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New insights into cognitive decline in chronic kidney disease

Wei Ling Lau & Mark Fisher

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Chronic kidney disease (CKD) is known to be associated with cognitive impairment, but the mechanisms that underlie this kidney–brain connection are unclear. A recent study provides evidence that CKD is an independent risk factor for cognitive decline due to cerebral small vessel disease.

REFERS TO Scheppach, J. B. et al. Association of kidney function measures with signs of neurodegeneration and small vessel disease on brain magnetic resonance imaging: the Atherosclerosis Risk in Communities (ARIC) study. *Am. J. Kidney Dis.* https://doi.org/10.1053/j.ajkd.2022.07.013 (2022).

Chronic kidney disease (CKD) is a risk factor for cognitive decline, and CKD stage has been strongly associated with severity of cognitive impairment in multiple epidemiological surveys[1,2]. However, this finding has tended to raise more questions than answers. A recent study by Scheppach et al. provides new data that could improve understanding of the brain–kidney connection[2].

The first question regarding the association between CKD and cognitive decline is whether this relationship reflects a true kidney–brain connection or is simply the result of the effects of CKD comorbidities. This question has been answered by epidemiological studies that clearly demonstrate that the relationship between CKD and cognitive decline cannot simply be explained by the presence of hypertension and other CKD risk factors[3].

The second question relates to the proximate cause of the cognitive decline: is this primarily CKD-induced neurodegeneration or CKD-induced vascular cognitive impairment? Early studies that examined this question emphasized a vascular origin, rather than a neurodegenerative process such as Alzheimer's disease[3–5]. Brain parenchymal consequences of cerebral small vessel (microvascular) disease encompass small deep infarcts (lacunes), microinfarcts, white matter disease (hyperintensities) and cerebral microbleeds (microhaemorrhages) and can be distinguished from brain findings of Alzheimer's disease and other neurodegenerative disorders.

Scheppach et al. provide the most definitive answer yet by focusing on MRI stigmata of cerebral small vessel disease in CKD[2]. This study included a subset of 1,527 participants of the Atherosclerosis Risk in Communities (ARIC) longitudinal cohort study. This subset comprised participants with cognitive impairment and a stratified random sample of participants without cognitive impairment who underwent brain MRI between 2011 and 2013. In this cohort, 5% of participants had dementia and 34.4% had mild cognitive impairment. On brain MRI, 26.1% of participants had infarcts and 24.3% had microbleeds. Cross-sectional regression analyses included adjustment for dementia risk factors.

Scheppach et al. report that participants with stage 4 and higher CKD (estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 according to the CKD-EPI equation using plasma cystatin C) and higher levels of albuminuria had increased white matter hyperintensities and brain atrophy. The atrophy was similar across brain cortex regions and did not co-localize with regions typically involved in neurodegenerative disorders[2]. Importantly, brain atrophy can result from microinfarcts and so does not necessarily imply a neurodegenerative process[6]. Another major finding of the study was that albuminuria (but not eGFR) was associated with infarcts (cortical and subcortical) and microbleeds.

The lack of association between low eGFR and imaging correlates of neurodegenerative conditions is consistent with previous reports. A post-mortem study of 50 patients on chronic haemodialysis found no increase in Alzheimer's disease pathology[4], and a neuropathology study of the brains of 40 deceased people with CKD noted a high prevalence of arteriolosclerosis (73%) and no evidence of an association with Alzheimer's neuropathology[5]. In a cohort of 166 community-dwelling participants from The 90+ Study with a mean age of 93 years, we reported no association between cystatin C-based eGFR and brain amyloid-β burden assessed using positron emission tomography imaging[7].

Recent studies examining the kidney–brain axis[2,3,7] favour cystatin C-based estimates of kidney function rather than creatinine-based equations. Unlike creatinine, cystatin C is not modulated by protein intake or muscle mass and is a more accurate biomarker of eGFR in the older population, which is often the focus of cognitive impairment studies. Of note, Scheppach et al. report that the associations between more advanced CKD and brain pathology (atrophy, infarcts, microbleeds and white matter lesions) held true in sensitivity analyses with other eGFR biomarkers (creatinine, a combination of creatinine and cystatin C, and β2-microglobulin). This finding lends further confidence in the observed associations as the trends were not changed by the method of assessment of kidney function.

