Non-invasive functional MRI techniques for early detection of kidney injury in chronic kidney disease: a positive step forward

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Introduction

In "*Capability of arterial spin labeling and intravoxel incoherent motion diffusion-weighted imaging to detect early kidney injury in chronic kidney disease*" (1), Mao *et al.* have explored non-invasive arterial spin labeling (ASL) and intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) as early detection tools for kidney injury in patients with chronic kidney disease (CKD) and normal estimated glomerular filtration rate (eGFR), notably to identify patients that requires evaluation with renal biopsy. The study involved 54 CKD patients, divided into groups with normal (≥90 mL/min/1.73 m^2) and abnormal (<90 mL/min/1.73 m^2) eGFR, along with 20 healthy volunteers. By analyzing parameters from ASL and IVIM-DWI images such as renal blood flow (RBF), true diffusion coefficient (D), pseudo-diffusion coefficient (D*), and perfusion fraction (f), the researchers highlighted the renal cortical f as the most powerful discriminator, outperforming eGFR in distinguishing CKD patients with normal eGFR from the control group. These findings suggest that ASL and IVIM-DWI hold the potential to become non-invasive and repeatable techniques for early-stage kidney injury assessment in CKD patients, particularly those with normal eGFR. This could lead to improved kidney disease prognosis and treatment strategies.

Scientific and medical background

CKD represents a significant public health concern with substantial costs, adverse outcomes, and detrimental impact on individuals' quality of life (2-4), afflicting around 14% of the population (5). However, less than 5% of patients with early CKD report disease awareness. However, early diagnosis and treatment are crucial for managing CKD and improving patient outcomes (6,7). Unfortunately, conventional biochemical markers may not accurately diagnose early-stage CKD, especially in patients with normal eGFR. Moreover, renal biopsy, the gold standard for CKD diagnosis, is an invasive and potentially risky procedure that is not easily repeatable in clinical practice (8).

In recent years, non-invasive techniques have emerged as promising tools for assessing renal function and detecting kidney injury, such as ultrasound localization microscopy, which has shown potential in assessing renal vascularization and glomeruli, the functional unit of the kidney, responsible for renal filtration (9,10). ASL and IVIM-DWI have shown potential in evaluating renal perfusion and microstructure

changes (11-17). ASL uses endogenous water molecules as tracers to measure RBF, providing valuable information on renal perfusion without requiring exogenous contrast agents (18). IVIM-DWI, based on a bi-exponential model of magnetic resonance (MR) signal intensity decay, assesses tissue capillary perfusion and water diffusion, reflecting microstructural changes in the kidney (15,19). However, for the time being, these techniques still need to be used in clinical routines.

Scientific contribution of the article

This scientific article delves into using ASL and IVIM-DWI to detect early kidney injury in CKD patients with normal eGFR. The study involved 54 CKD patients and 20 healthy volunteers, with the researchers analyzing various magnetic resonance imaging (MRI) parameters from the renal cortex, including D, D*, f (IVIM-DWI parameters), and RBF, thanks to ASL.

The results revealed significant differences in these MRI parameters among CKD patients with normal and abnormal eGFR and control group. Indeed, the renal cortical f and RBF values in the healthy volunteers were higher than those in the normal eGFR group ($P<0.05$). Moreover, renal cortical D*, f, and RBF values decreased significantly in the abnormal eGFR CKD group compared with the healthy volunteers ($P<0.05$) and normal eGFR CKD group ($P<0.05$). Nevertheless, renal cortical D values did not differ between the abnormal eGFR and normal eGFR CKD groups ($P>0.05$).

Then, a negative correlation was observed between the renal cortical D, D*, f, and RBF values and serum creatinine (SCr) and 24-hour urine protein (24 h-UPRO), while eGFR was significantly positively correlated with renal cortical D, D*, f, and RBF values (D: $r=0.299$, D*: $r=0.569$, f: $r=0.733$, RBF: $r=0.586$, all $P<0.05$). Remarkably, the study showed a positive correlation between renal cortical f and RBF values ($r=0.613$, $P<0.05$).

Finally, renal cortical RBF, D, D*, f values, and eGFR may identify normal eGFR CKD patients [area under the curve (AUC): 0.612 to 0.917]. The best-performing endpoint was renal cortical f value {[AUC: 0.917, 95% confidence interval (CI): 0.798–0.978]; (specificity: 85.0%, 95% CI: 62.1–96.8%), (sensitivity: 92.3%, 95% CI: 74.9–99.1%)} below the optimal cut-off value of 33.58%. Renal cortical f-value's AUC was significantly higher than eGFR's ($P<0.05$). Moreover, no significant differences were found between renal cortical RBF and f values in the AUCs.

The main results of this study demonstrated that IVIM-DWI and ASL enabled the noninvasive detection of early-stage kidney injury in patients with CKD, even those with normal eGFR. Nevertheless, renal cortical f-value was more able than eGFR to distinguish the CKD group with normal eGFR from healthy volunteers. This study showed that the IVIM-DWI could be a valuable tool to identify CKD at an early stage.

Strengths of the research

One of the primary strengths of this study lies in its prospective design, minimizing potential biases associated with retrospective studies. Then, including 54 CKD patients and 20 healthy volunteers enhances the study's credibility and provides a robust statistical analysis.

