently negatively associated with baseline 24-hour urinary protein excretion and kidney cortical R_2*, and positively associated with the slope of R_2* values in kidney parenchyma layers (ie, flatter R_2* slope was associated with more rapid eGFR decline).[30] In a study of 91 participants with CKD, multivariable analysis identified baseline T_2* (but not ADC), eGFR, and UPCR as independent predictors of eGFR slope over mean 5.13 years.[31]

However, not all studies demonstrate an association with MRI measure(s) and kidney parameters. In a post hoc analysis of a randomized trial of phosphate binder and nicotinamide, baseline ADC in 122 participants with CKD was associated with eGFR slope over 12 months, though not after adjustment for baseline albuminuria. Baseline R_2* was not associated with eGFR slope, and no significant differences were observed in MRI parameters over 12 months.[32] In a further study, medullary R_2* was the only MRI parameter independently associated with eGFR slope over 36 months in 24 participants. In serial MRI scans, medullary R_2* and cortical ADC decreased over 36 months, but cortical perfusion did not change significantly.[33]

Acute Kidney Injury

AKI is a heterogenous syndrome that affects >13 million people worldwide annually, conferring increased risk of

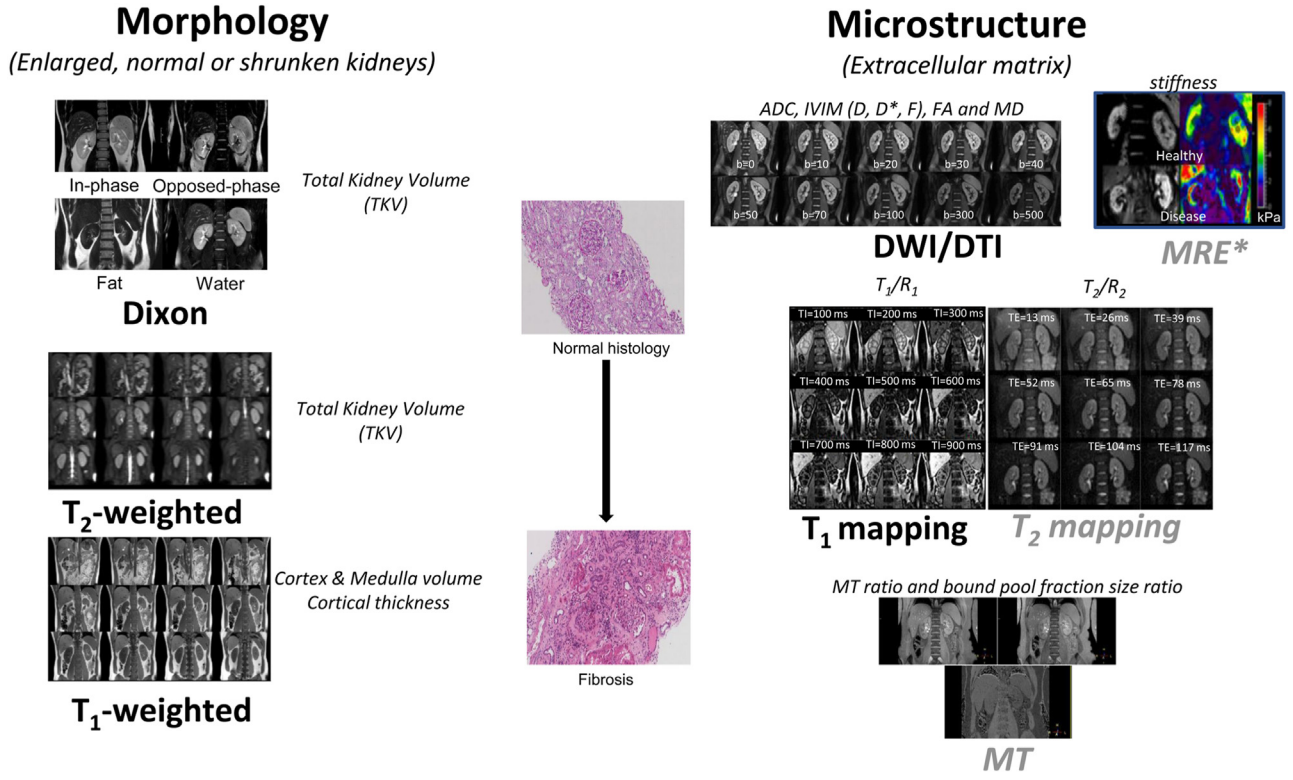

Figure 1. Quantitative MRI measures provided by morphology and microstructure. Measures are classified into those using core sequences widely available across MR vendors (shown in black) and more novel research sequences (shown in grey italic). Abbreviations: ADC, apparent diffusion co-efficient; D, molecular diffusion; D*, pseudo diffusion; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MD, mean diffusivity; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MT, magnetization transfer; T_1, longitudinal relaxation time to generated weighted images and mapping; T_2, transverse relaxation time to generated weighted images and mapping.

short-term and longer-term adverse outcomes.[34] In people who survive AKI, more than 20% develop CKD.[35-37] By identifying and quantifying the dominant processes of injury and maladaptive kidney repair, including capillary rarefaction, inflammation, and fibrosis,[38-41] potential applications of mpMRI include improving understanding of the etiology of AKI subphenotypes and the AKI to CKD transition. Further, MRI can reliably assess the renal medulla, an area that may play an important role in the pathogenesis of AKI.[42]

