Imaging the kidney using magnetic resonance techniques: structure to function

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Purpose of review
MRI can noninvasively assess the structure and function of the kidney in a single MRI scan session. This review summarizes recent advancements in functional renal MRI techniques, with a particular focus on clinical applications.

Recent findings
A number of MRI techniques now provide measures of relevance to the pathophysiology of kidney disease. Diffusion-weighted imaging, used in chronic kidney disease and renal transplantation, shows promise as a measure of renal fibrosis. Longitudinal relaxation time (T1) mapping has been utilized in cardiac MRI to measure fibrosis and oedema; recent work shows its potential in the kidney. Blood oxygen-level-dependent MRI to measure renal oxygenation has been extensively studied, but a number of other factors affect results making it hard to draw definite conclusions as to its utility as an independent measure. Phase contrast and arterial spin labelling can measure renal artery blood flow and renal perfusion without exogenous contrast, as opposed to dynamic contrast-enhanced studies. In general, current data on clinical use of functional renal MRI are restricted to cross-sectional studies.

Summary
Renal MRI has seen significant recent advances. Current evidence demonstrates its potential, and next steps include wider evaluation of its clinical application.

Keywords
arterial spin labelling, blood oxygen-level-dependent MRI, diffusion-weighted imaging, dynamic contrast-enhanced MRI, MRI

INTRODUCTION
In comparison with other specialities, advances in imaging techniques have been slow to translate in clinical nephrology. The potential of computerized tomography and MRI to provide improved structural characterization of the kidneys has long been appreciated. However, these modalities are used relatively infrequently outside of specific indications such as renovascular disease. Renal MRI in particular is an area of immense promise and there have been considerable recent advances, as previously summarized [1*]; the combination of highly detailed structural images combined with functional assessment of the kidney is particularly compelling (Fig. 1). In this review, we aim to summarize important recent developments in functional renal MRI, with a particular focus on potential clinical applications.

DETECTION OF FIBROSIS
Renal fibrosis can result from acute or chronic renal injury, and it is the degree of interstitial fibrosis and tubular atrophy that is often the most important determinant of long-term renal outcome [2]. Non-invasive characterization of fibrosis on a whole kidney basis would have significant utility in characterizing severity of disease, assessing recovery, and informing prognosis. A number of magnetic resonance (MR) techniques show promise in this area.
**Diffusion-weighted MRI**

Diffusion-weighted MRI (DWI) assesses Brownian motion of water within tissues, quantified by the apparent diffusion coefficient (ADC). Microstructural barriers, which differ depending on tissue composition, determine ADC. ADC may also be affected by factors such as tubular flow and capillary perfusion, which can be better distinguished using intravoxel incoherent motion to quantify pure diffusion ($ADC_D$). Diffusion tensor imaging (DTI) can assess the directionality of movement of water molecules, which provides information regarding the structural homogeneity of tissues, quantified by fractional anisotropy. As an example, greater structural homogeneity arises from the linear arrangement of medullary tubules as compared with the less ordered structure of the cortex.

A number of studies have used these techniques in patients with chronic kidney disease (CKD) and compared MRI measurements with renal function and renal biopsy. Li et al. [3] studied 12 healthy volunteers and 71 patients with CKD (all with chronic glomerulonephritis) who had renal DWI within 10 days of renal biopsy. Patients had their glomerular filtration rate (GFR) measured using isotope renography. More severe histological changes on renal biopsy correlated with lower ADC values. However, ADC values did not significantly correlate with GFR or serum creatinine concentration, and the usefulness of ADC values in differentiating renal pathology types was limited. Similar findings were reported by Zhao et al. [4], but in their study of 35 patients with CKD (25 who had renal biopsies), GFR as well as renal biopsy fibrosis scores correlated with ADC. Using DTI, a lower fractional anisotropy has been shown to be associated with the magnitude of GFR reduction and degree of fibrosis on renal biopsy in patients with glomerulonephritis and CKD stages 1–3, although there was less clear separation between CKD stages with fractional anisotropy as compared with ADC [5]. It should be noted that the varying grading systems to describe histological changes, as well as the choice of DWI b-values and directions, raise some concerns about comparisons across studies.