The findings of Scheppach et al. also suggest that albuminuria might be a more sensitive biomarker of systemic vascular injury than eGFR. A longitudinal study of 19,399 adult participants in the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study demonstrated that albuminuria and low eGFR are complementary but not additive risk factors for incident cognitive impairment[8]. When eGFR was normal, albuminuria independently associated with incident cognitive impairment, whereas low eGFR independently associated with cognitive impairment in the absence of albuminuria[8].

> "Albuminuria might be a more sensitive biomarker of systemic vascular injury than eGFR"

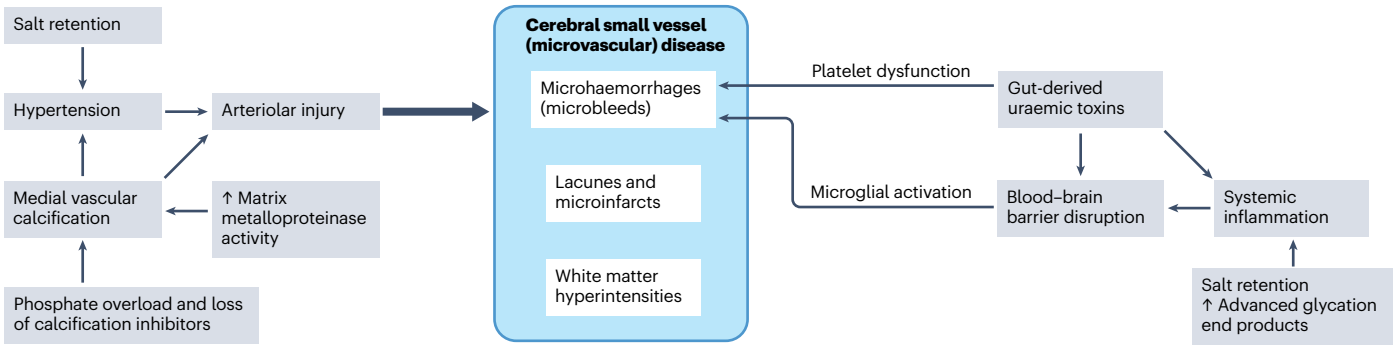

Fig. 1 | Mechanisms of microvascular injury in chronic kidney disease. Interplay of factors in chronic kidney disease that lead to cerebral small vessel (microvascular) disease, which encompasses cerebral microhaemorrhages (microbleeds), small deep infarcts (lacunes), microinfarcts and white matter hyperintensities. Adapted with permission from ref.[1], CCBY 4.0.

The third question is what the mechanisms are of microvascular injury in CKD. Identification of such mechanisms is challenging, but substantial progress has been made. Factors in the uraemic milieu that are suspected to contribute to cerebral microvascular injury include chronic inflammation, retained toxins and vascular calcification[1] (Fig. 1). Experimental data from in vitro and in vivo studies show that CKD results in microvascular injury, specifically cerebral microhaemorrhages (the pathologic substrate of microbleeds on MRI), independent of hypertension, and that this microvascular injury is associated with blood–brain barrier dysfunction induced by CKD serum[9]. These findings implicate soluble factors, including uraemic toxins derived from gut microbial dysbiosis (such as indoxyl sulfate and trimethylamine *N*-oxide), endotoxin (lipopolysaccharide) and urea, in microvascular injury. Further studies are needed to expand on these observations and characterize the role of microglia in microhaemorrhage formation[9].

The fourth and final question is which population is at risk of CKD-associated cognitive decline. Such decline is well recognized in patients on chronic dialysis[2,3], but whether those in the earlier stages of CKD are also at risk is unclear. Scheppach et al. report that those with cystatin-C-based eGFR <30 ml/min/1.73 m^2 are at increased risk of cognitive impairment[2], whereas other studies using cystatin C data support an increased risk at higher levels of eGFR[3].

> **"CKD is an independent risk factor for cognitive decline due to cerebral small vessel disease"**

In summary, the new findings add to the increasing evidence that CKD is an independent risk factor for cognitive decline due to cerebral small vessel disease. Of note, the brain MRI neurocognitive dataset analysed by Scheppach et al. pre-dates implementation of sodium–glucose cotransporter 2 inhibitors in combination with renin–angiotensin system blockade to delay CKD progression and decrease cardiovascular events[10]. Longitudinal studies are warranted to clarify the evolution of cerebral small vessel disease in patients with CKD receiving these therapies and to better define the at-risk population for dementia.

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Competing interests

The authors declare no competing interests.