Could MRI Be Used To Image Kidney Fibrosis? A Review of Recent Advances and Remaining Barriers

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Abstract
A key contributor to the progression of nearly all forms of CKD is fibrosis, a largely irreversible process that drives further kidney injury. Despite its importance, clinicians currently have no means of noninvasively assessing renal scar, and thus have historically relied on percutaneous renal biopsy to assess fibrotic burden. Although helpful in the initial diagnostic assessment, renal biopsy remains an imperfect test for fibrosis measurement, limited not only by its invasiveness, but also, because of the small amounts of tissue analyzed, its susceptibility to sampling bias. These concerns have limited not only the prognostic utility of biopsy analysis and its ability to guide therapeutic decisions, but also the clinical translation of experimental antifibrotic agents. Recent advances in imaging technology have raised the exciting possibility of magnetic resonance imaging (MRI)–based renal scar analysis, by capitalizing on the differing physical features of fibrotic and nonfibrotic tissue. In this review, we describe two key fibrosis-induced pathologic changes (capillary loss and kidney stiffening) that can be imaged by MRI techniques, and the potential for these new MRI-based technologies to noninvasively image renal scar.


The Importance of Fibrosis as a Final Common Pathway of Chronic Kidney Injury
Fibrosis is a final common injury pathway that drives CKD progression, for which no safe and effective therapies exist. Epidemiologic studies have consistently demonstrated that fibrotic burden is an important predictor of adverse renal outcomes (1). However, because kidneys are endowed with significant nephron reserve, renal fibrosis often progresses silently, with no overt manifestations such as increases in BP, serum creatinine, or urinary albumin excretion, until much of the kidney has already been replaced by scar.

Quantification of fibrotic burden during this “silent” scarring phase could theoretically identify patients at high risk for progression even before the development of significant renal dysfunction. As many new antifibrotic agents are being developed, this early identification might in the future enable intervention to prevent the subsequent development of renal dysfunction. Moreover, having the ability to monitor fibrosis progression could enable accurate tracking of the efficacy of these agents.

Even when patients present with impaired kidney function, measurement of renal fibrotic burden is still warranted, as clinicians currently have no means to separate the contributions of scarring from other reversible forms of injury, such as inflammation. Such distinctions are important, as quantification of irreversible scar burden could help predict the degree of renal function recovery after treatment of irreversible injury, and thus could guide: (1) whether potentially toxic therapies for reversible disease should be used, and (2) the timing of RRT initiation. For example, in the setting of renal allograft rejection, clinicians may make different decisions regarding the use of antirejection therapies (that come with risks of over-immunosuppression) for a patient with a kidney that is 15% scarred versus a kidney that is 85% scarred. Thus, being able to quantify renal scar burden may not only expedite the future development of new antifibrotic agents, but also aid in present-day clinical decision-making.

Kidney Biopsy, the Gold Standard for Renal Fibrosis Assessment, Is Fraught with Limitations
The only current way to examine renal scar burden is the histologic evaluation of needle biopsy samples. Although a biopsy is often performed to establish the cause of renal dysfunction, its use as a way to quantify scar burden is fraught with limitations. First, biopsy is associated with significant bleeding risk. Second, because biopsy samples are only 2 mm in diameter, even “satisfactory” samples represent much <1% of one kidney, and almost never include the medulla. As fibrosis is often heterogeneously distributed, renal biopsy analysis is thus inherently subject to sampling bias.

Given these safety and sampling concerns, patients are often reluctant to undergo a biopsy. For similar reasons, clinicians reserve biopsy for situations when noninvasive testing fails to provide a diagnosis, meaning that in many cases, fibrotic burden is never assessed. Thus, clinicians are often left without a critical piece of information that would help with management, resulting in undue reliance on nonspecific measures such as eGFR that provide no insight into the underlying renal pathophysiology. Importantly, these same safety
and sampling issues have also been major barriers to recruitment for studies of novel antifibrotic agents, impeding the clinical translation of promising new drugs. Taken together, although biopsy is the current gold standard for renal scarring assessment, it is imperfect from both a clinical and a research perspective. New, noninvasive methods that safely and accurately assess whole-kidney fibrotic burden are clearly needed.