**KEY POINTS**

- A number of functional MRI techniques have been developed for the kidney.
- It is possible to measure renal artery blood flow, renal perfusion, oxygenation, and surrogates of fibrosis/inflammation noninvasively and without contrast agents.
- Current data show the potential value of these measurements in cross-sectional studies in CKD, AKI, and renal transplantation.
- Next steps include studies to demonstrate the clinical application and utility of these techniques.
A recent study applied DWI and DTI in 64 patients within 2 weeks of renal transplantation (33 with immediate graft function and 31 with delayed graft function) [6*]. Of these, 26 patients had transplant biopsies that were carefully analysed to quantify fibrosis, inflammation, and oedema. In patients with delayed graft function, ADC was significantly lower in the cortex and medulla, and fractional anisotropy lower in the medulla (the ability of DTI to detect changes in the medulla but not the cortex possibly reflected the greater structural homogeneity of the medulla). In those who had biopsies, both ADC and fractional anisotropy correlated positively with estimated GFR (eGFR) and inversely with degree of fibrosis, but interestingly a number of histological changes (inflammation, tubular injury score, capillary density, amount of oedema) had no relationship to ADC or fractional anisotropy. This suggests that although ADC and fractional anisotropy may be good noninvasive measures for fibrosis, these measures cannot differentiate between acute tubular injury and acute rejection. These data go some way to informing the mechanisms by which ADC and fractional anisotropy are reduced, implying the changes of fibrosis (e.g., increased cellular density and collagen) may be more important than changes in tubular function/flow or capillary perfusion.

Although there remain some knowledge gaps, particularly as to whether ADC or fractional anisotropy can inform long-term prognosis and whether findings of current studies are applicable to causes of CKD other than glomerulonephritis, taken together these studies suggest that DWI has a potential role in assessing degree of renal fibrosis.

**T₁ mapping**

The assessment of the longitudinal (T₁) relaxation time of tissue may provide an assessment of either fibrosis (because of association of collagen with supersaturated hydrogel) or inflammation (interstitial oedema, cellular swelling) [7]. T₁ values have been shown to correlate well with fibrosis and oedema in cardiac [8] and liver imaging [9]. In an animal model of acute kidney injury (AKI) induced by 30 or 45 min of ischaemia followed by reperfusion, Hueper et al. [10] demonstrated that the T₁ relaxation time of renal tissue increased significantly at days 1 and 7, and was associated with renal inflammation. At day 28, medullary and cortical tissue T₁ returned towards baseline values in milder AKI, but remained abnormal in the more severely affected animals, correlating with persistent inflammation and tubular injury scores. Changes in tissue T₁ at day 7 appeared to predict subsequent loss of kidney volume (as a marker of chronic damage), whereas histological changes did not. Although these results suggest the promise of the early characterization of AKI severity and prognosis, the method of inducing AKI in animal models is far removed from clinical AKI, and more human studies are now needed. In one recent study, Breidthardt et al. [11] demonstrated that chronic parenchymal damage as indicated by prolonged T₁ relaxation is a more prominent finding in cardiorenal syndrome as opposed to decreased perfusion.

**RENAOXYGENATION**

**Blood oxygen-level-dependent MRI**

Hypoxia has been implicated as a key process in the progression and failed recovery of many forms of acute and chronic kidney disease [12,13]. The emergence of blood oxygen-level-dependent (BOLD) MRI, which can provide an indication of tissue oxygenation, has therefore stimulated much interest. BOLD-MRI is relatively simple to implement, utilizing the paramagnetic effect that deoxyhaemoglobin exerts to shorten the transverse relaxation time constant (T₂*), which is also expressed as R₂* (1/T₂*). Higher R₂* (or lower T₂*) is an indicator of lower tissue oxygenation [partial pressure of oxygen (pO₂)]. Owing to their relative positions on the oxygen dissociation curve, BOLD-MRI is more sensitive at detecting changes in medullary as compared with cortical pO₂.

Despite the sometimes-demonstrated sensitivity of BOLD-MRI in animal models and healthy volunteers, clinical studies have produced inconsistent results. The large number of studies in CKD, diabetic nephropathy, and kidney transplantation, with some animal studies of AKI, are summarized in a comprehensive review by Neugarten and Golestaneh [14*]. Whereas some investigators have reported reduced oxygenation in CKD, a more recent study by Pruijm et al. [15] that compared healthy controls (n = 45), CKD patients (n = 95) and treated hypertensive patients (n = 58) found no differences in cortical or medullary R₂* between groups. On giving furosemide, medullary oxygenation increased in the healthy volunteers (a reduction in oxygen consumption results from inhibition of sodium transport in the ascending limb of the loop of Henle) with a slight and significant attenuation in this response in the hypertensive and CKD groups, respectively. Although these results may point away from hypoxia playing an important role in CKD, other explanations exist including BOLD-MRI being too insensitive (particularly as it is an indirect qualitative method which may be inaccurate if there is
heterogeneity in blood flow, oxygen delivery, and consumption across the cortex and medulla) or that an attenuated response to increased oxygen demand is more important than differences in baseline oxygenation. Overall, the strikingly different findings across the published literature make it difficult to draw firm conclusions. In part these differences may reflect issues related to both the origin and analysis of BOLD-MRI data, combined with a number of clinical factors that may affect BOLD-MRI image intensity other than oxygenation such as hydration status, age, haematocrit, dietary sodium, pH, or body temperature \([1^*,14^*]\). Pohlmann \textit{et al.} \[16^*\] demonstrated that \(T_2^*\) qualitatively mirrors changes in renal tissue \(PO_2\) but is also associated with confounding factors including vascular volume fraction and tubular volume fraction. At present, additional technical advances to unravel these links are required before the quantitative capabilities of BOLD-MRI can be integrated to clinical practice, as evidenced by the failure of BOLD-MRI to discriminate between different stages of CKD in 280 undifferentiated CKD patients \[17\]. As an example, quantitative susceptibility mapping is very sensitive to microstructure and chemical composition and can spatially resolve the source of the signal change in BOLD-MRI \[18\].

