THE IMPACT OF CHRONIC KIDNEY DISEASE ON COGNITIVE BRAIN HEALTH

EDITED BY: Dearbhla M. Kelly, Christopher D. Anderson, Anand Viswanathan, Bruce Miller and Deborah Blacker

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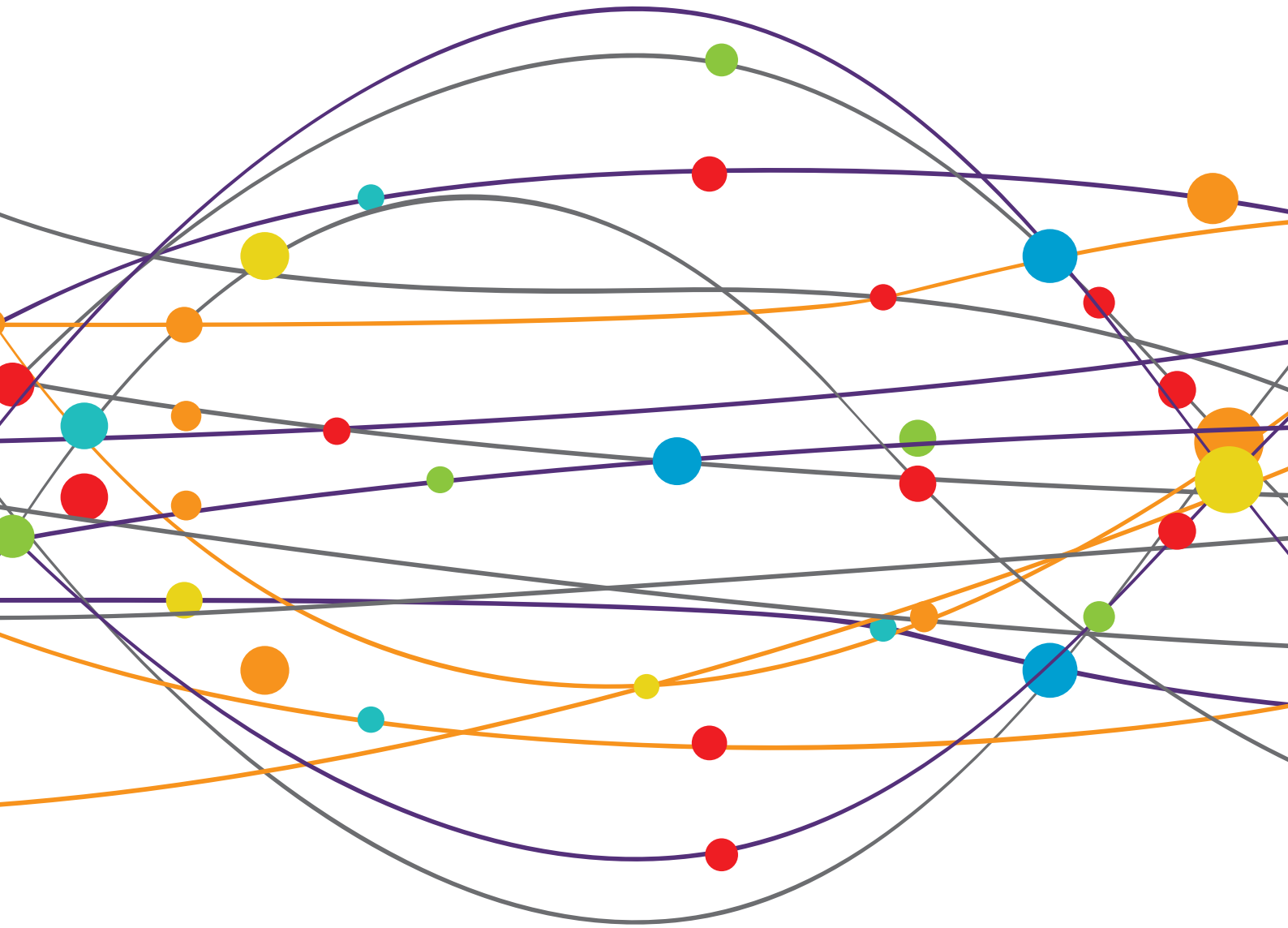

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THE IMPACT OF CHRONIC KIDNEY DISEASE ON COGNITIVE BRAIN HEALTH

Topic Editors:
Dearbhla M. Kelly, Trinity College Dublin, Ireland
Christopher D. Anderson, Harvard Medical School, United States
Anand Viswanathan, Harvard Medical School, United States
Bruce Miller, University of California, San Francisco, United States
Deborah Blacker, Harvard Medical School, United States

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Claudia Kimie Suemoto,
University of São Paulo, Brazil

*CORRESPONDENCE
Dearbhla M. Kelly
dkelly28@mgh.harvard.edu

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Editorial: The impact of chronic kidney disease on cognitive brain health

Dearbhla M. Kelly[1,2]*, Christopher D. Anderson[2,3,4], Deborah Blacker[5,6], Bruce L. Miller[7] and Anand Viswanathan[1]

[1]Department of Neurology, J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, United States, [3]Department of Neurology, Brigham and Women's Hospital, Boston, MA, United States, [4]McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA, United States, [5]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [6]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, United States, [7]Department of Neurology, UCSF Memory and Aging Center, University of California, San Francisco, San Francisco, CA, United States

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Editorial on the Research Topic
The impact of chronic kidney disease on cognitive brain health

Dementia is an increasing global health challenge that currently affects 40–50 million people (1, 2). The number of prevalent cases of dementia more than doubled from 1990 to 2016 driven by population aging and growth (3). It is the fifth leading cause of death and places a significant burden on caregivers and health-care systems with associated total economic costs >US$800 billion (4). Thus, there is a clear impetus to identify and address novel, modifiable risk factors that may account for some of this dementia burden (5).

One such novel risk factor may be chronic kidney disease (CKD). Epidemiologic data suggest that individuals at all stages of CKD have a higher risk of developing cognitive disorders and dementia, and thus represent a vulnerable population (6). The prevalence of cognitive impairment increases linearly as estimated glomerular filtration rate (eGFR) declines—~12% for each 10 ml/min/1.73 m^2 decrease in eGFR (7)—a figure that is comparable with or larger than that of other potentially modifiable risk factors for cognitive impairment including blood pressure (8) or hyperglycemia (9). In hemodialysis patients, the prevalence of cognitive impairment has been estimated to be as high as 30–70%, at least twice that compared to age-matched controls (10, 11).