Key Pathologic Features of the Fibrosing Kidney

Capillary Dropout and Reduced Microvascular Blood Flow
As the kidney scars, progressive capillary loss also occurs in parallel, leading to hypoperfusion of the renal parenchyma (2). An unfortunate consequence of this reduced microvascular blood flow is diminished oxygen delivery to tubular epithelial cells, which can lead to apoptosis, inflammation, and release of profibrotic stimuli that drive further fibrogenesis in a positive feedback loop (3). Thus, capillary dropout and hypoperfusion are not only key features of the fibrosing kidney, but also drivers of further fibrosis-associated injury (Figure 1).

Increased Kidney Stiffness
A second important, but often overlooked, feature of the fibrosing kidney is an increase in renal stiffness (Figure 1). Organ stiffening is driven by the replacement of compliant cells with rigid matrix (4), and is further increased by cross-linking of these matrix fibrils (Figure 1) (4). Interestingly, recent data suggest that fibrosis requires this stiffening to occur. Fibroblasts respond to TGF-β, a profibrotic stimulus, only when grown in a stiff environment similar to an injured, fibrotic organ, whereas fibroblasts grown on a soft, healthy organ-like surface fail to respond (5). These results suggest that kidney stiffening, like capillary dropout, is not just a manifestation of the fibrotic process, but also an important contributor to fibrosis progression.

Novel Gadolinium-Free Magnetic Resonance Imaging–Based Modalities for Kidney Fibrosis Imaging
Conventional magnetic resonance imaging (MRI) has generally failed to image fibrosis, in part because of the often diffuse distribution of scar tissue. Recent advances, combined with an improved understanding of fibrosis pathophysiology, however, have raised the exciting possibility of using MRI to image scar. At the forefront of these advances has been the use of gadolinium-enhanced MRI, which has become an accepted means of imaging cardiac fibrosis (6). Unfortunately, because of the risks of gadolinium in patients with renal dysfunction, these techniques have not been easily translatable to the kidney. Fortunately, other gadolinium-free techniques which show promise for renal fibrosis imaging have also been developed. Several articles have reviewed the use of a number of these gadolinium-free techniques in the kidney (7,8), including an excellent review of renal functional MRI by Ebrahimi et al. (9). Recognizing the importance of microvascular loss and renal stiffening

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Figure 1. | Multiple physical changes occur in the kidney as it scars. As the tubulo-interstitium scars, the deposited extracellular matrix fibrils compress and obliterate surrounding capillaries, resulting in reduced blood flow and oxygen delivery, diminished tissue water mobility, and an increased diffusion distance for oxygen to reach tubular epithelial cells. Progressive ischemic tubular injury leads to tubular cell apoptosis, and tubular atrophy/dilation. These processes reduce oxygen consumption, which can normalize blood oxygen levels in the chronically injured kidney, and induce the production of profibrotic stimuli that drive further fibrosis in a positive feedback loop. Replacement of compliant kidney cells with stiff, crosslinked extracellular matrix increases the stiffness of the scarring kidney, a phenomenon that also induces further fibrogenesis. Novel magnetic resonance imaging modalities can image a variety of these physical changes to provide estimates of whole-kidney scar burden.
to kidney fibrosis, in this review we will summarize recent advances in renal MRI that focus on these two key pathophysiologic processes.

**Diffusion MRI: Imaging the Mobility of Tissue Water Molecules**

Using magnetic field gradients to measure water molecule movements, diffusion MRI is a noncontrast technique that images both directional water motion such as blood and urine flow, and also random motion of intra- and extracellular water, via “diffusion weighting.” This weighting is reflected in the b value, with higher b values increasing the sensitivity to water motion. The most commonly used diffusion MRI metric is the apparent diffusion coefficient (ADC), which integrates both random diffusion and directed flow of water into a quantitative parameter. Recognizing that different diseases can alter random and directional water movement in divergent ways, two common methods to separate these phenomena have been developed. In the first, diffusion MRI images are acquired using low (<300 s/mm²) and high b values (>300 s/mm²) to estimate the contributions of directional flow and diffusion, respectively (10). In the second strategy, postprocessing techniques such as intravoxel incoherent motion imaging are applied. With these methods, investigators have estimated the individual contributions of diffusion (ADC_{diffusion}) and perfusion (ADC_{perfusion}) to the total ADC value. The remarkable sensitivity of diffusion MRI has permitted the imaging of diminished blood flow (reduced ADC_{perfusion}), increased cell density due to cellular infiltration and/or proliferation (reduced ADC_{diffusion} due to more cell membranes), and even disrupted cell integrity (increased ADC_{diffusion}). A further variant of diffusion MRI, called diffusion tensor imaging, measures water mobility along different axes using a parameter called fractional anisotropy. Disruption of ordered structures that favor water movement in certain directions, such as axons in the brain or tubules in the kidney, can thus be theoretically captured using diffusion tensor imaging. Given this multitude of applications, diffusion MRI has been extensively used in neuro-imaging, especially in the early detection of ischemic brain injury (11), and for tumor imaging (12).