Moreover, the reproducible nature of ASL and IVIM-DWI makes them valuable tools for monitoring disease progression and treatment response by limiting the risks of subjectivity. This study's test-retest reliability of these parameters were good, consistent with previous studies (15,20). Moreover, this study showed good intraclass correlation coefficients of the cortical D (0.86; 95% CI: 0.66–0.94), D* (0.95; 95% CI: 0.87–0.98), f (0.92; 95% CI: 0.81–0.97), and RBF (0.86; 95% CI: 0.67–0.95).

The results of this study are also pleasing in this sense since the authors demonstrate that in their study population, there was no significant difference in SCr, 24 h-UPRO, and eGFR between the normal eGFR CKD group and the healthy volunteers. This includes the fact that common biochemical markers have not been able to identify patients with CKD at an early stage.

Moreover, the authors try to provide a pathophysiological explanation for their results. They speculated that the reduced D value reflecting water molecule diffusion limitation could be caused by fibrosis and increased cell density in the renal parenchyma. In contrast, D* and RBF values connected the mean RBF, and the f value reflected with the fraction volume of capillary blood flow could reflect blood perfusion in renal tissue, based on the study of Wang *et al.* (21). The latter demonstrated that renal cortex blood perfusion was linked to peritubular capillary density. At the same time, pathologic changes in CKD (tubular atrophy, glomerular sclerosis, interstitial fibrosis, arteriolar wall thickening with degeneration) could deteriorate peritubular capillaries and conduct renal cortical perfusion reduction.

Finally, free-breathing acquisition with motion

correction was used in this study. This might be more suitable than apnea and breath-triggered technology, mainly due to shorter scan time and more comfortable acquisition for patients, especially the elderly and children.

Limitations and future directions

Despite its strengths, the study has limitations that should be considered.

The research was conducted at a single center, which may limit the generalizability of the findings to a broader population. The study population also included only adults, limiting the generalizability of the results. Future studies with multi-center collaborations are needed to validate the results across diverse patient cohorts.

Then, the manual drawing of regions of interest for MRI parameter measurements could introduce potential bias and inter-observer variability. Utilizing automated or semi-automated techniques could enhance the reproducibility and reliability of the results.

Furthermore, while the study demonstrates the potential of ASL and IVIM-DWI in early CKD detection, it does not directly compare their performance with other advanced imaging modalities or biomarkers. Comparative studies could further establish the clinical superiority of ASL and IVIM-DWI over new methods.

Implications and impacts

The implications of this research are significant, as early diagnosis and treatment of CKD can significantly impact patient outcomes and reduce healthcare costs. Traditional biochemical markers may not accurately diagnose early-stage CKD, especially in normal eGFR patients. The study's use of ASL and IVIM-DWI as non-invasive tools to assess kidney function and perfusion could offer a promising alternative to invasive renal biopsy.

The high specificity and AUC values of the renal cortical f value obtained from IVIM-DWI make it a more effective discriminator for identifying early-stage CKD in patients with normal eGFR compared to traditional eGFR measurements and highlight its potential clinical importance.

These techniques may also have implications for public health policies. Indeed, early detection of kidney injury through functional MRI could prompt timely interventions and help reduce the burden of CKD on healthcare systems while offering a safer and more repeatable alternative to renal biopsy.

The study builds on and reinforces the work of previous studies in the field. Indeed, it has been demonstrated that IVIM-DWI could assess renal function in CKD (15,22) and renal fibrosis (22-24) and could evaluate renal graft function (21,25). Moreover, ASL may access kidney perfusion in CKD (26) and assess renal pathologic alterations in acute kidney injury (27). They could aid in noninvasively distinguishing renal allograft fibrosis degree and predicting long-term allograft dysfunction, according to Yu *et al.* (28); it could also provide insight into tumor biology, as demonstrated by Laothamatas *et al.* (29).

It should also be noted that these techniques have also shown potential in diagnosing and evaluating pathologies in other organs, such as the brain (30-33) or otolaryngology (34). This research and advances in different organs can have benefits in all disciplines.

Positioning

ASL and IVIM-DWI seem to be able to detect subtle pathologic changes in the kidney. The most crucial strength is the potential for early intervention. Even in patients with normal eGFR, these techniques could provide valuable insights into the functional and structural shifts occurring during the initial stages of CKD. Another significant advantage lies in their noninvasive and reproducible nature.

ASL and IVIM-DWI could serve as complementary tools in the clinical evaluation of CKD patients, providing valuable information that traditional biochemical markers may miss. They may open new avenues for proactive and personalized patient care. However, it is essential to acknowledge the study's limitations, such as the relatively small sample size and single-center design, which may limit the generalizability of the findings. Thus, further multi-center studies with larger cohorts are needed to validate these findings and establish standardized protocols for ASL and IVIM-DWI.

Conclusions

This scientific article unveils the potential of non-invasive ASL and IVIM-DWI techniques. The study's findings suggest that these tools could identify early-stage kidney injury in CKD patients, particularly those with normal eGFR. Renal cortical f emerges as a particularly effective discriminator, outperforming traditional eGFR measurements in distinguishing CKD patients from healthy

volunteers. These non-invasive imaging techniques may improve prognosis and treatment strategies. Despite some limitations, including a relatively small sample size and single-center design, this study lays the foundation for further research. Future studies with larger and more diverse populations and the exploration of standardized protocols are required to validate these findings fully.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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