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Cognitive Impairment in Dialysis Patients: Focus on the Blood Vessels?

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Cognitive impairment is common in individuals with chronic kidney disease (CKD), particularly among those treated with dialysis.[1–4] There are many potential causes, including metabolic abnormalities associated with kidney failure, although results from recent imaging studies in dialysis patients and epidemiologic studies in earlier stage CKD patients are more consistent with the hypothesis that vascular disease is the major contributing factor.[4–12] Critically, cognitive impairment carries substantial risk, including depression and worse perceived quality of life,[13–14] as well as a marked increase in mortality.[15–17] Therefore, understanding the pathogenesis and exploring possible preventive treatments for cognitive impairment in CKD are critical to improving dialysis patient care. In this issue of *AJKD*, 2 studies evaluate cognitive function: the first, by Kurella Tamura and colleagues, reports the effects of frequent dialysis on cognitive function in individuals participating in the Frequent Hemodialysis Network (FHN) trials,[18] while the second, by Yaffe and colleagues, examines the association between retinopathy and cognitive function in individuals with CKD stages 3–4 participating in the Chronic Renal Insufficiency Cohort (CRIC).[19] This editorial focuses on the findings from the FHN trials, using the results from CRIC to provide important information on the potential impact of microvascular disease on cognitive function in people with CKD in order to place the results from Kurella Tamura et al into context.

In the general population, vascular dementia is the second most common dementia subtype after Alzheimer dementia. Vascular dementia is caused by underlying cerebrovascular disease, often involving the microvasculature.[20] Cognitive impairment associated with cerebrovascular disease often manifests with changes in processing speed and executive functioning—abilities that are necessary for complex attention, shifting between mental tasks, and initiating and stopping actions—while in Alzheimer dementia, memory is most prominently affected.[20] In the Renal REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, Kurella Tamura and colleagues described an association between baseline albuminuria and incident cognitive impairment at higher estimated glomerular filtration rate (eGFR) levels, while among individuals with minimal albuminuria but with lower eGFR, the eGFR itself was more predictive of cognitive risk.[7] This study

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defined incident cognitive impairment using the 6-item screener, a brief screening test which focuses on memory rather than executive functions.

Why might albuminuria and eGFR have different associations with cognitive performance? Several studies help to answer this question, particularly when viewed in the context of general population evidence that demonstrates an increased risk of vascular-type but not Alzheimer-type cognitive impairment in individuals with markers of kidney disease.[21] The first, a cross-sectional study of 335 older adults in Boston that assessed albuminuria, cognitive function using a detailed cognitive battery, and brain lesions using brain magnetic resonance imaging, demonstrated that while albuminuria was associated with both worse executive functioning and greater white matter hyperintensity burden on brain imaging, there was no association with performance on tests of memory; eGFR was not associated with cognitive function in this study.[11] The second, an evaluation of the Cardiovascular Health Study cohort, showed a 22% increased risk of dementia with each doubling of the urine albumin-creatinine ratio; findings were more consistent with a vascular dementia pattern than an Alzheimer-type pattern and albuminuria was associated with increased brain white matter hyperintensity burden on imaging.[22] The third, the evaluation of the CRIC Study from Yaffe et al, showed an association between retinal microvascular abnormalities and poor performance on tests of executive functioning and attention in a stage 3–4 CKD population; notably the relationship between retinopathy and cognitive performance was more robust at eGFR above rather than below 30 mL/min/1.73 m^2.[19] Taken in sum, these findings support the hypothesis that cognitive impairment in most individuals with earlier stages of CKD likely is a primary vascular process, with albuminuria serving a marker of systemic microvascular damage, including small vessel cerebrovascular disease, and that this microvascular disease manifests with worse performance on cognitive tests that assess executive function. In contrast, at low eGFR levels, there could be multiple factors, including but not limited to pre-existing microvascular disease, that influence cognitive performance, although very low eGFR also largely may be a marker of vascular disease.

Among dialysis patients, the prevalence of cognitive impairment is extremely high. Murray and colleagues showed moderate or severe cognitive impairment in approximately 70% of hemodialysis patients,[2] with a similar pattern noted in individuals treated with peritoneal dialysis.[1] The Boston Dialysis Study showed a high prevalence of poor cognitive performance, particularly on tests of executive functioning[9]; poorer performance on these tests was strongly associated with the concurrent presence of systemic cardiovascular disease.[4] Similar to the general population, limited studies performed in dialysis patients demonstrate a high prevalence of brain white matter disease,[5–6] which, when considered in conjunction with the vascular dementia pattern on cognitive tests, suggests that brain microvascular disease may be complicit in cognitive impairment in dialysis patients. However, it is also possible that retained uremic solutes—even among patients receiving adequate urea clearance by conventional measures—contribute directly to this impairment. The limited evidence for this hypothesis is derived from small studies that show variation in cognitive performance across the intradialysis cycle and improvements in function after initiating frequent hemodialysis or receiving a kidney transplant.[23–25] Critically, several studies performed in the era of high-flux dialysis have shown no association between lower Kt/V and worse cognitive function,[2, 26–28] although these studies are limited by their

observational nature and possible confounding by nutritional status. Accordingly, studies directly testing the association between dialysis clearance and cognitive function in dialysis patients are essential.