The processes that lead to renal fibrosis, including microvascular loss, but also fibroblast proliferation and matrix deposition, would be expected to: (1) decrease water mobility, either by impairing perfusion or water diffusion (Figure 2); and (2) disrupt the ordered structure of the renal parenchyma. Multiple case-control studies have indeed reported lower ADC_{total} levels (13–17) and fractional anisotropy (18–20) in a variety of CKDs as compared with healthy controls, with ADC_{total}, ADC_{perfusion}, and fractional anisotropy falling with worsening renal function (Table 1) (13–15,17,20). When correlated with histology, ADC_{total} levels were found to decrease with progressive

![Figure 2](image-url)
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<td>↓ water mobility (as measured by ADC\textsubscript{total}) in patients with CKD (13–17) and with worsening fibrosis (13,15,21) ↓ microvascular perfusion (as measured by ADC\textsubscript{perfusion}) in patients with CKD (17)</td>
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fibrosis in mice subjected to unilateral ureteral obstruction (10) and allogeneic kidney transplantation (Table 1) (21). Similarly, several studies have found moderately strong correlations between increasing fibrosis and declining ADC in humans (Table 1) (13,15,21).

Although these studies suggest that reduced ADC\text{total} and ADC\text{perfusion} are modestly associated with scar burden and kidney dysfunction, their results are somewhat disappointing given the much stronger relationship between ADC and tissue injury in other settings (22). A potential explanation for this poorer performance is that, despite the simplistic model described above, multiple processes in the chronically injured kidney can affect ADC measurements in a dynamic and complex manner. Renal blood flow, for example, can be affected by intravascular volume and medications such as diuretics and renin-angiotensin-aldosterone system blockers. Because these parameters can vary between patients and within a patient over time, their influence on ADC measurements may be highly relevant.

To further complicate matters, the kidney, unlike other organs, contains a second fluid conduction system composed of tubules that carry urine. The effects of tubular urinary flow and water diffusion, which can change in response to hemodynamic, hormonal, or mechanical stimuli, have not been examined in detail, although a recent report suggested that tubular dilatation in the chronically injured kidney may increase ADC\text{diffusion} (23). A second reason why renal ADC measures have not correlated tightly with fibrosis may be that scar burden has historically been measured by biopsy. Studies correlating ADC values with biopsy fibrosis scores typically measured whole-kidney ADC, without matching to the area that was sampled (13,15). As fibrosis is often heterogeneously distributed, it is not surprising that these studies demonstrated only a modest correlation between whole-kidney ADC and biopsy-derived fibrotic burden (13,15). Future studies will be required to test whether ADC values taken from the area sampled by biopsy correlate more tightly with biopsy-derived fibrosis scores.

Although these limitations must be addressed, diffusion MRI offers a number of exciting, and as yet untapped, opportunities. First, unlike biopsy analysis, which samples a highly-restricted area, MRI can serially examine both kidneys in their entirety. Sequential ADC studies could thus potentially be used to analyze changes in the patterns of perfusion and diffusion as fibrosis progresses. Although ADC levels differ between the cortex and medulla likely because of differences in perfusion and/or tissue architecture (24), how ADC patterns evolve over time may shed light on where fibrosis develops in different types of CKD. Second, given that microvascular loss drives renal injury and fibrosis, whole-kidney changes in perfusion and diffusion may also permit better prediction of the risk of fibrosis and CKD progression. Future studies examining these potential applications of diffusion MRI are clearly warranted.