**\(T_2\) relaxation under spin tagging**

The relationship between the \(R_2\) tissue relaxation rate and oxygen saturation can be used to quantify the oxygen dependence of an organ or tissue. Using a method of \(T_2\) relaxation under spin tagging, it is possible to enhance separation of the blood and tissue signal. In the brain, combining this with measures of blood flow allows calculation of the global metabolic rate of oxygen \[19\]. Theoretically, it should be possible to apply the same methods to assess renal oxygen metabolism [renal oxygen metabolic rate (RMRO\(_2\))] providing an alternative to BOLD-MRI. Alternatively, recent studies have described the use of two-dimensional multiecho gradient and spin echo or triple echo asymmetric spin echo, combined with arterial spin labelling (ASL) to form spatial maps of RMRO\(_2\) \[20\]. To our knowledge, there are no clinical studies in this area at present.

**MEASURING BLOOD FLOW AND PERFUSION**

Changes in large vessel flow, as well as changes in tissue perfusion at the capillary level, have relevance to a number of different renal diseases, but importantly may also provide insights into efficacy of therapies. Measurement of renal perfusion can be separated into those techniques that require exogenous contrast agents [dynamic contrast-enhanced (DCE) MRI] and those that do not (ASL).

**Phase contrast MRI**

Phase contrast MRI is the current standard for the measurement of renal blood flow (RBF) in the renal artery and veins. Phase contrast MRI uses the velocity-induced phase changes of moving blood to quantify blood flow. Apart from in patients with significant anatomical variations, this technique has been shown to correlate well with a number of alternative measures \[21\]. In 11 patients with CKD (mean creatinine 215 ± 78 \(\mu\)mol/l) phase contrast MRI was used to measure RBF, and showed good reproducibility (coefficient of variation of 12.9%), with RBF being significantly lower in CKD patients compared with healthy volunteers \[22\]. Interestingly, the reproducibility of BOLD-MRI was better in the same cohort of patients (coefficient of variation of 8.0%). Prowle \textit{et al.} \[23\] demonstrated that it was possible to use phase contrast MRI to measure RBF in 10 critically ill patients with AKI and sepsis. Compared with healthy volunteers, blood flow was reduced. These pilot studies pave the way for additional research to understand changes in RBF across the evolution of acute and chronic kidney diseases, how this contributes to different disorders and assessing changes in RBF in response to therapy. Importantly, phase contrast MRI can also be applied in the aorta to provide a contemporaneous measurement of cardiac output, allowing assessment of RBF alongside systemic haemodynamics and cardiac function.

**Arterial spin labelling**

ASL uses magnetically labelled water protons in blood as a diffusible tracer, providing an alternative to exogenous intravenous contrast. Tissue perfusion is determined by subtracting control images (no labelling applied to arterial blood) from the labelled image (radiofrequency magnetic labelling). Animal studies have shown that ASL can detect changes in renal perfusion commensurate with the degree of induced ischaemia, which correlate with histological damage and change in renal function \[24\]. A number of recent studies have employed ASL in the assessment of kidney disease. In two separate studies, Rossi and Tan \[25,26\] both used ASL to compare CKD patients (\(n = 9\) and \(n = 5\), respectively) with healthy volunteers and found that cortical perfusion levels were lower in CKD. ASL has also been used in AKI; Dong \textit{et al.} \[27\] reported a reduction in both
cortical and medullary perfusion in a group of 11 patients with AKI mostly caused by intrinsic renal disease. Although the first human study in AKI, the clinical description of the AKI episodes was limited with a lack of clarity around the timing of MRI with respect to onset or peak of AKI, severity of AKI, and baseline CKD status. Furthermore, the cross-sectional nature of the study obscured the relationship between ASL measurements and renal recovery. In renal transplant patients, Heusch et al. [28] employed ASL in a heterogeneous group of 98 renal transplant patients who underwent MRI-ASL between 3 days and 11 years after renal transplantation. Despite the wide variation in patient selection, the results demonstrated that renal perfusion was lower in those patients with reduced eGFR. Importantly, this is one of the few studies with a prospective follow-up of at least 6 months. Twelve patients, all of whom had reduced eGFR, subsequently had graft loss and these patients had significantly lower baseline ASL measurements compared with those patients with a baseline eGFR less than 30 ml/min/1.73 m² who had stable transplant function. However, a lack of detail as to other differences between those with and without graft loss prevented a full assessment of how useful ASL-MRI may be to inform individual patient risk. Similar associations between reduced perfusion and GFR have been shown in a cross-sectional study of 62 renal transplant patients [29]. Finally, a study from our centre demonstrated the potential of MRI to assess response to treatment. Multiphase ASL was used to measure changes in renal perfusion in healthy volunteers in response to two different colloid fluid regimens [30].

