Albuminuria and Cognitive Impairment

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There is a high prevalence of cognitive impairment and dementia in individuals with ESRD. It has been proposed that the high prevalence of cognitive impairment is related to cerebrovascular disease, and the pattern of cognitive impairment is consistent with vascular dementia (1). Individuals with CKD have an increased risk of white matter changes and subclinical strokes, which are findings associated cognitive impairment (2,3). Whether mild CKD, in particular albuminuria, is associated with cognitive decline has been less well studied. In this issue, Sajjad *et al.* (4) evaluate albuminuria and estimated GFR (eGFR) with cognitive decline in a longitudinal analysis of the Nurse's Health Study, a cohort study of registered nurses. Cognitive testing, plasma creatinine, and urine albumin/creatinine ratio were available in a subset of individuals. Cognitive testing was repeated every 2 years and included a battery of six tests.

Microalbuminuria is typically defined as urine albumin excretion >30–300 mg/d (>20–200 μg/min). The criterion was developed to identify individuals with diabetes and renal involvement (incipient nephropathy), who were at risk of developing overt nephropathy (5). Given high day-to-day variability, it was recommended that the definition of incipient nephropathy be based on elevated albuminuria levels in two of three consecutive samples in a 1- to 6-month period. Despite the selected cutoff of 30 mg/g, it was recognized that the risk of progression to overt nephropathy was elevated in individuals with type 1 diabetes and albuminuria in the high normal range (6,5). This has been confirmed in a recent study by Babazano *et al.* (7), which found that higher albuminuria levels predicted greater decline in eGFR in individuals with diabetes. The increased risk began at 5–9 mg/g in men and 10–29 mg/g in women.

Microalbuminuria also predicts cardiovascular events and mortality in individuals with and without diabetes (8). More recently, it has been recognized that the mortality risk begins at lower albuminuria levels. In the Reasons for Geographic and Racial Differences in Stroke study, there was progressive increase in risk for all-cause mortality beginning around 10 mg/g (9). This increased risk was seen across all eGFR levels and in those with and without coronary artery disease at baseline. In a collaborative meta-analysis of 14 studies involving 105,872 individuals, an albumin/creatinine ratio >10 mg/g predicted both cardiovascular and all-cause mortality (10). Do the results of Sajjad *et al.* (4) suggest that the risk of cognitive decline begins at lower levels of albuminuria? Perhaps. Sajjad *et al.* analyzed ≥5 and 10 mg/g and found that elevated albuminuria levels were associated with faster cognitive decline. This does not necessarily mean that a level of 5–10 mg/g is associated with higher risk, because the category of ≥5 mg/g includes all individuals with higher levels. They did not look at mutually exclusive categories or splines to assess where the risk begins, and it may be that the risk is driven by those with the highest values. From the results, we also do not know whether there is a linear relationship of albuminuria with cognitive decline or whether there is a threshold above which the risk begins.

How should one interpret the association of albuminuria with cognitive decline? Does it represent kidney disease? The present study did not find an association with low eGFR and cognitive decline, measured by either creatinine or cystatin C. In longitudinal analyses, studies evaluating the association of eGFR with cognitive decline have found mixed results (11–15). Slinin *et al.* (14), in an analysis of The Osteoporotic Fractures in Men Study found a higher prevalence of cognitive dysfunction at baseline in those with lower eGFR, but there was not a significant association with incident cognitive dysfunction. In contrast, Wang *et al.* (15), in a community-based study in China, found a significant association of eGFR <60 ml/min per 1.73 m^2 with cognitive decline (adjusted odds ratio of 2.73 compared with eGFR >90 ml/min per 1.73 m^2). Most of the recent studies evaluating kidney function and cognitive decline have used estimated clearance (eGFR or creatinine clearance). In the Cardiovascular Health Study (CHS), an elevated creatinine ≥1.3 in women and 1.5 in men was associated with a 37% risk of incident dementia and 48% risk of vascular dementia (13). An elevated creatinine was not associated with an increased risk of Alzheimer's type dementia. Given the older age in the CHS, this elevation in creatinine represents a lower level of eGFR (closer to <45ml/min per 1.73 m^2). Kidney disease may need to be more advanced to affect cognitive function, and population studies where most individuals with CKD have stage 3A CKD may not see an association with cognitive decline. Consistent with this hypothesis, Etgen *et al.* (11)found that, in adjusted analyses, a creatinine clearance <45 ml/min was associated with incident impairment, but 45–59 ml/min was not. The current study did not present results in individuals

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with more severe kidney impairment, although one would expect that there are not many individuals with severe CKD.

An alternative explanation for the disparate results of albuminuria and eGFR on cognitive function decline is that albuminuria is representing something other than kidney disease. In Sajjar *et al.* (4), those with elevated microalbuminuria had a higher prevalence of hypertension, diabetes, and cardiovascular disease. The association of albuminuria persisted after adjustment for these vascular risk factors. However, these risk factors were based on a one-time evaluation and do not provide information on the duration or severity of risk factors over time. Midlife risk factors such as hypertension, obesity, and glucose levels predict dementia later in life (16). In the Hisayama Study, individuals with midlife hypertension had an increased risk of vascular dementia, regardless of whether BP was elevated in later life (17). There was no association with Alzheimer's type dementia (17), although in the Honolulu-Asia Aging Study, higher midlife systolic BP was associated with increased neuritic plaques and neurofibrillary tangles on autopsy (18). Albuminuria could reflect the cumulative vascular damage over years related to hypertension, abnormal glucose metabolism, and other risk factors. In the Monitoring of Trends and Determinations in Cardiovascular Disease-Augsburg/Cooperative Research in the Region of Augsburg study, the prevalence of left ventricular hypertrophy increased across tertiles of urine albumin level (19). The odds ratio for LVH was 2.1 in the second quartile (4.32–8.75 mg/g in men; 4.60–9.48 mg/g in women) compared with the lower quartile, indicating that the association with organ damage begins at urine albumin values <30 mg/g. This suggests that albuminuria may be a relatively simple, low-cost test that identifies vascular damage to the kidney, heart, and brain.

It should be noted that the current criterion for microalbuminuria was designed for use as a screening test to help guide treatment, as well as predict risk. Any selected cutpoint for a test is somewhat arbitrary but needs to balance both sensitivity (ability to predict disease if present) and specificity (does not detect disease if disease is not present). In an individual with diabetes and microalbuminuria, there are potential treatments that can decrease future risk of renal and cardiovascular events. If low levels of albuminuria predicts cognitive decline, how would this change clinical management? It would make sense to ensure that cardiovascular risk factors, which are also risk factors for cerebrovascular disease and cognitive decline, are controlled. Would more specific treatments directed at improving or preventing albuminuria decrease the risk of cognitive decline? In individuals with diabetes, tight glucose control decreases the risk of new albuminuria. The results of the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes study, an ancillary study to the Action to Control Cardiovascular Risk in Diabetes study to test whether intensive glucose control decreases decline in cognitive function, have not yet been reported. There are also no trial data that, in individuals without a history of stroke, treatment of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers compared with other antihypertensives decreases cognitive decline. Future studies should evaluate whether intensive risk factor management or targeted treatment decreases cognitive decline.

Disclosures

None.

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See related article, "Kidney Dysfunction and Cognitive Decline in Women," on pages 437–443.