The goal of this focused topic was to foster original research papers and state-of-the-art reviews that may serve to highlight the burden and spectrum of cognitive disorders in this population as well as to identify and inform important knowledge gaps in the field. Our aim was to provide a platform for a meaningful exchange of ideas, findings, and practices from a diverse range of specialties that overlap in the care of CKD patients with neurocognitive disorders including Neurology, Nephrology, Pediatrics, and Psychiatry.

Our hope is that by better defining the scope of CKD as a risk factor for dementia and the essential mechanisms in this relationship, we will discover novel ways to reduce the overall global dementia burden and to improve brain health.

The mechanisms underpinning the association between CKD and cognitive decline are not well-understood and as a consequence, prevention and treatment strategies may be suboptimal for this group. Kelly et al. explore potential mediating and confounding factors in this relationship. They highlight the preponderance of risk factors associated with dementia in patients with CKD including lower cognitive reserve (advancing age, lower educational, and occupational attainment), vascular risk factors (hypertension, diabetes, stroke), neuropsychiatric comorbidities (depression, sleep disorders) and dialysis factors (uremia, cerebral hypoperfusion). Canavan and O'Donnell focus in more detail on the specific mechanisms through which hypertension causes cognitive decline, including its overlapping role in the natural history of CKD and cerebrovascular disease.

Neurocognitive deficits have also been well-described in the pediatric population (12). As per the adult population, a number of putative risk factors have been proposed with a particular focus on the potential role of advanced uremia and anemia mediated through changes in neuronal myelination and synaptic development (13). Using data from 1,003 children and adolescents with CKD in the North American CKiD Study, Hooper et al. found no difference in neurocognitive measures between those with glomerular kidney disease and those with non-glomerular kidney disease, though further examination of the heterogeneity of pediatric CKD on neurocognition is needed. Steinbach and Harshman outline some of the underlying structural brain changes that have been observed in children with CKD including global cerebral atrophy, silent white matter infarcts, ventriculomegaly, and more recently, global abnormalities in the white matter microstructural integrity.

Similarly, Miwa and Toyoda summarize the clinical evidence linking structural brain abnormalities with CKD in adults along with its cerebrovascular and cognitive implications. They report that studies find strong associations between CKD and all imaging markers of cerebral small vessel disease (SVD) including white matter hyperintensities, silent lacunar infarcts, microbleeds, and perivascular spaces. In addition, they highlight the increased prevalence of intracranial atherosclerotic stenosis, white matter microstructural changes, global and regional brain volume losses, and reductions in cerebral blood flow that are found in this group. They suggest that early detection of these neuroimaging abnormalities in the asymptomatic or subclinical phase may help risk stratify these patients and allow earlier implementation of stroke prevention therapies.

The burden of cognitive impairment is particularly high in dialysis patients (14), increasing these subjects' multimorbidity, and affecting their transplant eligibility and graft success (15, 16). In a cross sectional study of new start hemodialysis patients, Schorr et al. found a high prevalence of cognitive deficits in the early initiation period with 55% of them showing impaired verbal skills, 43% impaired reasoning, and 18% short-term memory loss. Crowe et al. provide a comprehensive overview of the epidemiology of cognitive disorders in dialysis, their natural history, implications for patients including "brain fog" and impaired quality of life, cognitive testing options and validity, and how best to manage these patients including the potential impact of transplantation on their cognition.

Marini et al. discuss the evolving role of human genetic studies to help elucidate causal relationships between kidney and brain diseases from polygenic risk scores to pairwise genome-wide association studies (GWAS) and Mendelian randomization analyses. Genetic epidemiology is a particularly useful way to help clarify the temporality and directionality of these associations, and by leveraging the power of large GWAS, we may gain greater insights into biological mechanisms and identify novel targets for disease prevention.

Finally, Noel et al. review the limited therapeutic options for neurocognitive disorders in CKD and explore the potential role of sodium-glucose transport protein 2 inhibitors (SGLT2i). Although there is no direct evidence of their benefit in the prevention and treatment of cognitive decline, SGLT2i have several putative effects including attenuation of oxidative stress, diuresis, and blood glucose lowering that may lead to an improvement in important vascular risks. In addition, they have been associated with a reduction of stroke in CKD patients in a meta-analysis of randomized trials, as well as improved cognitive performance in animal models.

With this Research Topic, we intended to provide the latest insights and evidence review of the impact of CKD on cognitive brain health. One of the most striking themes that emerged from this collection is that despite increasing recognition of the breadth and depth of the issue in this vulnerable population, there is still a paucity of evidence in all domains including pathobiology, assessment, prevention, and treatment strategies. We hope that this special issue will encourage more collaborative research to address these important knowledge gaps.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Interactions Between Kidney Function and Cerebrovascular Disease: Vessel Pathology That Fires Together Wires Together

Sandro Marini[1], *Marios K. Georgakis*[2,3,4] *and Christopher D. Anderson*[3,4,5]*

[1] Department of Neurology, Boston Medical Center, Boston University School of Medicine, Boston, MA, United States, [2] Institute for Stroke and Dementia Research, University Hospital of LMU Munich, Munich, Germany, [3] McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA, United States, [4] Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, United States, [5] Department of Neurology, Brigham and Women's Hospital, Boston, MA, United States

The kidney and the brain, as high-flow end organs relying on autoregulatory mechanisms, have unique anatomic and physiological hemodynamic properties. Similarly, the two organs share a common pattern of microvascular dysfunction as a result of aging and exposure to vascular risk factors (e.g., hypertension, diabetes and smoking) and therefore progress in parallel into a systemic condition known as small vessel disease (SVD). Many epidemiological studies have shown that even mild renal dysfunction is robustly associated with acute and chronic forms of cerebrovascular disease. Beyond ischemic SVD, kidney impairment increases the risk of acute cerebrovascular events related to different underlying pathologies, notably large artery stroke and intracerebral hemorrhage. Other chronic cerebral manifestations of SVD are variably associated with kidney disease. Observational data have suggested the hypothesis that kidney function influences cerebrovascular disease independently and adjunctively to the effect of known vascular risk factors, which affect both renal and cerebral microvasculature. In addition to confirming this independent association, recent large-scale human genetic studies have contributed to disentangling potentially causal associations from shared genetic predisposition and resolving the uncertainty around the direction of causality between kidney and cerebrovascular disease. Accelerated atherosclerosis, impaired cerebral autoregulation, remodeling of the cerebral vasculature, chronic inflammation and endothelial dysfunction can be proposed to explain the additive mechanisms through which renal dysfunction leads to cerebral SVD and other cerebrovascular events. Genetic epidemiology also can help identify new pathological pathways which wire kidney dysfunction and cerebral vascular pathology together. The need for identifying additional pathological mechanisms underlying kidney and cerebrovascular disease is attested to by the limited effect of current therapeutic options in preventing cerebrovascular disease in patients with kidney impairment.

