Editorial

To Predict Dementia, Should We Be Mindful of the Kidneys?

Manjula Kurella Tamura

Division of Nephrology, Stanford University School of Medicine, Palo Alto, California; and Geriatric Research and Education Clinical Center, Veterans Affairs Palo Alto Health Care System, Palo Alto, California

Correspondence: Dr. Manjula Kurella Tamura, Division of Nephrology, 780 Welch Road, Suite 106, Palo Alto, CA 94304. Phone: 650-721-6617; Fax: 650-721-1443; E-mail: mktamura@stanford.edu

Dementia is a growing public health problem, expected to affect more than 8 million Americans by the year 2050 at a cost of more than $100 billion annually (1). Therapies aimed at slowing dementia progression have thus far proved disappointing, prompting a shift in research emphasis from development of dementia-modifying therapies to dementia-prevention strategies. The shift in emphasis to disease prevention has in turn fueled the search for biomarkers that can identify earlier stages of cognitive decline or high-risk individuals.

At the same time, a growing body of research points to brain microvascular disease as playing a key role in the development of cognitive decline and dementia. Using newer magnetic resonance imaging (MRI) techniques, the prevalence of microvascular (lacunar) infarcts among community-dwelling adults with no history of stroke is estimated to be approximately 30%. Beyond these subclinical infarcts, white matter hyperintensities, described by some as "incomplete infarcts" related to arteriolosclerosis of penetrating vessels, are also common in asymptomatic individuals. These lesions are present in 20% of adults aged ≥64 and up to 95% of adults aged ≥80 years (2). In numerous studies in clinical and community-based cohorts, the presence of small vessel infarcts or white matter hyperintensities doubled the risk for dementia (2).

The vascular beds of the brain and kidney have similar hemodynamic properties as high-flow, low-resistance end organs with tightly autoregulated perfusion, so it seems logical that microvascular disease in the kidney and brain might travel together. The relations among estimated GFR (eGFR), a biomarker of kidney filtration function, albuminuria, a biomarker of glomerular permeability, and macrovascular events has now been well described. Albuminuria and eGFR each correlate with microvascular lesions in the brain (3,4), independent of traditional vascular risk factors. How do albuminuria and eGFR relate to microvascular outcomes such as cognitive impairment?

The study by Joosten *et al.* (5) in this issue of *CJASN* addresses this question. Using data from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, a community-based cohort study in the Netherlands, Joosten *et al.* evaluated the association between baseline and longitudinal measurements of albuminuria and eGFR with cognitive function in 4095 participants with a mean age of 55 years. Albuminuria was measured using the average of two 24-hour urine collections, and GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation at baseline and 6 years later. Cognitive function was measured at the follow-up assessment using a single cognitive test. Higher levels of albuminuria at baseline and worsening albuminuria over time were associated with poorer cognitive function, independent of measured demographic and vascular risk factors. The association varied by age, such that it was present in younger individuals (35 to 48 years) but not in older individuals. Among younger individuals, the findings were consistent in lower-risk subgroups: Those without diabetes, those without cardiovascular disease, or those without chronic kidney disease (eGFR >60 ml/min per 1.73 m^2). The authors estimated that individuals with albuminuria >30 mg/d had cognitive performance scores roughly equivalent to individuals who were 7 years older.

There are some limitations of this study, including the use of a single screening test of cognitive function rather than a comprehensive evaluation and the lack of longitudinal assessments of cognitive function. As with other observational studies, residual confounding from factors that are difficult to account for completely in statistical models, such as the duration and severity of hypertension, may exist. The PREVEND cohort was enriched with individuals who had albuminuria and did not include nonwhite participants, which might raise questions about the generalizability of the results to non-European populations.