### Arterial Spin Labeling: Evaluation of Microvascular Perfusion

The success of diffusion MRI in measuring perfusion changes has fueled the development of other MRI-based techniques that measure blood flow. One method, called

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|                      |            | Kidney stiffness can be influenced by other factors besides fibrosis (e.g., renal blood flow, hydronephrosis, edema) | Kidney stiffness can be influenced by other factors besides fibrosis (e.g., renal blood flow, hydronephrosis, edema) | Measures both kidneys entirely | Noninvasive!

arterial spin labeling (ASL), has shown particular promise. In ASL, a combination of radiofrequency and magnetic gradient pulses is used to tag inflowing blood without gadolinium. Images are acquired with and without this tagging, and a subtraction between the two acquisitions provides information on the volume of tagged blood that flows into the imaged slice (25).

Application of ASL in animals (26) and humans (27) has demonstrated that this technique provides reasonable and reproducible estimates of renal cortical microvascular blood flow when compared with gold-standard measurements. In the setting of CKD, ASL-derived microvascular flow rates are decreased, with varying degrees of correlation with eGFR (Table 1) (28–30). Given that fibrosis is associated with capillary loss and impaired microvascular perfusion, the decrease in ASL-derived blood flow seen in CKD may be a surrogate measure of whole-kidney fibrotic burden, and may also predict progression risk. Correlation of ASL measurements with histologic injury has been limited, however, with only one study showing reduced cortical blood flow after ischemia-reperfusion injury in mouse kidneys (Table 1) (31). To our knowledge, no studies have examined whether ASL-measured renal blood flow reduction correlates with fibrotic burden.

Although renal ASL represents a potential addition to our fibrosis imaging armamentarium, further study is clearly required. In addition to more detailed imaging-histology correlation studies, a number of limitations need to be addressed. First, ASL measurements are plagued by poor signal-to-noise ratios and consequently low resolution, which limit their ability to separately assess the cortex and medulla, especially in chronically injured kidneys with cortical thinning. Second, ASL measures of medullary perfusion are difficult to perform because the medulla receives only 10% of total renal blood flow, making the ASL signal generally weaker than in the cortex. Moreover, much of the transient ASL label can decay before reaching the medulla because most blood flowing to the medulla must first pass through glomerular capillaries. Multiple acquisitions can be performed to improve signal measurement, but this prolongs scan time, rendering ASL more sensitive to respiratory motion artifact. This susceptibility is relevant, as ASL is a subtraction technique that requires the pretagging and post-tagging images to be superimposable. Respiratory motion compensation techniques have thus been developed to minimize patient motion between images. Finally, as with diffusion MRI, we need a better understanding of how ASL measures might be affected by hemodynamic and neurohormonal stimuli that can dynamically alter cortical and medullary blood flow independent of fibrotic burden.

**Blood Oxygenation Level–Dependent MRI: Evaluating Oxygen Delivery to the Kidney**

With reductions in blood flow, oxygen delivery is compromised, which in turn can lead to local changes in blood and tissue oxygenation. Taking advantage of this phenomenon, Ogawa et al. (32) described a technique sensitive to changes in blood oxygenation. Called blood oxygenation level–dependent (BOLD) MRI, this technique depends on the difference in magnetic properties between oxy- and deoxyhemoglobin. Hemoglobin in red blood cells becomes paramagnetic when deoxygenated, reflected by a decrease in the observed transverse relaxation time (T2*), which takes into account magnetic field inhomogeneity/susceptibility and is shorter than the inherent T2 of tissue. Acquiring images weighted by T2* thus allows estimation of tissue oxygen levels, and indeed BOLD MRI has been extensively validated as a measure of brain oxygenation (32).

Prasad et al. were the first to test BOLD MRI in the kidney, demonstrating that the medulla exhibits a lower T2* signal than the cortex (33), in line with the fact that the medulla operates in near hypoxic conditions. Later reports demonstrated reasonable correlation between T2* and directly measured tissue pO2 (34,35). Multiple studies have thus examined whether BOLD MRI could be used to non-invasively detect hypoxia in the injured kidney as decreased T2* signal. Somewhat surprisingly, although a number of early studies demonstrated that renal T2* is decreased in CKD (15,36,37), growing evidence now suggests that T2* is generally either preserved or even increased in both animals and humans with CKD, declining only in very late-stage disease (Table 1 and Figure 3) (38–45).