Keywords: stroke, genetic epidemiology, chronic kidney disease, intracerebral hemorrhage, small vessel disease (SVD)

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Chengxiang Qiu, University of Washington, United States
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Valentina Arnao, ARNAS Ospedali Civico Di Cristina Benfratelli, Italy

***Correspondence:**
Christopher D. Anderson
cdanderson@partners.org

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INTRODUCTION

Chronic kidney disease (CKD) affects around 10% of the general population globally and has an increasing prevalence, posing a major burden on public health systems (1). While the effects of kidney dysfunction on cardiovascular disease have long been explored, recent literature has provided evidence for the role of kidney disease in both early and advanced stages of cerebrovascular atherosclerosis and cerebral small vessel disease (SVD) (2). However, the mechanisms underlying associations between CKD and cerebrovascular disease have been underinvestigated (3). In this narrative review, we highlight work exploring the intersection of chronic kidney disease and cerebrovascular disease. We also discuss pathophysiological features connecting vascular damage in the two organs and summarize epidemiological data supporting the effect of CKD on acute and chronic manifestations of cerebrovascular disease. Furthermore, we provide an overview of recent genetic findings that support these associations, suggest possible new pathological pathways combining kidney and brain disease, and summarize data that may help to disentangle correlations from causal associations between the two organs. Finally, we discuss therapeutic options for patients suffering from chronic kidney disease, among whom cerebrovascular disease treatment is under recognized and insufficiently treated.

HEMODYNAMIC PROPERTIES OF THE KIDNEY AND BRAIN VASCULATURE

Both the kidney and the brain are high-flow end organs that receive blood through the renal arteries and the carotid and vertebrobasilar circulation, respectively. Their microvasculature is composed of small arteries, penetrating arterioles, capillaries, and venules, overall referred to as small vessels. The small vessels of the kidney and the brain are unique as their cells receive continuous high-volume flow throughout systole and diastole against very low vascular resistance.

Given the particular anatomy and physiology of small vessel circulation, kidney and brain tissue are susceptible to the same microvascular insults in response to aging and exposure to vascular risk factors. As a result, these two tissues are more prone to developing what is commonly referred as SVD (4). This term encompasses a range of pathological processes including fibrosis, development of inclusions in the basement membrane, and hyalinization of the vessel wall with the final common effect of narrowing of the vascular lumen leading to stenosis or occlusion and ultimately ischemia (5). Hypertension and hyperglycemia are the two most common vascular risk factors leading to SVD (6). Early studies showed that increasing blood pressure (BP) and consequently pulsatile stress led to tearing of endothelial and smooth muscle cells within small arteries, causing disruption to the vessel (7). Similarly, hyperglycemia, especially in tissue with specific high flow needs, leads to changes in insulin signaling, oxidative stress, and inflammation which promote the progression of microvascular pathologies (8).

It has been hypothesized that the pathophysiology of SVD in the kidney is similar to that of the brain. The same features of small arterial dilations and aneurysms as well as lipohyalinosis and fibrinoid necrosis are seen in the brain as in the kidneys. Because of these shared hemodynamic properties between the brain and the kidney, kidney disease has been proposed to progress in parallel with cerebrovascular pathology and particularly SVD.

EPIDEMIOLOGY OF KIDNEY DYSFUNCTION AND CEREBROVASCULAR DISEASE: ASSOCIATIONS WITH STROKE

Several epidemiological observations support the hypothesis that kidney impairment is associated with higher risk of stroke, independent of the etiological subtype. When assessing the association between kidney dysfunction and stroke, studies have used reduced estimated glomerular filtration rate (eGFR), albuminuria, and CKD diagnosis as indices of kidney dysfunction. GFR, representing the process of ultrafiltration of plasma from glomerular capillaries into Bowman's space, is estimated from serum concentrations of endogenous filtration markers, such as creatinine or cystatin via equations which account for non-GFR related factors (9). The glomerular capillary wall generally blocks the passage of albumin and other large serum proteins. An increase in the normal albumin excretion rate is called albuminuria and reflects an alteration in structure of the glomerular capillary wall (9). Levels of albumin ranging from 30 to 300 mg in a 24-h urine collection are referred to as microalbuminuria and represent a relatively early marker of kidney disease. Macroalbuminuria is defined as a urinary albumin excretion of $\geq$300 mg/24 h. CKD is defined by having more than 3 months of decreased eGFR or evidence of kidney damage including albuminuria (9).

In the Northern Manhattan Study, a decreased eGFR (defined throughout this section as $<$60 ml/min/1.73 m^2) was associated with a 2.5-fold higher risk of developing stroke [hazard ratio (HR) = 2.65; 95% confidence interval (CI) = 1.47–4.77] (10). Similar associations were observed in the prospective Atherosclerosis Risk in Communities study, where subjects with decreased eGFR had nearly double the risk of stroke (HR = 1.81; 95% CI = 1.26–2.02), even after adjustment for conventional vascular risk factors (11). A meta-analysis which included 284,672 individuals also found a higher relative risk [RR] for developing incident stroke among those with decreased eGFR (RR = 1.43; 95% CI = 1.31–1.57) (12). Similarly, in the largest meta-analysis conducted to date with over 5 million individuals, participants with decreased eGFR had an increased stroke risk (RR = 1.73; 95% CI = 1.57–1.90) (13). Interestingly, the association was attenuated after adjustment for multiple BP measurements, but still remained significant (RR = 1.10; 95% CI = 1.02–1.18). Lastly, the European Rotterdam Study followed 5,993 community-dwelling individuals for 11.6 years and found a 10% increased incidence of any stroke (HR = 1.11; 95% CI = 1.01–1.23) per standard deviation (SD) decrease in

creatinine-based eGFR. Similar results were obtained when eGFR was assessed *via* cystatin-C.

As for other indices of kidney disease, albuminuria has been independently associated with risk of stroke in a dose-dependent manner. A study with almost 50,000 individuals found the presence of microalbuminuria to almost double the risk of stroke independently of other cardiovascular risk factors (14). In a meta-analysis, both micro- and macroalbuminuria were associated with higher risk of incident stroke (RR = 1.58 and RR = 2.65, respectively) (15). Interestingly, recovering from microalbuminuria is associated with a slight reduction but not normalization of risk of cardiovascular events [individuals with regression from microalbuminuria had a HR of 2.62 (95% CI = 1.95–3.54)] (16).