In separate cohorts of critically ill patients with sepsis[43] and COVID-19-associated AKI,[44] kidney blood flow (PC-MRI) and cortical perfusion (ASL) have been shown to be significantly reduced compared with similar patients without AKI and healthy controls. A further small study reported reduced cortical perfusion in acute presentations of glomelulonephritis and interstitial nephritis.[45]

In a study that evaluated patients 2 weeks after lung transplantation with DWI, cortical and medullary ADC values were lower in patients who developed AKI compared with patients without AKI and healthy controls.[46] They showed this ADC reduction was a result of both reduced perfusion and molecular diffusion, consistent with inflammation, tissue edema, or tubular injury.

In the first study of mpMRI in AKI, 9 patients with stage 3 AKI were scanned at the time of AKI and serially until 1 year later.[47] The changes in TKV (increased, possibly due to tissue edema), cortex and medulla T_1 (increased, suggesting edema/inflammation), and cortical perfusion (reduced) were substantial. Despite biochemical recovery, some MRI measures remained abnormal after 1 year.

It may also be expected that changes in kidney oxygenation occur in AKI, but studies using BOLD-MRI have not clearly demonstrated this. In part, this may reflect the additional factors that can affect BOLD-MRI measures; for example, edema and increased kidney volume may result in changes in BOLD-MRI measures in the opposite direction to hypoxia. In 1 study, BOLD-MRI measures did not correlate well with kidney function at varying time points up to 10 days after AKI[48]; in another, a wide range of R_2* values was observed without clear patterns.[49]

MRI measures may be useful in identifying subphenotypes of AKI that could relate to different pathological processes, and MRI performed during recovery may be a valuable method to quantify long-term damage after AKI that cannot currently be detected using GFR. However, the relatively few published clinical studies of mpMRI in