It is promising that the clinical studies employing ASL have so far produced relatively consistent results and the technique has great potential. However, there are still technical considerations that need to be addressed before ASL can become more widely utilized, including the variation in ASL acquisition schemes that may prevent comparisons, differences in postprocessing, and complex analysis requirements.

**Dynamic contrast-enhanced MRI**

DCE-MRI can be used to determine renal perfusion and provide a direct measure of GFR but requires administration of an exogenous contrast agent. Zollner et al. [31] investigated the results of different pharmacokinetic models in a quantitative analysis of RBF and GFR in an animal model of AKI using deconvolution analysis and a two-compartment renal filtration model. Significant differences between control and AKI animals were detected by functional parameters (GFR and RBF), suggesting that this technique is useful to determine renal damage as evidenced by spatially resolved abnormal changes in renal tissue.

Opinion is still divided as to the extent to which these techniques should be utilized in patients with impaired renal function in view of the association of gadolinium and nephrogenic systemic fibrosis. Recent studies are therefore limited to those patients with less severe reductions in eGFR and are less numerous compared with those employing ASL. Woodard et al. [32] used DCE-MRI to automatically estimate the volume of cortex, medulla, collecting system, fat, and fibrosis based on the patterns of tissue enhancement following gadolinium administration. From a larger population study of the elderly in Iceland, 493 patients with an eGFR more than 30 ml/min/1.73 m² were randomly selected to undergo MRI of whom 40% had CKD. Total and segmental (cortical and medullary) volumes correlated with eGFR and albuminuria, and after adjustment for these factors DCE-MRI measurements associated with a number of risk factors for CKD progression. Although prospective data are still required, the authors concluded that this automated methodology could add to the assessment of patients with CKD and would be easily translated onto clinical scanners. However, the reluctance to use DCE-MRI in patients with more advanced CKD may limit generalisability.

**CHALLENGES AND NEXT STEPS**

A number of challenges remain prior to functional renal MRI techniques becoming commonplace in the clinical environment. Some are technical barriers to their development and translation. Many of the newer MRI techniques (such as ASL and T₁ mapping) are currently performed only in dedicated research centres because of the need for specialized scan sequences, intensive postprocessing, highly specialized support or in-house development. Some of the methodologies are not standardized and it is difficult to compare results from different centres. Solutions require a degree of unification in acquisition and processing between centres and across different MR platforms. Alongside this, collaborative infrastructure development for multicentre studies is needed around scan capabilities, data handling, quality assurance, processing, and analysis. Collaboration with manufacturers will also be key for the development of enhanced technology, such as the use of higher field strength MRI scanners to move renal imaging from 3 to 7 Tesla to gain significant improvements in signal to noise ratio and spatial resolution [33] or in-vivo sodium (²³Na) MRI [34].
Second, there is a clear need to design and deliver clinically led studies that incorporate prospective follow-up, so we can build on the existing evidence base that mostly comprises cross-sectional studies with relatively small patient numbers. There is a challenge to demonstrate how renal MRI can be used to improve diagnosis, assist prognosis, and assess response to therapies in patients with different forms of kidney disease.

Finally, we propose that the strength of renal MRI lies in the potential to deliver multiparametric image acquisition to simultaneously assess structure, function, blood flow, perfusion, and fibrosis. By doing so, not only is an inclusive assessment of the kidney made, but different functional techniques may provide complementary information to address some of the technical issues when performed in isolation. To illustrate this, one of our current studies evaluating MRI in patients with CKD is utilizing structural images, angiography, phase contrast, ASL, BOLD-MRI, DWI, and DTI within a 1-h scan protocol and relating MR results to histology, measured GFR and progression of CKD over 1 year (summarized in Fig. 1).

CONCLUSION

The recent, exciting advances in renal MRI illustrate that complimentary measures of kidney structure and function are now possible within a single MRI scan session that may provide unparalleled insights into the pathophysiology of renal disease in man. The techniques must now be tested in clinically led studies that demonstrate the value of this approach to clinicians; this will be essential prior to translation to clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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