However, the major pathophysiological and causal differences between stroke etiologies highlight the need for a more elaborate exploration of the effects of kidney disease on stroke risk across the different stroke subtypes. Such analyses could provide deeper insight into the underlying mechanisms and define the right patient subgroups for developing preventive strategies. Stroke is divided into ischemic stroke and intracerebral hemorrhage (ICH). The main sources of ischemic stroke include large artery atherosclerosis, cardioembolism, and cerebral SVD. Although a recent epidemiologic study designed to assess whether CKD is associated with a specific stroke subtype failed to find that CKD increases risk of any individual etiology (17), associations between CKD and different mechanisms of ischemic stroke can be inferred by several studies.

The strength of association between kidney function and cerebrovascular disease highlights a pressing need to determine appropriate timing of screening assessments of kidney function. In the United States alone, 14%-15% of individuals aged 20 years or older suffer from some form of kidney dysfunction (18). Patients with vascular risk factors have an even higher risk of developing renal dysfunction, with downstream implications for cerebrovascular events. A comprehensive determination of vascular risk should therefore include assessment of renal function.

Cardioembolic Stroke

CKD appears to increase the risk of cardioembolic stroke predominantly through atrial fibrillation (AF). Population-based studies have confirmed a higher prevalence of AF among patients with CKD. For example, the prevalence of AF was up to 3 times higher in The Chronic Renal Insufficiency Cohort than in the general population (19). CKD triggers several mechanisms which may result in an increased risk for AF. Renin-angiotensin-aldosterone dysfunction, chronic inflammation, vascular calcification, and left ventricular hypertrophy all increase the risk of cardioembolic stroke through AF as its predisposing risk factor (20). Beyond AF, CKD also increases the risk of thromboembolic events. A meta-analysis reviewing 25 studies of patients with AF and end stage renal disease (ESRD) showed that the presence of severe kidney impairment doubles the risk of stroke (21). Another study showed that kidney dysfunction (defined as either reduced eGFR or proteinuria) is associated with a higher incidence of thromboembolism independent of other stroke risk factors (HR = 1.39; 95% CI = 1.31–1.71 for eGFR < 45 and HR = 1.54; 95% CI = 1.29–1.85 for proteinuria) (22). Taken together, this evidence suggests that CKD increases the risk for developing AF as well as the risk of thromboembolic events in the context of AF, both of which increase the risk for cardioembolic stroke.

Large Artery Stroke

CKD is an established risk factor for atherosclerosis, and as such may increase the risk of large artery stroke (LAS) via promoting extra- and intracranial atherosclerosis. In the Japanese Suita Study of urban residents, CKD was associated with carotid artery stenosis [adjusted odds ratio (OR) = 3.16; 95% CI = 2.05–4.88] independent of hypertension (23). Similarly, in the Intervention Project on Cerebrovascular Diseases and Dementia, a community-based cohort study with 3,364 participants, individuals in the lower quartile of eGFR had the greatest increase in carotid intima-media thickness (2.4%; 95% CI = 2.0–2.7%), an ultrasound marker of carotid atherosclerosis (24).

Arterial stiffness represents another clinical measure proven to be independently predictive of fatal and non-fatal cardiovascular events and as such is a useful surrogate end point for cardiovascular disease outcomes (25). It reflects the functional and structural changes in the vascular wall and correlates with atherosclerosis of the large arteries often involved in LAS (26). Even mildly impaired renal function is associated with increased arterial stiffness and subsequent independent increase in stroke risk (27, 28). This association between renal impairment and large artery atherosclerosis results in an increased risk of atherosclerotic ischemic stroke.

In the CHOICE study, which evaluated stroke in dialysis patients, the overall stroke incidence was almost ten times the incidence in the general population, with large-vessel atherosclerosis found in 11% (29). In a Japanese study of 639 subjects, severe kidney dysfunction almost doubled the risk of the atherosclerotic stroke (OR = 1.81; 95% CI = 1.23-2.68) (30). A recent study which followed subjects after a transient ischemic attack (TIA) or minor stroke found that microalbuminuria was associated with recurrent events and significant internal carotid artery stenosis (OR = 3.4; 95% CI = 2.2–5.2) independent of other vascular risks factors (31).

Small Vessel Stroke

There are few epidemiological studies which have specifically assessed the contribution of CKD to the SVD subtype of ischemic stroke, commonly referred to as lacunar infarction. The Cardiovascular Health Study reported a linear association between decreasing kidney function and prevalence of lacunar infarction (OR = 1.20; 95% CI = 1.09–1.32 for each SD of decreased cystatin C clearance) after multivariable adjustments (32). Similar ORs were also reported in the Rotterdam Scan Study for decreased eGFR (33). These findings were confirmed in a meta-analysis which showed a nearly three-fold increased risk of silent cerebral infarctions in patients with low eGFR (OR = 1.77; 95% CI = 1.36–2.11) (34). In contrast, in a retrospective observational study of 639 patients with stroke and ESRD, severe kidney dysfunction was associated with atherothrombotic stroke

(OR = 1.81; 95% CI = 1.23–2.68) and cardioembolic stroke (OR = 2.25; 95% CI = 1.32–3.83) and showed an OR of similar magnitude for lacunar stroke, which however did not reach the level of statistical significance (OR = 1.67; 95% CI = 0.98–2.84) (30). While some studies may not have found an excess risk of lacunar stroke in CKD patients, associations have been reported for SVD neuroimaging features beyond lacunar stroke. The United Kingdom Young Lacunar Stroke DNA Study recruited 1,023 patients with lacunar infarction. In this study, decreased eGFR did not represent a risk factor for multiple lacunar infarcts vs. isolated lacunar infarcts, but increased the risk of moderate/severe white matter hyperintensity (WMH), a marker of chronic cerebral SVD (35). Similarly, a meta-analysis including 37 publications and 20,379 subjects calculated the risk of having renal impairment for patients with lacunar stroke compared to patients with non-lacunar stroke. Although no specific association between renal impairment and lacunar stroke was found (OR = 0.88; 95% CI = 0.6–1.30), the presence of SVD features on imaging was associated with worse renal function (36).

Embolic Stroke of Undetermined Source (ESUS)

Available data of kidney function in patients with ESUS are limited and few studies assess the relationship between CKD and ESUS. In the largest ESUS dataset, patients with intact or impaired renal function had the same risk of suffering from ESUS (37). As such, whether kidney dysfunction could lead to ESUS or other forms of cryptogenic stroke remains uncertain.