In this issue of *AJKD*, Kurella Tamura and colleagues report results from the FHN trials on the effects of 12 months of frequent hemodialysis versus standard thrice-weekly hemodialysis on measures of neurocognitive function.[18] As previously reported, 2 parallel trials, one involving nocturnal home dialysis as the frequent dialysis modality and the other involving daily in-center dialysis, were conducted, with increases in weekly standardized Kt/V compared to conventional hemodialysis of 40% in the Daily Trial and 73% in the Nocturnal Trial.[29–30] FHN participants tended to be younger and had fewer comorbid conditions than the general US hemodialysis population. After 12 months, the primary cognitive outcome of change in performance on the Trail-Making Test, Form B, a test of executive function and set-shifting, did not differ between the standard versus frequent-dialysis groups, with a majority of participants in both groups showing improved performance. Likewise, there was no significant difference in change on the secondary cognitive outcome of performance on the Modified Mini-Mental State Examination, a widely-used screening test of general cognitive function. In the FHN trials, a subset of participants received a more extensive neurocognitive battery of 6 additional tests encompassing multiple domains of cognitive function, with performance on tests of complex attention considered the primary ancillary outcome. Overall, there were no significant differences in performance on these tests with frequent dialysis, although greater improvements were observed in 2 tests of verbal learning and fluency in the Daily Trial only.

This investigation represents by far the largest and most rigorous examination to date of the effects of increased dialysis frequency/intensity on neurocognition. The few contemporary studies examining this topic have involved small samples of patients without randomized control groups. Jassal et al conducted an uncontrolled observational study among 12 younger dialysis patients, noting modest improvements in psychomotor speed and attention 6–12 months after converting from thrice-weekly in-center to nocturnal home dialysis.[24] In contrast, Vos et al, in a study of 10 hemodialysis patients, reported that 6 months of short daily hemodialysis did not significantly change cognitive or electrophysiologic brain function compared with a control group despite an increase in weekly standardized Kt/V of 20%.[28]

The strengths of the current study by Kurella Tamura include the parallel-group randomized design of the FHN trials, the relatively large sample size, and the careful attention to timing of administration of the neurocognitive testing. The latter is important because neurocognitive function may vary acutely across the interdialysis cycle and even within the course of a single dialysis treatment.[23] The expanded neurocognitive battery, even though only applied to a subset of participants, permitted a more detailed examination of different domains of cognitive function using tests more sensitive to change than the Modified Mini-Mental State Examination. The logistical challenges in conducting repeated administrations of a multi-item neurocognitive battery to dialysis patients across multiple sites at fixed time points in the interdialysis cycle are considerable, and the investigators should be

commended on their efforts; however, as acknowledged by the authors, there are important limitations in this trial that should be considered in interpreting the results. Loss to follow-up for cognitive testing was high at 12 months (28% for the extended cognitive battery), although perhaps not unexpected for a longitudinal study in dialysis patients. The finding that both groups improved performance on the primary and secondary cognitive outcomes likely represents the well-known problem of learning or practice effects with repeated cognitive testing, which may mask true declines over time in function. These practice effects also highlight the importance of appropriate control groups when assessing longitudinal changes in neurocognitive function.

Overall, the results can be interpreted as refuting the hypothesis that increasing small molecule clearance beyond that provided with standard thrice-weekly high-flux hemodialysis improves neurocognitive function in hemodialysis patients. Critically, it remains possible that a longer duration of frequent dialysis beyond 12 months could lead to improvements in neurocognition, but likely via a different mechanism. The remarkable finding from the FHN trials was a significant beneficial effect on the composite outcome of all-cause mortality and improvement in left ventricular mass.[29] Given that cognitive impairment in dialysis patients appears related to cardiovascular disease, if more frequent dialysis is able to attenuate the systemic vascular disease burden in dialysis patients, a beneficial effect on cognitive decline may follow, although it is likely that this will take longer to manifest.

Accordingly, a reasonable interpretation of the FHN results is that impaired cognitive function in dialysis patients is determined largely by factors other than uremic solute clearance; therefore, given the robust relationship between microvascular disease and cognitive function in earlier stages of CKD, to address this impairment treatments need to address microvascular disease. Future trials could examine longer term effects of frequent dialysis and vascular disease modification strategies in individuals requiring dialysis but also should focus on altering vascular disease risk factors in the earlier stages of CKD, potentially through exercise, obesity management, blood pressure, diabetes and lipid management, and other risk factor modification strategies.

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References

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