Nevertheless, these findings in the PREVEND cohort are corroborated by a recent publication from the Ongoing Telmisartan Alone and in combination with Ramipril GlobalEndpoint Trial (ONTARGET) and the Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) involving >28,000 patients with diabetes or vascular disease. Similar to the PREVEND cohort, worsening albuminuria or incident albuminuria was associated with a 30% to 77% increased risk for cognitive decline in ONTARGET and TRANSCEND (6). Furthermore, as compared with placebo, treatment with an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or a combination of the two

roughly halved the rate of cognitive decline in patients with macroalbuminuria at baseline, whereas there was no benefit among those with micro- or normoalbuminuria. Dual therapy (*i.e.*, ACEI + ARB) seemed to confer no additional advantage as compared with monotherapy (*i.e.*, ACEI or ARB) for preventing cognitive decline. Importantly, renal and cognitive outcomes seemed to parallel one another in the two trials.

But what about eGFR? In the PREVEND study, eGFR was not independently correlated with cognitive function after accounting for albuminuria, whereas in the ONTARGET/TRANSCEND analysis, eGFR was included as a covariate in adjusted models, but its association with cognitive function was not reported. As the PREVEND investigators noted, several previous studies that reported independent associations between low eGFR and risk for cognitive decline did not account for albuminuria as a confounder (7,8), whereas most subsequent studies that did account for albuminuria have not found an association between eGFR and risk for cognitive decline (5,9). Should we conclude that eGFR is not an independent risk factor for microvascular outcomes but merely a confounder? In the PREVEND study, participants with albuminuria were oversampled, and most with chronic kidney disease had very modest reductions in eGFR (*i.e.*, 45 to 59 ml/min per 1.73 m^2). In contrast, in recent cross-sectional analyses from the Chronic Renal Insufficiency Cohort (CRIC) involving only participants with eGFR <70 ml/min per 1.73 m^2, lower eGFR but not albuminuria was associated with poorer cognitive function (10). One possible alternative explanation, then, is that similar to macrovascular outcomes, the risk for cognitive decline increases modestly when eGFR is 45 to 59 ml/min per 1.73 m^2 and more steeply when eGFR falls below 45 ml/min per 1.73 m^2. In addition to differences in the target population, differences in the study design and cognitive outcome or misclassification of individuals with low muscle mass from creatinine-based GFR estimates may also underlie these divergent observations.

The studies from PREVEND and ONTARGET/TRANSCEND support the idea that albuminuria is independently related to cognitive decline. Whether or how it might be causally related to cognitive decline cannot be determined from the current studies, although the hypothesis that both represent manifestations of systemic microvascular disease certainly seems plausible. For the moment, the question of whether eGFR is correlated with microvascular outcomes such as cognitive decline independent of albuminuria is not settled. The answer to this question may provide greater understanding about the types of vascular disease that occur in patients with chronic kidney disease and which kidney biomarkers are correlated with these different expressions of vascular disease. Ultimately, it may lead to the identification of novel microvascular disease risk factors and, hopefully, new therapeutic targets.

Neither study directly addresses whether kidney biomarkers can be used to predict dementia or monitor the effectiveness of therapies to prevent or slow cognitive decline, although both provide tantalizing hints that kidney outcomes and cognitive outcomes track together. The attractiveness of kidney biomarkers for this novel

application is obvious. Albuminuria, creatinine, and even cystatin c are considerably easier and cheaper to measure as compared with microvascular disease with brain MRI. A dementia risk index developed from the Cardiovascular Health Study (CHS) relies on brain MRI assessments of microvascular disease, which is not practical for widespread clinical application (11). Two other dementia risk prediction tools incorporate a number of vascular risk factors such as hypertension, diabetes, smoking, and obesity (12). Perhaps the contribution of these vascular risk factors to dementia risk might be more simply or fully summarized by measurement of albuminuria and eGFR. Others are investigating genetic markers, functional MRI methods, and cerebrospinal fluid assays as potential tools for improving early detection of dementia. As the search for dementia biomarkers intensifies over the next few years, it might be wise to remind our colleagues in neurology to be mindful of the kidneys.

Disclosures

None.

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