Intracerebral Hemorrhage

CKD increases the risk of ICH. Up to 46% of patients presenting with ICH are also affected by CKD (38, 39). In a retrospective cohort study of 516,197 adults, individuals with CKD had almost double the RR of hemorrhage (including ICH) (RR = 1.9; 95% CI = 1.5–2.4) when compared to subjects with normal kidney function (21). A prospective population-based cohort study in China found that subjects with proteinuria had almost double the risk of ICH (HR = 1.90; 95% CI = 1.35–2.67) compared to those without. This association was confirmed after adjustment for established cardiovascular risk factors for proteinuria, but not for low eGFR (40). A cohort study conducted with more than 10,000 people with ESRD found a similar increase in risk of ICH when compared to the general population (41). Concordant findings were also reported in a population-based study from UK primary care (42). In contrast, a more recent retrospective cohort study in South Korea which analyzed almost 200,000 subjects did not find any association between eGFR and ICH (43).

The high comorbidity between ICH and CKD is in part attributable to the burden of hypertension. Around 30% of patients affected by CKD have elevated ambulatory BP with normal office BP (masked hypertension), and up to 40% suffer from resistant hypertension (44). Therefore, the impact on risk of ICH is likely substantial considering that patients with a higher than normal systolic BP had a 5.5 (95 % CI = 3.0–10.0) fold increased rate of ICH compared with normotensive individuals (45).

Other hypothesized mechanisms include metabolic derangements common in advanced renal disease, such as high serum phosphate and low serum calcium levels. Calcium and phosphorus are pivotal in the maintenance of cell function in the endothelium and vascular smooth muscle, hence their abnormality can result in endothelial dysfunction and impairment of cerebral autoregulation (46). In a prospective study of patients on dialysis, when comparing patients with different levels of phosphate, every 1 mmol/L increase in serum phosphate corresponded to a two-fold increased risk of developing ICH (HR = 2.07; 95% CI = 1.10–3.81) (47). Lastly, patients suffering from CKD may exhibit uremia, which affects the balance between platelet adhesion activators and inhibitors, resulting in a net activation defect. Uremia also reduces platelet receptor glycoprotein, leading to impaired platelet adhesion to the sub-endothelium (48). As a consequence, patients with advanced CKD are at increased risk of hemorrhage (49, 50).

Further, CKD can increase the risk of ICH via the use of AF-related anticoagulants. As discussed earlier, the incidence and prevalence of AF in patients with CKD are higher than in the general population. A systematic meta-analysis showed that AF in patients with ESRD increased the risk of stroke, ICH and mortality, although with a high degree of variability (21).

EPIDEMIOLOGY OF KIDNEY DYSFUNCTION AND CEREBROVASCULAR DISEASE: ASSOCIATIONS WITH CEREBRAL SMALL VESSEL DISEASE

Beyond acute manifestations of cerebrovascular disease, there are multiple studies supporting associations between kidney dysfunction and neuroimaging markers of subclinical chronic cerebral SVD. Classical neuroimaging biomarkers for SVD, such as WMH, silent lacunes and cerebral microbleeds each have evidence for association with SVD and are themselves worthy of further exposition outside the context of the present review. Briefly, a meta-analysis of 31 studies and 23,056 participants found microalbuminuria to be associated with a higher risk of all markers of cerebral SVD including WMH (OR = 1.70; 95% CI = 1.43–2.01), lacunes (OR = 1.86; 95% CI = 1.49–2.31), cerebral microbleeds (OR = 1.78; 95% CI = 1.30–2.43), and enlarged perivascular spaces (OR = 1.78; 95% CI = 1.02–3.09 in the basal ganglia, and OR = 3.27; 95% CI = 1.49-7.20 in the centrum semiovale) (51). Similarly, several other studies have found linear associations between eGFR and markers of cerebral SVD in the general population (12). Nonetheless, on the basis of these conventional study designs, it is not possible to delineate whether the reported associations represent causal effects of kidney dysfunction on the development or progression of cerebral SVD or if they are the result of a shared pathology, such as systemic endothelial and microvascular dysfunction that underlies both kidney and cerebral SVD.

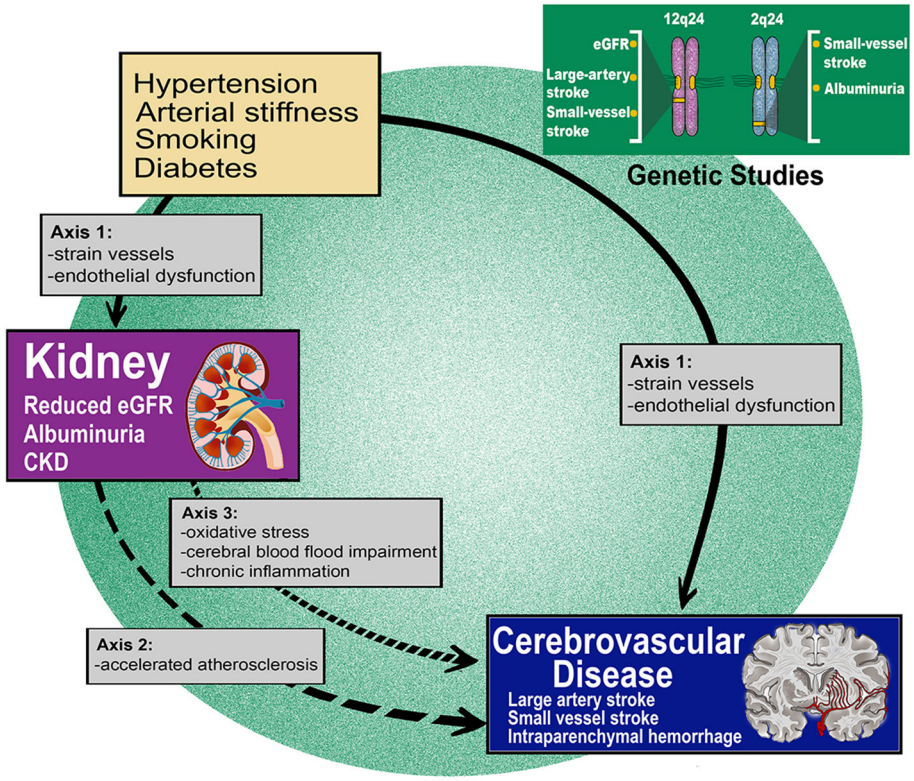

FIGURE 1 | Renal dysfunction is robustly associated with acute and chronic forms of cerebrovascular disease. Mechanisms through which renal dysfunction leads to cerebral small vessel disease and other cerebrovascular events can be summarized in three axes. Genetic epidemiology findings reinforce the causality of the highlighted connections.

