Vitamin D: An Intervention for Cognitive Impairment in Hemodialysis Patients That Could Make Sense

Anne M. Murray

The relationship between vitamin D and cognitive impairment has been a subject of intense interest recently because of the multiple roles that vitamin D is reported to have in neurologic function. Recent studies have described an association between vitamin D, global cognitive function, and cognitive decline in community-based populations without identified CKD (1–3) and patients with Alzheimer’s disease (2,4) and stroke (2).

In an important report in this issue, Shaffi et al. (5) found that lower 25-hydroxyvitamin D [25(OH)D] levels were associated with an increased likelihood of impairment in the cognitive domain of executive function but not memory in a cross-sectional analysis of 255 hemodialysis patients in the Dialysis and Cognition Study. Shaffi et al. (5) used a well designed detailed battery of cognitive tests that measured global function, immediate and delayed memory, and several aspects of executive function, including processing speed, attention, and abstract reasoning. The primary limitation of the analysis is that it is a cross-sectional study, describing the association between low levels of 25(OH)D and prevalent cognitive impairment; thus, whether 25(OH)D levels predict cognitive decline is unclear.

The finding that low 25(OH)D levels were associated with executive function impairment but not memory impairment may be a function of the demographics of the Cognition and Dialysis Study. Relative to most studies of cognitive impairment in the general non-CKD population, this cohort is relatively young; mean age was 63 ± 15 years, and some participants were as young as 18 years old (6). From a dialysis population perspective, as noted by Shaffi et al. (5), this young group was compared with the US Renal Data System age distribution, and dialysis vintage was short; over 40% of the cohort were incident dialysis patients (<12 months), and mean vintage was 14 months. Thus, the duration of the cognitive impairment process that could be attributed to dialysis treatment was also relatively short.

In a previous report in this same study population, Sarnak et al. (6) found that, although global cognitive function as measured by the Mini Mental State Exam was only borderline low, prevalence of clinically significant impairment in executive function was high, but prevalence of memory impairment was not. However, in a previous study by our group of 338 hemodialysis patients of slightly older age (mean = 72 years) and longer mean dialysis vintage (33 months), we found a high prevalence of global cognitive impairment as well as substantial impairment in both memory and executive function (7). Possibly, in hemodialysis patients with shorter dialysis vintage, the areas most susceptible to global cerebral hypoperfusion during dialysis are affected first (i.e., the subcortical areas most dependent on perforators in the watershed areas of the cerebral arteries), leading to subcortical infarcts and white matter disease; these areas, in turn, are correlated with impairment in executive function. With time, however, the entire brain may become more susceptible to hypoperfusion after repetitive dialysis cycles, resulting in increased risk of cortical infarcts, including the medial temporal lobe, entorhinal cortex, and hippocampus, and leading to memory loss. Cortical infarcts, in turn, lead to cerebral atrophy.

Vitamin D is believed to exert its neuroprotective effects through multiple pathways well described by Shaffi et al. (5); it can modulate neuronal calcium homeostasis and vascular calcification, hypertension, inflammation, and immune function among other roles. An association between the vitamin D receptor gene and Alzheimer’s disease has also been described, with the implication that the receptor genotype may be related to neurodegenerative disease and neuronal damage by altering vitamin D-mediated pathways (8).

Drew et al. (9) also recently reported results of brain magnetic resonance imaging (MRI) in 45 hemodialysis patients compared with 67 controls in a younger subsample (mean = 55 years) of the same population (9). The study by Drew et al. (9) found significantly greater degrees of cerebral and hippocampal atrophy, typical findings in Alzheimer’s disease, as well as greater numbers of infarcts in the hemodialysis patients compared with controls.

In a recent review, Bugnicourt et al. (10) proposed a detailed model of the complex pathophysiology of cognitive impairment in CKD that emphasizes three primary pathways to cognitive impairment: traditional cardiovascular risk factors, nontraditional factors such as inflammation, oxidative stress, and hypercoagulable state, and uremic toxins including cystatin C. In this model, these pathways, in turn, lead to either primarily vascular cognitive impairment or neurodegenerative cognitive impairment. However, a
combination of multiple pathologies is more likely. We know that vascular risk factors increase the risk of both CKD and Alzheimer’s disease. Before and after CKD patients develop renal disease, it is possible that they have similar or even greater risk than non-CKD patients of neurodegenerative disease, such as Alzheimer’s disease.

In autopsy studies of patients with dementia in the Religious Order Study and Rush Memory and Aging Study in community-dwelling elderly ($n=804$), mixed pathologies (Alzheimer’s disease, infarcts, and Parkinson’s disease/Lewy Body disease) accounted for over 50% of dementia cases (11). In fact, the failure of the multitude of Alzheimer’s disease clinical trials has been attributed in large part to lack of a specific pathologic target.

The natural history of cognitive impairment in the CKD population is critical to understand to time potential interventions, such as vitamin D, appropriately. A frequently cited elegant model of the natural history of the pathologic biomarker cascade leading to Alzheimer’s disease by Jack et al. (12) describes brain imaging pathology as preceding clinical symptoms by several years. The model also describes the molecular biomarkers of low-cerebrospinal fluid $A\beta$-amyloid and elevated $\tau$ as preceding the brain imaging pathology by several years and the clinical symptoms, such as memory loss, preceding the brain imaging pathology by 10 years or more (12).

We currently lack an equivalent longitudinal biomarker model of the natural history of cognitive impairment in CKD. However, to begin to unravel the story, it will be important to determine whether the cerebral atrophy observed on brain imaging studies in CKD and hemodialysis patients is an early marker of future symptomatology, such as memory loss. It will also be very interesting to see the extent to which both $25$-$\text{OH}D$ deficiency and cognitive impairment are associated with vascular pathology or atrophy on the brain MRIs conducted in this dialysis population. Because of the multitude of factors that may contribute to the high levels of cognitive impairment in hemodialysis patients, teasing out which factors are most critical as targets amenable to intervention is key.

This study suggests that $25$-$\text{OH}D$ deficiency may play a role in cognitive impairment in relatively young hemodialysis patients with, on average, 1–2 years dialysis vintage. The ongoing pilot trial discussed in ref. 13 of oral vitamin D at 50,000 units weekly for 6 months in hemodialysis patients will be important to watch, but larger trials in more typical hemodialysis populations will be needed. More importantly, if vitamin D levels are found to predict measures of brain atrophy and infarcts, such as in the case of other biomarkers in Alzheimer’s disease, and brain pathology precedes clinical symptoms, treatment of hemodialysis patients with vitamin D based on brain MRI findings may be a potential preventive early intervention strategy.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.