This normalization of T2* in CKD is likely due to multiple processes. First, although blood flow and oxygen delivery are reduced due to capillary dropout in CKD, the effects of this change can be offset. In particular, reduced glomerular filtration due to glomerulosclerosis leads to lower sodium reabsorption by downstream tubules. This phenomenon, combined with tubular cell apoptosis, decreases oxygen consumption, which counteracts the effects of reduced oxygen delivery. Thus, renal T2* will decrease only at very late stages of disease, when renal blood flow (and thus oxygen delivery) is extremely compromised. Second, a decline in hemoglobin concentration is often observed in CKD because of erythropoietin deficiency. With a decreased hemoglobin concentration, for any given renal pO2, absolute deoxyhemoglobin levels will also decrease, leading to increased T2*.

Finally, because of their effects on renal blood flow and tubular function, diuretics, non-steroid anti-inflammatory drugs, and renin-angiotensin-aldosterone system antagonists have all been shown to influence T2* (44,46–48). Taken together, these data suggest that BOLD MRI, on its own, may not be a useful measure of renal fibrotic burden. Although basal BOLD T2* measurements may not be that informative, changes in T2* after a pharmacologic challenge may be of more utility. Furosemide has shown particular promise as a pharmacologic stimulus, because it is commonly used and reduces medullary sodium reabsorption, a process that is energy-dependent and hence consumes oxygen. By blocking sodium reabsorption, furosemide increases renal oxygenation, primarily in the medulla. BOLD MRI detects this improved medullary oxygenation in young, healthy adults as an increase in medullary T2* (47). Interestingly, this furosemide-induced increase in medullary T2* was not seen in settings that can be associated with renal fibrosis, such as in elderly but otherwise healthy adults (47), patients with essential hypertension (40), CKD (40), or hemodynamically significant renal artery stenosis (Table 1) (43). Although in CKD the attenuated effect of furosemide may have been due to reduced diuretic tubular exposure, taken together these results suggest that medullary oxygen
homeostasis may be impaired with chronic renal injury. This altered oxygen balance, which is not apparent using standard clinical measures, suggests that tubules in the fibrotic kidney could already be dysfunctional. Future studies will be required to clarify whether furosemide-enhanced BOLD MRI could already be dysfunctional. Future studies will be required to clarify whether furosemide-enhanced BOLD MRI can detect early functional changes associated with renal fibrosis, especially in patients with CKD.

**Magnetic Resonance Elastography: As Kidneys Scar, They Stiffen**

As alluded to previously, organ stiffening is a common but under-recognized complication of fibrosis (4). This stiffening can be captured using elastography, a technique that involves the external application of a gentle compressive or vibratory force over the organ of interest, followed by imaging of the resulting deformation. When vibratory forces are applied, shear waves are generated in the underlying tissue that can be captured by motion-synchronized imaging. The velocity of wave propagation varies according to tissue stiffness, with stiffer, fibrotic tissues propagating more rapidly moving waves of longer wavelength than softer, healthy tissues (49). These wave differences are then converted into a stiffness map (Figure 4).

MRI-based elastography (MRE) techniques that capitalize on these principles were initially developed for imaging of the liver, a large, homogenous, superficial organ, with multiple studies demonstrating its utility as a measure of liver fibrosis (50,51). More recently, MRE has also been applied to deeper organs such as the kidney (Figure 4) (52–56). In initial animal studies, for example, MRE was used to detect kidney stiffening induced by nephrocalcinosis in rats, a condition that is associated with mild fibrosis (54), as well as medullary fibrosis induced by chronic renal artery stenosis in swine (56). Preliminary human studies have demonstrated that MRE-measured kidney stiffness in healthy volunteers correlates with stiffness values predicted from *ex vivo* biomechanical measurements of animal kidneys (52,57). Finally, in a small study of eleven renal transplant patients with varying degrees of renal dysfunction undergoing protocol biopsies, whole-kidney MRE stiffness scores were higher in patients with moderate versus mild fibrosis, although considerable variability existed (53). Taken together, MRE-derived kidney stiffness measurements show promise as a measure of scar burden.

