Kidney Medicine

Cognitive Function and Kidney Transplantation: Putting Current Data into Clinical Perspective

Aditi Gupta

Cognitive impairment is highly prevalent in patients with kidney failure treated by dialysis, affecting up to 87% of patients receiving maintenance hemodialysis.[1] Patients with kidney failure treated by dialysis have

Related article, ● ● ●

nondialysis–related traditional risk factors for dementia such as hypertension, metabolic syndrome, diabetes, and smoking, as well as dialysis-specific factors, such as anemia, uremic metabolites, metabolic acidosis, mineral bone disease, and intradialytic hypotension.[2]

In this study, Binari et al[3] assessed cognitive function in 32 patients with kidney failure at baseline (pretransplant) and at 3 months and 1 year after kidney transplant. They used the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) to assess global cognitive function and Trail Making Test Parts A and B to assess attention and executive function. The RBANS scores did not change significantly after transplantation. Performance on the Trail Making Test Part B improved at 3 months posttransplant, and this improvement persisted at 1-year posttransplant. Trail Making Test Part A performance also improved at 1 year compared to baseline. Although the change in specific neuropsychological tests may not corroborate with some other prospective studies observing changes in alternate neuropsychological tests, most studies, similar to this study, report improvement in cognitive impairment after kidney transplantation.[4,5] These results are also supported by prekidney transplant to postkidney transplant changes in dialysis-associated alterations in brain structure and function.[6] We have previously shown that abnormal cerebral blood flow, white matter integrity, and brain neurochemical concentrations normalize after kidney transplantation.[7]

Cognitive impairment adversely affects quality of life, sense of wellbeing, health care costs, and mortality. The improvement in cognitive function after transplantation is intriguing and differentiates kidney failure from most other causes of cognitive impairment where cognitive impairment is essentially irreversible. Although mildly or moderately reduced glomerular filtration rate may not be associated with cognitive impairment or brain atrophy, retention of uremic metabolites may contribute to cognitive impairment in individuals with advanced chronic kidney disease, including those receiving dialysis, and therefore may be at least partially reversible after kidney transplant.[8-11] Furthermore, improvement in cognitive impairment after transplant suggests that all kidney replacement therapies are not equivalent for brain health as cognitive function and brain alterations do not improve with dialysis as they do with transplantation.

Despite the benefits of transplant on cognitive functioning among individuals with kidney failure, patients with cognitive impairment are less likely to get listed for kidney transplant, and, when they do get listed, it takes them longer to complete the transplant evaluation process.[12] Pretransplant cognitive impairment has also been associated with worse posttransplant outcomes.[13] Indeed, kidney transplant recipients have a higher prevalence of cognitive impairment than the general population, and cognitive function, despite improvement posttransplant, does not reach normal levels after kidney transplant.[14] Although some dialysis-associated brain alternations can improve after a kidney transplant, other cognitive and brain alterations may not normalize after transplantation. Middle cerebral artery velocity and cerebrovascular response to exercise—risk factors for future dementia—remain altered in kidney transplant recipients.[15]

How do we put these data into clinical context? Should pretransplant cognitive function play a role in evaluation of potential kidney transplant candidates? The findings from the study by Binari et al[3] and similar prospective studies that show improvement in cognitive function pre-to postkidney transplant argue against using pretransplant cognitive function as an eligibility criterion.[2] Moreover, pretransplant cognitive function is not a strong predictor of posttransplant cognitive function.[16] The worse posttransplant outcomes in patients with prekidney transplant cognitive impairment are likely not due to posttransplant cognitive impairment, and, by extension, nonadherence due to cognitive impairment as is often feared by the transplant team.

Perhaps patients with cognitive impairment are older and 'sicker' with a higher burden of comorbid conditions than those without cognitive impairment.[1,17] Patients with kidney failure treated by dialysis have multiple comorbid conditions that are often inadequately adjusted for in studies, but their effect on an individual is discernable clinically. For example, a patient with well-controlled diabetes mellitus for a short duration is clinically different from another patient with uncontrolled diabetes mellitus for a long duration. Although the statistical adjustment in most studies will only account for the presence or absence of diabetes mellitus, a good clinician will account for this difference while determining kidney transplant eligibility. Indeed, in our study,[12] the transplant selection committee was more likely to deem patients with cognitive impairment as ineligible despite being blinded to patients' cognitive status. This decision cannot be

attributed to perceived cognitive status either, because mild cognitive impairment and sometimes even dementia are difficult to diagnose during a routine pretransplant clinic visit. We have previously shown that transplant physicians and nurses are often biased in their perception of cognitive status and are not able to determine cognitive function accurately without objective testing.[18] Transplant eligibility is thus based on the burden of comorbid conditions and clinical judgment of risks versus benefits with kidney transplantation, rather than pretransplant cognitive function.

