Imaging as a Noninvasive Tool for Evaluating Interstitial Fibrosis in Kidney Allografts

Emilio D. Poggio

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Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio

Correspondence:
Dr. Emilio D. Poggio, Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk Q7-103, Cleveland, OH 44195. Email: poggioe@ccf.org

Interstitial fibrosis is an almost universal histologic finding in progressive kidney parenchymal disease, both in native and transplanted kidneys. When established, it is a nonreversible lesion. In kidney transplantation, chronic kidney allograft dysfunction is clinically characterized by progressive loss of kidney function associated with ongoing histologic damage in the form of deposition of extracellular collagen (interstitial fibrosis) and loss of functional structures such as kidney tubules (tubular atrophy) and microvasculature, in the presence of glomerulosclerosis and or transplant glomerulopathy (1). The simultaneous finding of interstitial fibrosis and tubular atrophy is commonly referred as IFTA. This entity is the common pathway to several causes of injury and when present it is a chronic lesion that is generally progressive and nonreversible. In kidney transplantation, both immune- and nonimmune-mediated mechanisms of injury sustained over time eventually lead to IFTA (2). IFTA is important because it is associated with poor clinical outcomes (3). The Banff classification includes IFTA as one of its pathologic components to define chronic allograft nephropathy, the histologic findings of chronic allograft dysfunction. In chronic active T cell–mediated rejection, inflammation in areas of IFTA also helps define the disease. The degree of IFTA is central to the grading system of these entities (4). On the basis of the Banff 2017 criteria, interstitial fibrosis is graded independently (none, 0%–25%, 25%–50%, and >50%) but has histopathologic implications when considered together with tubular atrophy (also graded as none, 0%–25%, 25%–50%, and >50%) (4). Therefore, IFTA has diagnostic and prognostic value.

In this issue of *CJASN*, Wang *et al.* (5) studied 103 kidney transplant recipients who underwent a for-cause biopsy and 20 kidney transplant patients with stable kidney allograft function and a normal biopsy. These patients simultaneously had a functional magnetic resonance imaging (MRI) to study how this noninvasive approach correlated with allograft interstitial fibrosis. In native kidneys, functional MRI has been shown to noninvasively assess kidney fibrosis through the assessment of three functional measures (6,7). First, blood oxygen level–dependent imaging detects altered deoxyhemoglobin levels and serves as a surrogate marker of tissue oxygenation. It correlates with nonactive functional tissue like fibrosis because less cellular activity requires less oxygen to maintain function (cortical hypoxia). Second, diffusion-weighted imaging quantifies tissue water molecule free movement, which is found with deposition of extracellular collagen and microstructure disorganization, as noncellular matrix contains less water. Finally, arterial spin labeling assesses inflowing blood to kidney tissue, and serves as a surrogate for tissue microvascular perfusion. Taken together, all three functional measures obtained from MRI were hypothesized by the investigators to estimate kidney allograft interstitial fibrosis. In this study, Wang *et al.* (5) show that functional MRI measures highly correlate with histologic findings and degree of interstitial fibrosis, therefore the authors suggest that this noninvasive modality could serve as a tool to assess chronic allograft injury.

For at least the past two decades, there has been an increasing interest in the search for noninvasive biomarkers in kidney transplant (8). There are various ways biomarkers can be classified and useful to the clinician. One such approach is, for example, to use techniques to detect molecular changes in blood or urine that denote alloimmune-mediated injury. Alternatively, one could divide noninvasive tools, independent of the technique utilized, on the basis of their ability to predict, diagnose, or prognosticate an important clinical condition. Predictive noninvasive tools or biomarkers are those that provide information on conditions not yet clinically evident (subclinical or in very early stages of the pathophysiologic process) or detectable using standard laboratory tools. Any information derived from these biomarkers provides the clinician with an earlier opportunity to diagnose and treat a particular condition. Test sensitivity is important in this case. Diagnostic noninvasive tools or biomarkers are those that lead to the diagnosis of a particular condition using an approach that is less invasive, has less adverse events, or it is less expensive than the gold standard. In these cases, test specificity and positive predictive value are needed. Finally, when considering prognostic tests or tools, the clinician is looking for information that will help determine if a particular intervention will lead to a desire outcome, or whether a particular finding will help the clinician infer outcomes and provide an opportunity to plan future steps in the

care of the patient. Kidney fibrosis determination by functional MRIs would fit in this last category.

The current emphasis in noninvasive testing is aimed at detecting acute pathophysiologic processes with potential for intervention, and this interest is mostly in developing biomarkers in blood and urine samples. Imaging is a growing field in medicine, especially driven by advances in technology. MRIs are now a common procedure, yet not routinely used in the setting of kidney transplantation. Other forms of imaging, such as kidney ultrasonography and kidney computed tomography, are more frequently utilized. These imaging modalities are performed to look for anatomic abnormalities in the setting of other clinical signs, such as kidney allograft dysfunction, urological pathology, and allograft tenderness. Magnetic resonance angiography is reserved for the evaluation of kidney transplant vasculature. Likewise, kidney allograft biopsy is also a relatively common procedure. It is frequently used to evaluate either acute allograft dysfunction or evidence of parenchymal kidney disease such as hematuria or proteinuria. Recurrent glomerular disease, virus-induced nephropathies (*i.e.*, BK nephropathy), calcineurin inhibitor nephrotoxicity, and alloimmune-mediated injury (*i.e.*, any type of rejection, acute and chronic) are often diagnosed by this approach. Although kidney allograft biopsies are more frequently used to evaluate acute or subacute graft dysfunction, in some occasions they are also used to evaluate unexplained chronic allograft dysfunction. Kidney allograft biopsy is an invasive procedure that can be costly and is associated with complications, albeit at a lower rate than in native kidneys (9). It is also subject to sampling errors and interobserver visualization bias (10). Hence, although kidney allograft biopsies are commonly performed in transplant recipients, they are reserved mostly for the diagnosis of acute active events that have potential for treatment. Regardless of the limitations of this invasive procedure, it remains the gold-standard approach for diagnosis of most treatable conditions in kidney transplantation.

MRI has been used to study the anatomy of the kidney and its vasculature in various settings, such as in the evaluation of living kidney donors and polycystic kidney disease. Another potential of functional MRIs is the study of kidney fibrosis as shown by Wang *et al.* (5). Despite initial work, functional MRIs have not yet entered the clinical arena. Several reasons explain this, such as small study sizes, lack of reproducibility, and inconsistent correlation of findings with the gold-standard approach, which is kidney histology in the case of interstitial fibrosis (7). This study is another step toward incorporating functional MRIs into clinical practice. In the way it has been applied and proposed, a functional MRI would be very useful as a prognostic tool, considering its ability to provide information about the degree of fibrosis. Lack of kidney fibrosis would reassure the patient and clinician by prognosticating a favorable clinical outcome. Although we currently lack therapeutic options in kidney transplantation to mitigate progression of kidney fibrosis, having this information could help to plan retransplantation when needed, in a timely manner. Although MRI is considered a noninvasive test and is available in most tertiary care centers where transplantation is performed, it remains an expensive procedure. Regardless, it is important to expand noninvasive testing methodologies such as functional MRIs, an approach that could eventually complement other noninvasive tools. Further research is needed in the field, but the introduction of functional MRIs in kidney transplant to evaluate kidney allograft fibrosis could help provide more comprehensive and individualized care for our kidney transplant recipients.

Disclosures

Dr. Poggio reports personal fees from CareDx and Renalytix outside the submitted work.

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