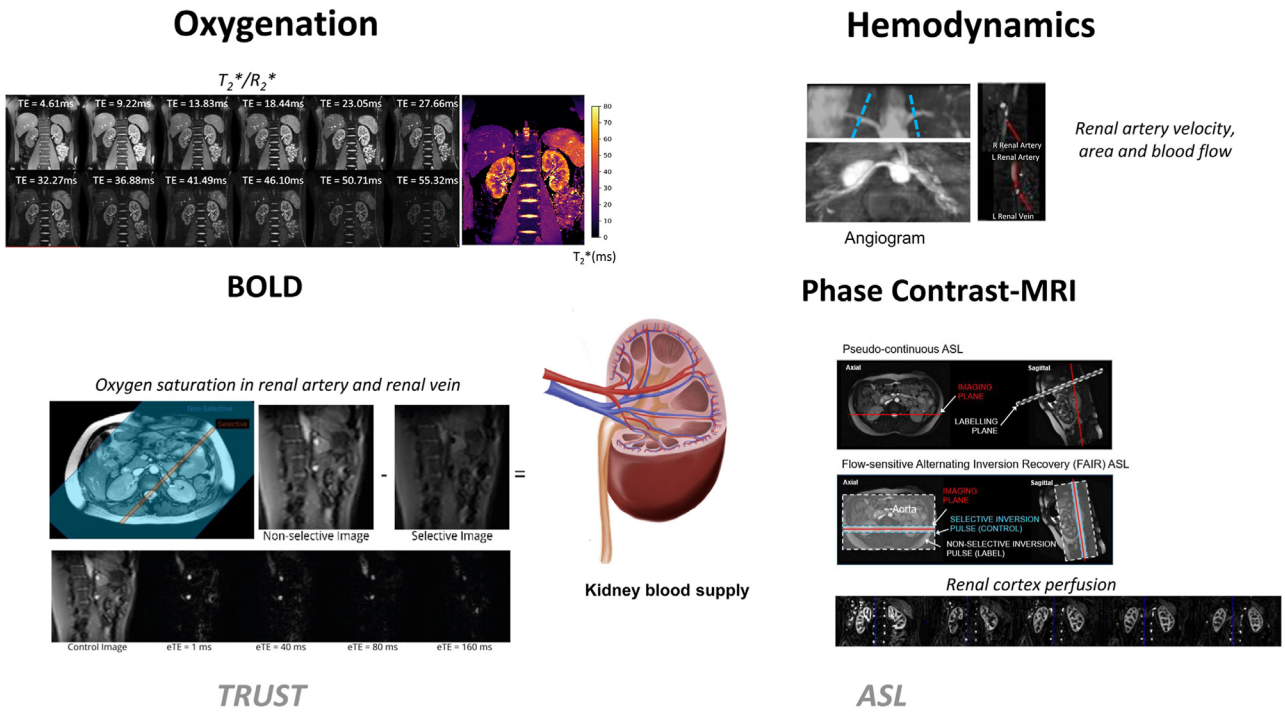

Figure 2. Quantitative MRI measures of oxygenation and hemodynamics. Measures are classified into those using core sequences widely available across MR vendors (shown in black) and more novel research sequences (shown in grey italic). Abbreviations: ASL, arterial spin labeling; BOLD, blood oxygenation level–dependent imaging; MRI, magnetic resonance imaging; TRUST, T_2 relaxation under spin tagging.

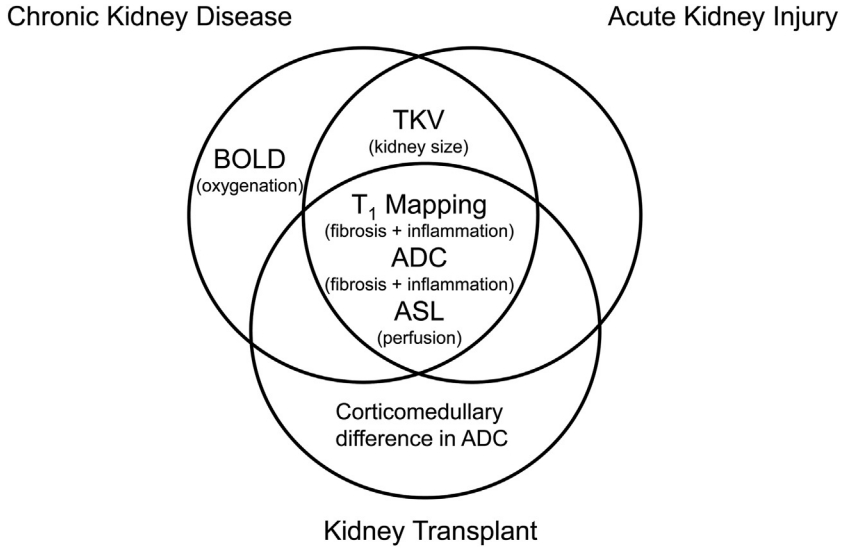

Figure 3. Venn diagram showing the MRI measures with strongest published evidence of clinical value for each clinical condition. ADC is the apparent diffusion coefficient, a measure derived from diffusion-weighted imaging (reflects movement of water molecules) that gives higher values in the setting of inflammation and lower values with fibrosis. BOLD indicates blood oxygenation level–dependent imaging, a measure of tissue oxygenation derived from the paramagnetic properties of deoxyhemoglobin. It is reported as T_2* or R_2* (the inverse of T_2*), where a higher R_2* and lower T_2* reflect lower tissue oxygenation. Corticomedullary difference indicates some MR measures providing better prognostication when the difference between cortical and medullary values is considered. To date the most robust evidence for this is ADC in the context of kidney transplants. T_1 mapping is longitudinal relaxation time, which gives higher values in the setting of fibrosis or inflammation. TKV, the total kidney volume, is useful for prognosis in adult polycystic kidney disease and is also increased early in acute kidney injury.