Pretransplant cognitive function may be a surrogate for vascular disease burden and associated endothelial dysfunction, a confounding variable when determining the association between kidney disease and cognitive function.[19] This hypothesis also explains the worse post-transplant outcomes in patients with pretransplant cognitive impairment. Older age and more comorbid conditions are indeed associated with worse outcomes.

Another clinical conundrum is whether to use cognitive function as a surrogate for vascular disease burden while determining transplant eligibility. The answer will depend on the survival advantage with a kidney transplant for that patient and needs to be individualized using clinical judgment—at least until we can accurately predict life expectancy with and without a kidney transplant for an individual patient. Current transplant policies, however, move this decision away from the patient and may make some transplant centers risk averse. Kidney transplant program-specific reports assess a program with observed versus expected outcomes, with inadequate adjustment for cognitive impairment and vascular disease burden in the calculation of these outcomes. Transplant centers struggle to maintain a balance between access, equity, and utility. With limited access (limited number of deceased donor kidneys for the large number of kidney failure patients awaiting transplantation), balancing utility of an organ (making best use of an organ) versus prioritizing an individual's survival benefit can be hard.

It is crucial for transplant centers to realize that cognitive impairment is not only associated with worse outcomes after kidney transplant but also increased mortality while receiving dialysis.[20] Along with absolute survival, the relative survival advantage with kidney transplantation compared with remaining dialysis-dependent should also be considered when determining transplant eligibility. Denying a kidney transplant to patients with reversible cognitive impairment essentially means depriving patients of their (only) treatment for cognitive impairment and improved survival.

Additional clinically relevant questions include whether existing comorbid conditions and associated endothelial dysfunction result in cognitive impairment that is not reversible with kidney transplant, which domains of cognition improve after transplant, and which domains remain persistently impaired. Can the degree of improvement postkidney transplant be predicted pretransplant? To answer these questions, we need larger studies with more detailed assessment of cognitive function.

Neuropsychological assessments usually take 2-3 hours; this duration of testing may not be practical for patients who already have multiple clinic visits both for dialysis as well as for management of other comorbid conditions. Thus, studies in dialysis patients use shorter assessments, often limited to screening tests such as the Montreal Cognitive Assessment, Mini-Mental State Examination, and Modified Mini-Mental State Examination. Although these tests may be useful for screening for dementia, they have limited value in discriminating among patients with different degrees of cognitive impairment, determining domains of cognition affected, and determining prognosis. In addition, most of the screening tests were developed for the aging population and Alzheimer's disease and may not perform well in patients with kidney failure. Importantly, neuropsychological testing should be performed by a trained person in a quiet room without distractions when the patient is relaxed. Performing cognitive assessments during transplant evaluation or inpatient admission for kidney transplantation, when the patient is tired or anxious, can yield inaccurate results. Clinical determination of cognitive status and disease progression also involves additional considerations including but not limited to age, level of education, occupation, medical history, depression and other mood changes, brain imaging, genetic testing, observations by family and friends, and subjective reports on cognitive function. These assessments are generally incomplete in most hemodialysis studies. For example, in the current study, the authors used RBANS and Trail Making Parts A and B for assessment of cognitive function.[4] RBANS takes about 20-25 minutes to assess global cognitive function. Although a more thorough test than some other commonly used screening tests, such as the Mini-Mental State Examination, Modified Mini-Mental State Examination, or Montreal Cognitive Assessment, RBANS does not provide detailed domain-specific information that can help understand the mechanisms underlying cognitive impairment in kidney failure treated by dialysis and its possible reversal after kidney transplantation. Trail Making Parts A and B partly cover domains of attention and executive function, but many other domains remain unassessed. In addition, patients participating in research studies have a higher level of education, further biasing results and their interpretation.

The study by Binari et al[3] adds to the growing literature suggesting at least partial reversibility in cognitive impairment with successful kidney transplantation.[5] Despite these optimistic data, our work is not done. Many clinically relevant questions remain unanswered. Studies are needed to better predict domain-specific cognitive function after kidney transplantation to identify patients who will benefit from transplantation despite pretransplant cognitive impairment. Meanwhile, transplant centers should observe caution in using cognitive function as a determinant of kidney transplantation eligibility.

ARTICLE INFORMATION

Author's Full Name and Academic Degrees: Aditi Gupta, MD, MS

Authors' Affiliations: Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kanas Medical Center, Kansas City, Kansas.

Address for Correspondence: Aditi Gupta, MD, MS, Division of Nephrology and Hypertension, Department of Medicine and Department of Neurology, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160. Email: agupta@kumc.edu

Support: This work is supported by NIH K23 AG055666 (AG) Cognitive Impairment in End Stage Renal Disease.

Financial Disclosure: The author declares that she has no relevant financial interests.

