Prediction of Chronic Kidney Disease Progression by Magnetic Resonance Imaging: Where Are We?

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Chronic kidney disease (CKD) is characterized by a glomerular filtration rate (GFR) under 60 mL/min/1.73 m² or kidney damage as defined by structural or functional abnormalities other than decreased GFR [1]. CKD is a worldwide health issue, afflicting around 14% of the population [2]. This progressive and often irreversible process of renal function decline may reach an endpoint of end-stage renal failure, requiring renal replacement therapy. The capability to diagnose progressive CKD at an early stage and predict which patients are prone to progress is critical for timely therapeutic interventions. As such, researchers have expended enormous efforts in the development of novel biomarkers that may identify subjects with early CKD at risk of progression.

Chronic hypoxia has been recognized to play a pivotal role in CKD [3]. Tissue injury factors, like capillary drop-out, mitochondrial dysfunction, and inefficient oxygen utilization, may decrease renal perfusion and induce tissue hypoxia, which subsequently trigger tubular injury and interstitial fibrosis. These in turn damage adjacent

capillaries, glomeruli, and tubules, which exacerbates kidney hypoxia and fibrosis and sets in motion a vicious cycle leading to end-stage renal failure. Therefore, accurate assessment of renal parameters such as perfusion, oxygenation, and fibrosis may allow the gauging of CKD stage and potentially the prediction of CKD progression.

Magnetic resonance imaging (MRI) provides powerful tools for noninvasive assessment of renal function. Arterial spin labeling (ASL) uses endogenous blood as a tracer to measure renal perfusion. Blood oxygenation-level-dependent (BOLD) MRI probes renal oxygenation level by taking advantage of the paramagnetic property of deoxyhemoglobin, which increases the effective transverse relaxation rate R_2^* . Diffusion MRI measures tissue apparent diffusion coefficient (ADC), which is consid-

This editorial is based on the article: Cortical Perfusion and Tubular Function as Evaluated by MRI Correlate with Annual Loss in Renal Function in Moderate CKD.

ered to be lowered by renal fibrosis. In the current issue of the *American Journal of Nephrology*, Prasad et al. [4] evaluated the utility of these MRI techniques in the assessment of renal function and prediction of CKD progression in patients with diabetes and stage 3 CKD, an early stage CKD with important clinical implications. The investigators enrolled 41 patients with moderate CKD and 13 healthy controls. In the renal cortex, tissue perfusion by ASL was found dramatically decreased in CKD patients compared to the controls, but no statistically significant differences were observed in the ADC and R_2^* . The authors also investigated the predictive value of MRI parameters on annual loss in estimated GFR (eGFR slope), and reported moderate to good predictability of basal cortical perfusion and furosemide-induced medullary R_2^* changes. The strength of their study is in recruiting 41 patients with mild-moderate diabetic kidney disease. While their study raises some questions regarding the specificity of non-contrast-enhanced MRI techniques for renal assessment in CKD, it also sheds light on the promising application of MR renography for CKD management.

The ASL technique successfully detected a large drop in renal cortical perfusion in CKD, which was also significantly associated with the eGFR slope. These observations are in line with the notion that renal function loss is triggered by capillary dropout-induced perfusion insufficiency in CKD. Although ASL does not require exogenous contrast injection, the use of endogenous blood as perfusion tracer actually makes it a contrast-enhanced MR technique. Therefore, ASL offers high specificity to renal perfusion and was able to capture its early changes in CKD.

By contrast, diffusion MRI and BOLD-MRI are non-contrast enhanced, and therefore have limited specificity to their biological targets, that is, renal fibrosis and hypoxia. Specifically, the ADC is an overall measurement of the water mobility in tissue, which is literally affected by a composite of factors, including tissue perfusion, vascularity, tubular flow, and true water diffusion. Notably, the perfusion-induced water mobility has been reported to be an order magnitude larger than the true water diffusivity in human kidneys [5]. Although the authors were careful to use relatively high b values in this study, this does not preclude the potential influence of perfusion on diffusion measurement, especially considering the reported significant association between the ADC and renal perfusion [4]. Similarly, R_2^* by BOLD-MRI depends on many factors other than deoxyhemoglobin, such as renal perfusion, vascular volume, presence of inflammatory cells and

edema, hydration status, and anemia. Changes in these factors may offset the effect of deoxyhemoglobin in decreasing T_2^* [6]. This may account for the observation that BOLD-MRI is effective in measuring tissue hypoxia in acute kidney diseases with less confounding factors but is less consistent when applied in CKD [6]. Therefore, the mere fact that diffusion MRI and BOLD-MRI failed to detect renal fibrosis and tissue hypoxia in CKD does not rule out their contribution to the pathogenesis of early CKD.