MECHANISMS THROUGH WHICH RENAL DYSFUNCTION LEADS TO CEREBRAL SMALL VESSEL DISEASE AND OTHER CEREBROVASCULAR EVENTS

The complex relationship between kidney dysfunction and cerebrovascular disease can be summarized in three axes: (axis 1) shared unique susceptibility to vascular risk factors and the same resultant tissue pathology; (axis 2) over-representation and accentuation of vascular risk factors in patients with renal disease; (axis 3) sequelae of renal disease playing a role in stroke pathogenesis (**Figure 1**). These axes are theoretical and serve to illustrate complex relationships and pathways with several points of contact between them.

Strain Vessel Hypothesis (Axis 1)

The "strain vessel hypothesis," based on hypertensive vascular damage, has been suggested as a possible mechanism explaining the association between CKD and stroke (52). Kidney and brain share commonalities in terms of vascularization, as previously discussed. Both organs have vessels therefore referred to as "strain vessels," as they are systems with low vascular resistance allowing continuous high-volume perfusion (53). These features make the kidney and the brain extremely vulnerable to hypertension. In fact, high BP not only impacts the histopathology of arterioles leading to a replacement of smooth muscle cells by lipohyalinosis, but also impacts the hemodynamics of large arteries mostly via arterial stiffness which in turn exacerbates the deleterious effects on strain vessels (54). As a result, these cerebral subcortical perforating arteries and renal juxtamedullary afferent arterioles lose their autoregulation and thus impair regional blood flow. Furthermore, damage to renal juxtamedullary afferent arterioles leads to glomerular hypertension and sclerosis as well as impaired downstream circulation in the vasa recta and medulla (55). The first causes a progressive loss of renal function, while the second affects the sodium balance with an overall summative effect on worsening systemic hypertension (55).

Endothelial Dysfunction (Axis 1)

Albuminuria occurs when podocyte density decreases below a certain threshold. It represents a marker of glomerular barrier impairment, specifically glomerular endothelium damage. Given the similarities in the anatomy of the kidney and brain, it has been hypothesized that the endothelial dysfunction which occurs at the glomerular level and causes albuminuria happens simultaneously at a systemic scale (56, 57). In this sense the presence of albuminuria reflects a more generalized impairment of vascular endothelial function, and the vascular leakage which occurs as a consequence will ultimately impair tissue perfusion with

resultant ischemia. In the Framingham Heart Study, any level of urinary albumin excretion was associated with progressively increased cardiovascular risk and mortality, independent of diabetes or hypertension (58).

Additional evidence is provided by research on derivatives of the aminoacid L-arginine, such as asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). ADMA and SDMA are elevated in patients with kidney dysfunction as well as in patients with other SVD manifestations, independent of classical vascular risk factors (59). ADMA levels were found to correlate with the extent of WMH, risk of small vessel disease, and were found to be elevated in subjects affected by heritable forms of SVD such as Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL) (59). L-arginine derivatives, similar to albuminuria, may represent biomarkers of the same systemic endothelial pathology shared by the kidney and the brain.

Accelerated Atherosclerosis (Axis 2)

Accelerated atherosclerosis has been described in patients with kidney dysfunction. Dyslipidemia is common in patients affected by CKD. As a result of proteinuria and lipoprotein transport impairment, CKD patients often have an increase in serum triglycerides, very-low-density lipoprotein, and low-density lipoprotein (LDL) cholesterol, all of which have significant atherogenic potential (60, 61). Hypercholesterolemia may also be worsened by the upregulation of 3-hydroxy-3-methylglutaryl CoA reductase in patients with CKD (62).

Modified lipoproteins from elevated LDL have been hypothesized to trigger innate immune reactions, which result in inflammation and accelerated diastasis of lipids in the intima of the vessel. Additionally, CKD has been described as a pro-inflammatory state, and enhanced levels of fibrinogen and matrix metalloproteinases have been variably described in this patient population. Inflammation is known to affect atherosclerotic lesions' stability and risk of rupture.

Instability and rupture of atherosclerotic carotid plaques have been found to be significantly higher in patients with CKD compared to patients with normal renal function in a retrospective study of patients undergoing carotid endarterectomy (83 vs. 52%, $p = 0.001$, and 59 vs. 36%, $p = 0.039$, respectively) (63). However, data showing that patients with CKD have higher percentages of calcification and lower collagenous content of carotid plaques when compared to subjects with normal renal function represent an important counterfactual observation, as heavily calcified plaque is typically considered less prone to rupture and cause ischemia (64).

Taking this evidence together, increased atherosclerosis in CKD patients is likely to arise in the setting of combined insults of dyslipidemia and accentuated inflammation (65, 66). Concomitantly, higher levels of factor VIII and von Willebrand factor, which have been described in CKD patients as compared to the normal population, may further increase the risk of thrombotic and atheroembolic events.

Closely related to atherosclerotic changes, even moderate stages of CKD have been associated with changes in the biomaterial and biological characteristics of the vessels, resulting in arterial stiffness (67). Most likely via impaired renal excretion of vascular toxins and metabolic derangements of the calcium homeostasis, kidney disease promotes vascular calcification and eventually arterial stiffness. A prospective study evaluating patients with mild to moderate CKD found that progression to ESRD was an independent determinant of carotid stiffness (HR = 2.48; 95% CI = 1.63–3.78) (68), with the above mentioned impact on stroke risk and cardiovascular events.

Cerebral Blood Flow Impairment (Axis 3)

Cerebral vasculature is able to maintain stable cerebral blood flow (CBF) despite changes in BP. Impaired kidney function can lead to impaired cerebral autoregulation and subsequently make brain perfusion more strictly dependent on systemic BP (69, 70). In this scenario, patients with CKD are at risk for both cerebral hypoperfusion and hyperperfusion depending on systemic pressure. This disconnection between tissue perfusion and metabolic demand can be measured by deviation from the expected CBF. Demonstrating this autoregulatory failure, studies have reported that patients with CKD have both higher and lower CBF compared to patients with normal kidney function. In the Systolic Blood Pressure Intervention Trial, reduced kidney function was independently associated with higher global and white matter CBF (71). In the Rotterdam Study, lower eGFR was independently associated with lower CBF (0.42 ml/min/100 ml decrease in CBF for each standard deviation of eGFR reduction) (72).