Peer Review: Received August 29, 2022 in response to an invitation from the journal. Direct editorial input from the Editor-in-Chief. Accepted in revised form September 24, 2022.

REFERENCES

1. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006;67(2):216-223. doi:10.1212/01.wnl.0000225182.15532.40
2. Tariq H, Ramakrishnan M, Gupta A. Insights into cognitive brain health in chronic kidney disease. *Gerontol Geriatr Res*. 2022;8(2):1074.
3. Binari LA, Kiehl AL, Jackson JC, et al. Neurocognitive function changes following kidney transplant: a prospective study. *Kidney Med*. 2022; xxxx.
4. Gupta A, Lepping RJ, Yu AS, et al. Cognitive function and white matter changes associated with renal transplantation. *Am J Nephrol*. 2016;43(1):50-57. doi:10.1159/000444334
5. Jurgensen A, Qannus AA, Gupta A. Cognitive function in kidney transplantation. *Curr Transplant Rep*. 2020;7:145-153. doi:10.1007/s40472-020-00284-0
6. Drew DA, Bhadelia R, Tighiouart H, et al. Anatomic brain disease in hemodialysis patients: a cross-sectional study. *Am J Kidney Dis*. 2013;61(2):271-278. doi:10.1053/j.ajkd.2012.08.035
7. Lepping RJ, Montgomery RN, Sharma P, et al. Normalization of cerebral blood flow, neurochemicals, and white matter integrity after kidney transplantation. *J Am Soc Nephrol*. 2021;32(1):177-187. doi:10.1681/asn.2020050584
8. Gupta A, Kennedy K, Perales-Puchalt J, et al. Mild-moderate CKD is not associated with cognitive impairment in older adults in the Alzheimer's Disease Neuroimaging Initiative cohort. *PLOS ONE*. 2020;15(10):e0239871. doi:10.1371/journal.pone.0239871
9. Grasing M, Kennedy K, Sarnak MJ, Burns JM, Gupta A. Mild to moderate decrease in eGFR and cognitive decline in older adults. *Nephrol Dial Transplant*. 2022;37(8):1499-1506. doi:10.1093/ndt/gfab226
10. Grasing M, Sharma P, Lepping RJ, et al. Association between the estimated glomerular filtration rate and brain atrophy in older adults. *Am J Nephrol*. 2022;53(2-3):176-181. doi:10.1159/000521892
11. Kurella Tamura M, Chertow GM, Depner TA, et al. Metabolic profiling of impaired cognitive function in patients receiving dialysis. *J Am Soc Nephrol*. 2016;27(12):3780-3787. doi:10.1681/ASN.2016010039
12. Gupta A, Montgomery RN, Bedros V, et al. Subclinical cognitive impairment and listing for kidney transplantation. *Clin J Am Soc Nephrol*. 2019;14(4):567. doi:10.2215/CJN.11010918
13. Thomas AG, Ruck JM, Shaffer AA, et al. Kidney transplant outcomes in recipients with cognitive impairment: a national registry and prospective cohort study. *Transplantation*. 2019;103(7):1504-1513. doi:10.1097/tp.0000000000002431
14. Gupta A, Mahnken JD, Johnson DK, et al. Prevalence and correlates of cognitive impairment in kidney transplant recipients. *BMC Nephrol*. 2017;18(1):158. doi:10.1186/s12882-017-0570-1
15. Ward JL, Ramakrishnan M, Jurgensen A, Billinger S, Gupta A. Cerebrovascular response during acute exercise in kidney transplant recipients. *Clin J Am Soc Nephrol*. 2022;17(1):111-113. doi:10.2215/cjn.08410621
16. Gupta A, Montgomery RN, Young K, et al. Pre-transplant cognitive screening is a poor predictor of post-transplant cognitive status. *Clin Transplant*. Published online August 21, 2022. doi:10.1111/ctr.14798
17. Seliger SL, Weiner DE. Cognitive impairment in dialysis patients: focus on the blood vessels? *Am J Kidney Dis*. 2013;61(2):187-190. doi:10.1053/j.ajkd.2012.12.002
18. Gupta A, Thomas TS, Klein JA, et al. Discrepancies between perceived and measured cognition in kidney transplant recipients: implications for clinical management. *Nephron*. 2018;138(1):22-28. doi:10.1159/000481182
19. Gupta A, Burns JM. A single point-in-time eGFR is not associated with increased risk of dementia in the elderly. *J Am Soc Nephrol*. 2020;31(12):2965. doi:10.1681/ASN.2020081119
20. Drew DA, Weiner DE, Tighiouart H, et al. Cognitive function and all-cause mortality in maintenance hemodialysis patients. *Am J Kidney Dis*. 2015;65(2):303-311. doi:10.1053/j.ajkd.2014.07.009