One method to increase the specificity of non-contrast-enhanced MRI techniques in measuring renal function is to perform a stress test, such as water loading or furosemide challenge. This diuretic inhibits active solute transport in the thick ascending limb of Henle's loops, which results in decrease in medullary oxygen consumption and thus increases medullary oxygenation [7]. Hence, a robust response to furosemide mandates adequate delivery of furosemide to the tubules, but mainly indicates available mass of active medullary tubules engaged in solute transport. Prasad et al. [4] performed the furosemide stress test (FST) in CKD patients and reported a good correlation between the measured medullary ΔR_2^* and eGFR slope. Subsequent receiver operating characteristic analysis showed an area under curve of 0.88, indicating a good predictive power of FST on CKD progression. The reason that FST performed better than absolute R_2^* values may be related to the modest reliability and reproducibility of basal R_2^* alone measured by MRI. Interestingly, tubular function was found somehow disassociated from renal filtration function, as indicated by the poor correlation between medullary ΔR_2^* and eGFR [4], which warrants further investigation.

Nevertheless, the inability of BOLD-MRI to distinguish patients from controls might be related to the modest degree of CKD in these patients, with an eGFR value of merely 51.2 ± 12.6 mL/min/1.73 m². In contrast, a recent multicenter study showed decreased cortical and medullary absolute R_2^* and ADC in 127 patients with advanced CKD (eGFR 33.4 ± 7.2 mL/min/1.73 m²), despite a more mixed underlying etiology of CKD [8]. Whether the ability to detect these parameters in advanced CKD was related to the larger number of patients or the greater severity of CKD needs to be determined.

Taken together, MR renography offers exciting opportunities for monitoring progression of CKD. However, different MR techniques may show variations in their performance, depending on the specificity to their respective physiological targets and the severity of the

disease. Plausibly, a fall in renal perfusion precedes loss of oxygenation and development of fibrosis in CKD. Furthermore, the combination of FST and BOLD-MRI is useful in assessing tubular function and predicting CKD progression. Finally, as CKD progression is multifactorial, a combination of multi-parametric MRI and other clinical tests may provide more reliable assessment of CKD stage and prediction of future progression.

Acknowledgments

This study was partly supported by the NIH grant numbers DK100081, DK104273, HL123160, and DK102325.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- 1 Kidney Disease: Improving Global Outcomes, Group Work: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;vol 3, pp 1–150.
- 2 United States Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2016.
- 3 Nangaku M: Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. *J Am Soc Nephrol* 2006;17:17–25.
- 4 Prasad PV, Li L-P, Thacker JM, Li W, Hack B, Kohn O, Sprague SM: Cortical perfusion and tubular function as evaluated by magnetic resonance imaging correlates with annual loss in renal function in moderate chronic kidney disease. *Am J Nephrol* 2019;49:114–124.
- 5 Sigmund EE, Vivier PH, Sui D, Lamparello NA, Tantillo K, Mikheev A, Rusinek H, Babb JS, Storey P, Lee VS, Chandarana H: Intravoxel incoherent motion and diffusion-tensor imaging in renal tissue under hydration and furosemide flow challenges. *Radiology* 2012; 263:758–769.
- 6 Prasad PV: Update on renal blood oxygenation level-dependent MRI to assess intrarenal oxygenation in chronic kidney disease. *Kidney Int* 2018;93:778–780.
- 7 Ho KM, Power BM: Benefits and risks of furosemide in acute kidney injury. *Anaesthesia* 2010;65:283–293.
- 8 Prasad PV, Li W, Raj DS, Carr J, Carr M, Thacker J, Li LP, Wang C, Sprague SM, Ix JH, Chonchol M, Block G, Cheung AK, Raphael K, Gassman J, Wolf M, Fried LF, Isakova T; CKD Optimal Management with BInders and Nicotinamide (COMBINE) study group: Multicenter study evaluating intrarenal oxygenation and fibrosis using magnetic resonance imaging in individuals with advanced CKD. *Kidney Int Rep* 2018;3:1467–1472.