Table 2. Summary of Cross-sectional Studies That Have Evaluated Multiple MRI Parameters in Participants With CKD

	T_1	T_2	T_2*/R_2*	ADC	FA	RBF	Perfusion	MRE Stiffness
CKD (n = 46) and Transplant (n = 118); Berchtold et al[30]								
Difference vs HV	—	—	—	—	—	—	—	—
Correlates with GFR	Neg[a]	No	—	Pos[a]	—	—	—	—
Correlates with UPCR	—	—	—	—	—	—	—	—
Correlates with fibrosis	Pos[a]	No	—	Neg[a]	—	—	—	—
CKD (n = 22) vs HV (n = 22); Buchanan et al[10]								
Difference vs HV	Higher	—	No	Lower	—	Lower	Lower	
Correlates with GFR	Neg	—	No	Pos	—	Pos	Pos	
Correlates with UPCR	Pos	—	No	Neg	—	Neg	Neg	
Correlates with fibrosis	Higher	—	No	Lower	—	—	Lower	
CKD (n = 12) vs HV (n = 20); Dillman et al[66]								
Difference vs HV	Higher	No	No	Lower	—	—	—	No
Correlates with GFR	Neg	No	No	Pos	—	—	—	No
Correlates with UPCR	Pos	No	No	No	—	—	—	No
Correlates with fibrosis	No	No	No	No	—	—	—	No
Correlates with inflammation	No	No	No	Neg	—	—	—	No
CKD (n = 91); Sugiyama et al[32]								
Difference vs HV	—	—	—	—	—	—	—	—
Correlates with GFR			T_2* Pos	Pos	—	—	—	—
Correlates with UPCR			No	No	—	—	—	—
Correlates with fibrosis	—	—	—	—	—	—	—	—
IgAN (n = 16) vs HV (n = 16); Lang et al[67]								
Difference vs HV	—	—	No	Lower	—	—	—	Less stiff
Correlates with GFR	—	—	No	No	—	—	—	Pos[b]
Correlates with UPCR	—	—	No	No	—	—	—	No
Correlates with fibrosis	—	—	—	—	—	—	—	—
Type 1 Diabetes (n = 32) vs HV (n = 10); Seah et al[68]								
Difference vs HV	—	—	R_2* Lower	No	Lower	—	—	—
Correlates with GFR	—	—	R_2* Pos	Pos	Pos	—	—	—
Correlates with UPCR	—	—	—	—	—	—	—	—
Correlates with fibrosis	—	—	—	—	—	—	—	—
Diabetic Kidney Disease (n = 30) vs HV (n = 13); Brown et al[69]								
Difference vs HV	—	—	—	—	—	—	Lower	Less stiff
Correlates with GFR	—	—	—	—	—	—	Pos	Pos
Correlates with UPCR	—	—	—	—	—	—	—	—
Correlates with fibrosis	—	—	—	—	—	—	Lower	No

Abbreviations: ADC, apparent diffusion coefficient; CKD, chronic kidney disease; FA, fractional anisotropy; GFR, glomerular filtration rate; HV, healthy volunteer; IgAN, immunoglobulin A nephropathy; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; Neg, negative; Pos, positive; RBF, renal blood flow; UPCR, urinary protein-creatinine ratio.
[a]In this study the strongest associations were observed with corticomedullary difference in ADC and T_1, rather that absolute cortical or medullary values.
[b]Positive correlation with shear wave speed.

AKI[50] have been small in size and often have lacked longitudinal follow-up. Further studies are needed to substantiate initial findings and address the questions around optimal timing of mpMRI, choice of MRI measures, and their relation to different clinical outcomes.

