Importance of Confounding Factors in the Evaluation of Surrogate Measures for Kidney Transplant Fibrosis

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Death-censored kidney transplant survival has significantly improved over the last 30 years; however, this is primarily as a result of decreased graft failure in the first year post transplantation, with failure rates beyond this period remaining relatively unchanged (1). Interstitial fibrosis and tubular atrophy (IFTA), along with global glomerulosclerosis, represents the final common histologic pathway of most causes of kidney transplant failure, including rejection, infection, drug toxicity, and recurrent and de novo disease. Determining the extent of IFTA is thus a critical component of the long-term management and risk stratification of kidney transplant patients (2).

The current gold standard for IFTA assessment remains kidney transplant biopsy histology (3), which is an invasive procedure associated with a small but significant risk of complications, including hemorrhage and graft loss. Therefore, there is a need for the development and implementation of novel noninvasive methodologies for evaluating IFTA in kidney transplant patients. Diagnostic imaging techniques provide a promising opportunity for the surrogate measurement of parenchymal scarring in both native and transplant kidneys, with various ultrasound and magnetic resonance imaging–based modalities, including magnetic resonance elastography (MRE), recently being investigated (4–11). However, these studies have shown conflicting results, with some reporting a positive correlation between surrogate and histologic measurements of kidney fibrosis, and some reporting no significant correlation.

In this issue of Kidney360, Chaveau et al. present the results of a prospective, single-center, 55-patient study comparing MRE-derived kidney transplant stiffness with established biopsy-based measures of renal allograft fibrosis, including Banff c5 score, percent quantitation, and digital pathology image analysis (12). Although they reassuringly observed strong correlations between the histologic methods of fibrosis evaluation, there was no significant correlation between MRE-derived stiffness and histologic fibrosis. In fact, their results suggest the opposite trend from what was expected—that the kidney may soften with progressive nephron loss. There was also no significant correlation between MRE-derived stiffness and subsequent kidney transplant function, represented by eGFR slope, although this was also the case with the gold standard histology methods of fibrosis quantification. These results support the findings from previous smaller studies suggesting that MRE-derived evaluation of kidney transplant stiffness is currently of limited clinical utility.

Of note, Chaveau et al. measured kidney stiffness by MRE in both the cortex and the medulla, whereas histologic fibrosis was only assessed in the cortex, as per current Banff guidelines (3). Although previous MRE studies have used a similar approach (8,9), others have attempted to limit MRE measurements to the cortex through manual user-defined regions of interest (13–15). Although anatomically appropriate, this method introduces the potential for interobserver reliability, particularly given the limited spatial resolution of MRE images relative to kidney cortex thickness. Furthermore, Kennedy et al., who utilized this methodology to evaluate MRE in kidney transplant patients, did not show improved correlations with the manual cortex-restricted segmentation approach (15).

Despite the negative result, the study by Chaveau et al. is a valuable additional contribution to the field. Nevertheless, there are some important limitations to note that can hopefully be addressed in future related work by these and other authors. These shortcomings include the need for further validation of the MRE technique to allow for improved understanding and correction for factors that may confound MRE-based kidney transplant stiffness. The potential significance of unknown confounding factors is highlighted by the highly variable MRE results observed between patients without significant fibrosis on histology. As suggested by the authors, this unexpectedly high variability between patients may be related to acute changes in kidney blood flow, which may be influenced by blood pressure, hydration status, food intake, and body mass index, among other potential factors. Therefore, it would be important for future studies to at least document if not correct for these variables so that the potential limitations and utility of MRE can be better evaluated.

If utilizing universal thresholds for MRE-based kidney transplant fibrosis is ultimately determined to be unfeasible, there may still be clinical utility in following relative changes within individual patients over time. However, in the study by Chaveau et al., MRE was only performed once per patient, which unfortunately precludes assessment of the potential role of
this alternate approach. Future studies would benefit from the inclusion of serial measurements, with correction for potential confounding variables, so that the significance of intraindividual variability and the utility of relative changes over time can be fully evaluated.

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References

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See related article, “Magnetic Resonance Elastography as Surrogate Marker of Interstitial Fibrosis in Kidney Transplantation: A Prospective Study,” on pages 1924–1933.