Impairment of CBF may be a repercussion of an effect of kidney disease on nitric oxide, which is crucial in vascular responsivity. As discussed above, kidney impairment increases ADMA and SDMA, which are inhibitors of nitric oxide synthase, and therefore have been implicated in vascular disease (73). Although limited by small sample size, studies have shown that doses of ADMA increase vascular stiffness and decrease cerebral perfusion in healthy subjects, and that increased concentrations of ADMA are associated with LAS and cardioembolic stroke (59, 74).

Lastly, CKD can also lead to CBF dysregulation and hence stroke through anemia. Anemia in fact is a well-known complicating feature of CKD, present in up to two thirds of subjects with severe kidney impairment (75). Concomitantly, anemia has been shown to increase the risk of stroke by almost 50%, possibly through impairment of oxygen delivery to tissue, blood supply and CBF (76). This relationship between anemia and CBF may explain the further increase in stroke risk observed in CKD patients with anemia, compared to CKD patients without anemia (11).

Oxidative Stress (Axis 3)

Chronic low-grade inflammation can be seen in patients at all stages of CKD. Levels of pro-inflammatory molecules Interleukin (IL)-6, IL-1 and Tumor Necrosis Factor (TNF)-α are higher even in patients in the early stages of CKD, and this inflammation appears to influence CKD progression. As CKD worsens, uremic toxins, indoxyl sulfate, and guanidino compounds enter the central nervous system and promote neuroinflammation

via macrophage and microglia polarization toward a pro-inflammatory phenotype (77).

Patients with CKD suffer from impaired production of many antioxidant sources, such as glutathione peroxidases and mitochondrial superoxide dismutase (78), with commensurate increases in uremic toxins such as indoxyl sulfate, p-cresyl sulfate, advanced glycation end products, oxidized LDL, and activated Nicotinamide Adenine Dinucleotide Phosphateoxidase (79). In this context, it is perhaps unsurprising that levels of biomarkers for oxidative stress (such as malondialdehyde) have been found to be increased in patients suffering from CKD and cardiovascular disease (80). Finally, iron therapy, frequently required in advanced stages of kidney dysfunction as a result of chronic disease anemia, may also contribute to oxidative stress (81).

This oxidative stress and consequent inflammation have profound vascular effects and influence on cerebral blood flow. Free radicals increase endothelial permeability, platelet aggregation, and alter reactivity to vasodilators (82). Oxidative stress eventually contributes to endothelial dysfunction, arterial stiffness and development of atherogenesis as discussed above in patients with CKD (83).

Impairment of Blood–Brain Barrier Function (Axis 3)

The blood–brain barrier (BBB) is made of vascular endothelium, a specialized basement membrane, astrocyte foot processes, and pericytes. Due to this specialized barrier, access to the brain from the blood is highly regulated. Animal experiments have demonstrated impairment of BBB integrity in the setting of both acute kidney injury and CKD (84). This BBB disruption can lead to leakage of toxic compounds and proteins into perivascular tissues. The consequent edema, arteriolar stiffening and impaired vasoregulation can contribute to hypo-oxygenation, hypoperfusion, and ultimately ischemic changes. Each of these features has been identified in SVD and chronic cerebrovascular diseases (85, 86).

The Role of Human Genetic Studies in Clarifying the Effects of Kidney Dysfunction on Cerebrovascular Disease

The aforementioned observational studies and many others have recognized the role of CKD in cerebrovascular disease and quantified the associations between the two. However, conventional analytical methods in observational research are limited in providing evidence for causal effects, and therefore insights about the mechanisms underlying the observed associations are constrained. In particular, it remains unclear whether both the kidney and the brain suffer concomitantly from similar injuries and ultimately perfusion failure or whether damage to one can lead to injury in the other. Human genetics can provide valuable information about the causal networks underlying CKD and cerebrovascular pathologies. Genetic variation is determined at conception and is therefore not influenced by confounding processes occurring later in life. Thus, studying genetic data can provide useful additional and orthogonal anchors to causality.

Conventional genetic research, genome wide association studies (GWAS) and post-GWAS research instruments, such as Mendelian randomization (MR), may clarify the complex relationship between the two diseases. In parallel with the axes inferred by epidemiological studies, genetic data may be used to test the following hypotheses: kidney dysfunction and cerebrovascular disease are the result of a single shared biological defect, as is the case in rare monogenic diseases (axis 1); kidney dysfunction and cerebrovascular disease share common pathologic pathways that contribute to both diseases (axis 2); kidney disease causally contributes to the risk of specific cerebrovascular pathologies that increase the risk of stroke (axis 3).

Axis 1

The presence of similar underlying susceptibility between kidney disease and stroke is supported by rare diseases in which a genetic mutation results in clinical presentation of concurrent kidney impairment and stroke. One example is Anderson-Fabry Disease, which is characterized by accumulation of glycosphingolipids. Deposits of glycosphingolipids in the vascular endothelia and smooth muscle cells cause vessel stenosis or occlusion. Stroke may result from either direct vessel involvement or cardioembolism. As the disease progresses, renal vasculature becomes affected as well, and failure occurs almost inevitably (87). Collagen IV (*COL4A1*) mutations have been described in clinical syndromes with invariable involvement of the eye, kidney, and brain. *COL4A1* mutations result in vessel abnormality and SVD with stroke and CKD (87). Lastly, patients affected by CADASIL, caused by a mutation on the *Notch3* gene, may display renal injury together with high risk of ischemic stroke (87). These clinical observations and genetic studies support the presence of an underlying organic pathway, the dysfunction of which leads to physiologic disarray in both the renal and cerebrovascular systems.

The hypothesis of accentuated vascular damage in patients with renal disease (axis 1) is further upheld by findings from genetic epidemiology. Recent GWAS have identified variants in genes and associated pathways which may contribute to alteration of renal function (88, 89). Among these, the *APOL1* gene has been consistently linked to severe hypertension-induced kidney impairment in African American individuals (90). Although the underlying mechanisms remain unclear, in a setting of hypertensive kidney injury, *APOL1* downregulation alters podocyte function and hastens glomerulosclerosis with secondary deleterious effects on BP and vascular risk (91).