Although these initial studies are certainly encouraging, a number of questions remain. First, unlike the relatively homogenous liver, the kidney is structurally very heterogeneous. Thus, whether MRE stiffness measurements taken from the biopsy-sampled pole (rather than the entire kidney) might correlate better with biopsy-derived fibrosis scores needs to be examined. Second, the kidney is subject to injury-induced processes besides fibrosis that can also affect stiffness, including renal blood flow changes, collecting system dilation, and edema formation. Whether MRE can detect fibrosis in these clinically relevant scenarios is not clear, and in fact initial studies in pigs suggest that reduced blood flow may interfere with MRE measurements (55). Thus, although MRE shows promise as a noninvasive tool to image renal fibrosis, further work is required to better characterize its utility and applicability.

**Other MRI-Based Techniques with Potential as Fibrosis Imaging Modalities**

Whereas our review focused specifically on MRI modalities that image either changes in microvascular perfusion/oxygenation or renal stiffening, MRI-based techniques that examine other properties of fibrosing tissue are also under development. For example, longitudinal relaxation time (T1), an MRI parameter that increases with progressive scarring, has been shown to correlate with cardiac fibrosis (58). Studies of this so-called T1 fibrosis mapping, however, have not been performed in the kidney to date. A modification of this T1 mapping approach that takes...
advantage of the different magnetic properties of water protons that are attached to macromolecules like matrix proteins (as compared with protons of free water molecules), called magnetization transfer imaging, has also been developed. Interestingly, a recent study has demonstrated that magnetization transfer imaging can detect renal fibrosis in a murine model of renal artery stenosis (59), although clinical application of this technique has not yet been reported. Finally, the recent development of nongadolinium contrast agents may enable the use of “molecular MRI” strategies that directly image scar by using contrast-tagged probes that bind to matrix proteins such as collagen (60). Clearly, many new promising strategies are being explored that deserve further study.

MRI offers a wide range of possibilities for the noninvasive imaging of whole-kidney scar burden, potentially overcoming the safety and sampling bias limitations of biopsy analysis. We have highlighted four MRI-based techniques that image the consequences of two important pathologic features of the fibrosing kidney: capillary dropout and renal stiffening. Each of these techniques has been validated for various uses in extrarenal organs such as the brain and the liver. Several issues specific to the kidney, including its anatomic complexity, respiration-induced motion, and a unique system of microvessels and tubules that is tightly controlled by multiple neurohormonal regulators, have made translation of these techniques to the kidney not a simple task. In recent years, however, a number of studies have demonstrated that these noncontrast MRI modalities may have the potential to image renal scar.

Moving forward, further validation studies need to be performed, beginning in animal models to enable comparison of MRI-based measurements with histologic assessment of the entire kidney, rather than using biopsy samples that are subject to sampling bias. The use of preclinical models would also permit a better understanding of the effects of potential nonfibrotic confounding variables such as fluid status and medications. In addition, as these MRI sequences can all be performed during a single, short imaging session, studies testing whether diagnostic accuracy is improved by combining these techniques into a multiparametric test should also be performed.

Fibrosis is major cause of chronic renal injury, which currently is quantified in a limited and invasive manner via renal biopsy histologic analysis. As described above, MRI holds promise as a novel modality to noninvasively image whole-kidney fibrotic burden, and thus could become an important research and clinical tool for the study of renal fibrosis.

Acknowledgments

This work was supported in part by an unrestricted research grant from Astellas Pharma Canada, a Collaborative Health Research Project Grant, a Physician’s Services Incorporated Foundation grant, a Kidney Research Scientist Core Education and National Training (KRESCENT) program Infrastructure Grant, and funding from the St. Michael’s Hospital Foundation.
Disclosures

S.G.S. was supported by an National Sciences and Engineering Research Council of Canada (NSERC) Canada Graduate Scholarship (Master’s). C.A.S. is the Canada Research Chair in Mechanobiology. D.A.Y. is supported by a Kidney Research Scientist Core Education and National Training (KRESCENT) program New Investigator and Canadian Diabetes Association Clinician Scientist Award, and is also a recipient of a Canadian Institutes of Health Research (CIHR) New Investigator Award. D.A.Y. and A.K. received an unrestricted research grant from Astellas Pharma Canada (Markham, Ontario, Canada), which supported the development of novel magnetic resonance imaging sequences for kidney fibrosis.

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*Received*: July 25, 2016 *Accepted*: December 19, 2016

Published online ahead of print. Publication date available at www.cjasn.org.