Kidney Transplantation

A transplanted kidney is vulnerable to immune-mediated rejection and in addition may develop chronic allograft nephropathy through multiple mechanisms that include chronic rejection, calcineurin inhibitor toxicity, vascular disease, inflammation, and fibrosis. Multiparametric MRI has potential as a noninvasive method to detect acute rejection and assess chronic damage in transplanted kidneys to enable early intervention and improve long-term graft survival. Studies have compared MRI measures in transplanted kidneys with GFR and kidney histology (often the degree of fibrosis), and some have evaluated prognostic value for subsequent graft function decline.

Cortical perfusion has been shown to correlate significantly with GFR ($r = 0.59$)[51] and be lower in transplant kidneys with normal function compared with healthy control (native) kidneys. ADC and cortical perfusion were lower in kidney transplants with reduced function when compared with kidney transplants with normal function.[52] In one study of 29 transplant kidneys, absolute T_1 and ADC values correlated poorly with eGFR and fibrosis scores on

biopsy.[11] However, the corticomedullary difference of T_1 and ADC performed better. Furthermore, the ADC corticomedullary difference was negative in all transplant kidneys with fibrosis > 40% and positive in those with fibrosis < 40%. A subsequent study included 103 kidney transplant recipients with allograft injury and 20 with normal protocol biopsies.[53] Cortical ADC and perfusion were lower in those with allograft injury and correlated with fibrosis (ADC, $r = -0.77$; perfusion, $r = 0.77$). Cortical R_2* was higher with allograft injury, correlated with fibrosis ($r = 0.61$) and cortical perfusion ($r = -0.52$). All 3 MRI parameters evinced good to excellent discrimination in identifying fibrosis at thresholds of >25% and >50%.

In a longitudinal study, 19 kidney transplant recipients had serial kidney biopsies and MRI scans an average of 1.7 years apart.[54] Over this period, no changes in GFR were observed, but the degree of fibrosis on biopsy increased, ADC corticomedullary difference decreased, and the 2 were correlated ($r = 0.51$). Thus, the change in ADC was more sensitive at detecting increasing transplant kidney fibrosis than the change in eGFR. In a further study using similar MRI measures that included 154 kidney transplant recipients and 43 participants with CKD, ADC corticomedullary difference was an independent predictor of the primary outcome, 30% eGFR decline, or dialysis initiation after a median of 2.2 years; those with a negative value of ADC corticomedullary difference evinced a hazard ratio of 4.62 (95% CI, 1.56-13.67) independent of age, sex, eGFR, and proteinuria ($r = -0.56$).[55]

In a study that included 17 participants with stable kidney transplant function and 12 with chronic dysfunction and fibrosis, the MRI parameters of cortical diffusion and ADC, and cortical T_1 as well as T_1 corticomedullary difference, were able to discriminate between healthy allografts and chronic allograft nephropathy. A combination of T_1 and ADC improved discrimination (AUC = 0.94), and cortical T_1 and ADC predicted eGFR decline of >4 mL/min/year with moderate discrimination.[56]

MRI is now being used in clinical trials. In a small substudy ($n = 12$) investigating the impact of early conversion from cyclosporin-based to everolimus-based immunosuppression on outcomes after 12 months, serial MRI showed a decrease in ADC and increase in R_2* with continued cyclosporin but an increase in ADC and decrease in R_2* with everolimus.[57] Neural networks have been applied to improve the diagnostic potential of MRI parameters. In one study of 252 kidney transplant recipients, neural networks were developed that included MRI data only, clinical and biochemical data only, and a combination of both. Performance to correctly identify acute rejection, chronic allograft nephropathy, and stable kidney function was assessed. Discrimination for all 3 networks was moderate but improved with the combination of clinical, biochemical, and MRI data (AUC = 0.705, 0.733, and 0.745, respectively).[58]

The Future of Kidney MRI

Specificity of MRI Measures

Although it is not uncommon for individual kidney MRI measures to be equated with a specific biological process, such as T_2* with oxygenation or T_1 and ADC with fibrosis, it is important to recognize that each MRI measure is inherently nonspecific. The relationship between MRI measures and different pathophysiological processes is complex; for example, BOLD R_2* indirectly quantifies kidney oxygenation but is also strongly sensitive to kidney blood volume, kidney blood flow, tubular function, and microstructure.[59] BOLD findings interpreted as confirmation that hypoxia is a driver for CKD progression[31] could also be due to a reduction of perfusion, and tissue edema in AKI can compromise the interpretation of BOLD R_2*.[47]

A future priority must be to improve the specificity of MRI measures for biological processes and understanding of how MRI measures interact. This can be facilitated by collecting multiple MRI sequences in mpMRI studies to aid interpretation of the specificity of MRI measures (and their combination), along with associations with histology. The choice of MRI biomarkers depends on the clinical question, availability of MRI methods, and scan time allowed. For example, it may be possible to build a discrete signature for fibrosis from T_1, T_2, DWI metrics, and cortical perfusion that could potentially improve specificity when used in combination.

Clinical Translation of Kidney MRI

A number of challenges are currently delaying widespread clinical adoption of kidney mpMRI. Networking of researchers interested in kidney MRI is important to enable multicenter studies and to raise awareness of kidney MRI among clinicians. The member-led RENALMRI.org (https://renalmri.org) (formerly PARENCHIMA) initiative aims to support a kidney MRI community, with an aim of speeding up translation into clinical practice. Alongside this, the International Society of Magnetic Resonance in Medicine's renal MRI study group supports the development, application, and translation of preclinical and clinical MRI of the kidney.

A key challenge is building evidence of clinical utility at scale and with rigor. The first steps in scaling up the evidence is the creation of a more harmonized and standardized approach to data collection across MRI vendors and assessment of the repeatability of kidney MRI measures. MRI sequences are complex and depend on many parameters that must be optimized and fine-tuned separately. A major step toward the standardization of acquisition and analysis of mpMRI measures has been made by the UK Renal Imaging Network Acquisition and Processing Standardisation (UKRIN_MAPS) project,[60] across the 3 major vendors (Phillips, Siemens, and General Electric). A network of sites across the United Kingdom is now in place with a standardized mpMRI protocol, central image storage, and analysis and quality control procedures,

which has allowed the development of multicenter clinical studies. For example, the AFIRM (Application of Functional Renal MRI to Improve Assessment of Chronic Kidney Disease) study[61] is using the UKRIN_MAPS mpMRI protocol in a multicenter cohort study in 450 persons with CKD at baseline and 2 years. The results will define the relationship of MRI measures to clinical parameters, histology, eGFR, and progression of CKD over the subsequent 10 years and provide important information about rate and magnitude of change in MRI measures over time.

In addition to MRI acquisition capabilities, another limiting factor for the successful clinical application of mpMRI is the standardized and automatic data postprocessing. This includes methods for data handling, quality assurance, and processing and analysis, which have a significant impact on data interpretation. At the preprocessing stage, respiratory motion can lead to a considerable variation in the position of the kidneys, and standardized methods for dealing with registration are needed,[62] such as the open source model-driven registration tools for quantitative kidney imaging.[63]

For quantitative analysis, organ segmentation is required to assess TKV and define borders of the cortex and medulla. So far, manual segmentation has predominantly been used. However, for large-scale clinical use, this time-consuming and laborious method must be replaced by more efficient automated segmentation deep learning techniques.[4]

Automating the processing of kidney mpMRI data for rapid quantification of parameters is key to accelerate translation of biomarker candidates. Currently, few kidney MRI software packages exist; the UK Renal Imaging Network Kidney Analysis Toolbox (UKAT) is an open-source Python package integrated within WEZEL (an application for visualizing and analysis) for TKV, image registration, field mapping, relaxometry, and diffusion mapping. Intravoxel incoherent motion (IVIM) analysis tools are increasingly being offered by MRI manufacturers. More software tools are particularly required for renal ASL.

Finally, in view of the high cost of MRI, health economic analyses are required to assess the cost-effectiveness of MRI measures and the additional information they provide. An area where kidney MRI may have an immediate impact is in the evaluation of new treatments. One such example is the EMPA-Kidney trial[64] in which a substudy is using mpMRI to investigate the effect of empagliflozin on kidney and heart structure and function.[65]

In conclusion, evidence for the clinical application of mpMRI of the kidneys is growing rapidly. In parallel, the coordinated efforts to standardize image acquisition and automate analysis pipelines bode well for the translation of this promising technique into nephrology practice in the not-too-distant future.

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