Axis 2

Large-scale human genetic studies have contributed to the study of the relationship between kidney and cerebrovascular disease (92). Polygenic risk scores (PRS), which combine genetic variants associated with a specific disease or trait, have proven to be a valuable tool to determine an individual's susceptibility to that disease across a normalized continuum of risk. In prior work, PRS capturing genetic predisposition for lower eGFR have

been associated with increased risk of stroke related to large artery atherosclerosis. Similarly, PRS reflecting predisposition to microalbuminuria have been associated with increased risk of stroke related to large artery atherosclerosis and SVD (93). A more recent study corroborated the genetic correlation between renal dysfunction and cerebrovascular disease and confirmed the shared heritability and genetic predisposition between CKD and risk of ischemic stroke (94). This study further dissected the shared pathogenesis among stroke subtypes, identifying that it is predominantly the genetic predisposition toward lower eGFR that drives associations with higher risk of LAS and SVD stroke (94). These genetic findings support the hypothesis that there are shared pathogenic mechanisms between the two diseases.

By applying a pairwise GWAS analysis, which explores shared genomic signals between two traits at the single locus level (95), genomic loci which may be involved in the shared pathogenesis of two diseases can be highlighted (94). Using this approach, this same study identified a locus at chromosome 12q24 which was found to be associated with both eGFR and LAS risk (94). Two genes in this region may highlight the mechanisms underlying this shared pathogenesis: *ATXN2*, which is involved in spinocerebellar ataxia type 2 and is associated with kidney disease, and *SH2B3*, which is associated with hypertension and vascular disease. These results reinforce the hypothesis that, once in place, the same pathologic pathways can drive both renal and cerebrovascular manifestations. The same study also demonstrated that the observed shared genetic pathways act independently of genetic susceptibility to hypertension. Taken together, these data compliment prior work in supporting the hypothesis that CKD, as estimated by impaired eGFR is associated with LAS risk and lend orthogonal support to the epidemiology theory that a different axis (axis 2) links the kidney and the brain beyond the already known shared susceptibility to vascular risk factors.

Similar inferences can be advanced regarding SVD. In the aforementioned genetic study, common genetic variants at 2q33 were associated with risk of small vessel stroke, CKD and severity of WMH. Three genes (*NBEAL1*, *FAM117B* and *WDR12*) within the 2q33 locus were found to be expressed in various cells of the nervous system including astrocytes, oligodendrocytes and neurons (96). Variants in the *WDR12* gene have also previously been associated with WMH burden, further corroborating these results (97, 98). Taken together, these data support the possibility that there are specific biological pathways, potentially involving the products of these genes, which once perturbed may lead to SVD pathology in those organs where small vessels are particularly represented, namely kidney and deep brain structures.

Axis 3

To explore whether the identified associations could also represent causal effects of kidney disease on the cerebral vasculature, bioinformatics methods have been applied to derive causal inference from genetic associations in a form of instrumental variable analysis (94). MR uses genetic variants associated with a trait as instruments and explores their effects on the outcome of interest (99). By anchoring on genetic variants, which are randomly allocated at conception and thus not influenced by confounders, MR can help elucidate causal relationships, as has been specifically demonstrated in stroke over the last several years (100). MR analysis has shown that genetic predisposition to CKD conveys a mildly increased risk of all types of stroke (OR = 1.07; 95% CI = 1.01–1.15). Assessing continuous indices of kidney dysfunction and subtypes of stroke, genetically determined lower eGFR and genetically determined microalbuminuria were found to increase risk of LAS by almost two-fold. Finally, genetically elevated microalbuminuria increased the risk of ICH, although the wide confidence interval of this finding makes the true estimate of excess risk difficult to ascertain (OR = 5.09; 95% CI = 1.02–26.41). In reverse, none of the cerebrovascular traits were found to have a causal link to any of the studied measures of kidney impairment. These MR findings support the presence of potentially causal mechanisms (possibly ones identified as axis 3), which when triggered by kidney dysfunction will increase the risk of cerebrovascular disease. To further corroborate this hypothesis, many of the genes found to be associated with risk of CKD (88, 89) are involved in biological mechanisms already identified by epidemiological and experimental observations; increased oxidative stress in the renal tubules, impaired function of podocytes, and altered renal hemodynamics are mechanisms also supported by recent GWAS findings (101).

THERAPEUTIC OPTIONS

There are no specific treatments aimed at reducing stroke risk in patients with CKD (102). Given the pathogenic processes described above, optimization of established vascular risk factors, which trigger the cascade leading to deterioration of the microvascular structure of the kidney and brain is currently the most principled strategy available.

Reducing abnormally high pulsatile stress in cerebral and renal small vessels may lead to an improvement in the risk of stroke. Studies on the effects of calcium channel blockers and angiotensin converting-enzyme inhibitors, which reduce arterial stiffness and hence pulsatile stress, have shown evidence of superiority to conventional diuretics and β-blockers in progression of microvascular disease (103–105).

The China Stroke Primary Prevention Trial evaluated the effect of BP modifiers in hypertensive patients with mild-to-moderate CKD. After multivariable adjustment and independent of medication adherence, systolic BP variability increased the risk of first stroke (HR = 1.41; 95% CI = 1.17–1.69) in this category of patients (106). Excessive lowering of BP can also be detrimental. The Secondary Prevention of Small Subcortical Strokes trial with 2,454 participants showed rapid kidney function decline in the lower-BP-target arm compared to the higher-target arm (OR = 1.40; 95% CI = 1.07–1.84). These data suggest the need for careful long-term BP monitoring in CKD patients and establishment of more refined BP targets beyond standard monotonic manometric values (107).

In terms of antiplatelet or anticoagulant therapies, there are no specific recommendations to reduce stroke risk in

patients with CKD. However, patients with CKD have both high thromboembolic risk and high bleeding risk. Patients with CKD may also have altered responsiveness to antiplatelet drugs and enhanced bleeding complications with antithrombotic treatment (108, 109). As such, weighing the balance of risks and benefits of antithrombotic or anticoagulant treatment is particularly challenging in this category of patients. The benefit of stroke prevention from warfarin use has conflicting evidence, and the adoption of novel oral anticoagulants in populations with advanced renal impairment is operationally challenging due to altered pharmacokinetics in the presence of reduced creatinine clearance (110). Similarly, limited data are available for stroke prevention with dual antiplatelet therapy in CKD patients. Studies have demonstrated the safety of dual antiplatelet therapy after coronary stenting in CKD patients, with no difference in 1-year composite outcomes (including all-cause death and major bleeding) when compared to patients with normal renal function (111). More specifically for cerebrovascular disease, two recent trials which showed benefit in stroke recurrence with short term dual antiplatelet therapy after minor stroke or TIA, did not exclude patients based on their kidney function (112, 113).

Statins have not been shown to reduce stroke risk in advanced CKD patients. A meta-analysis that included data from the largest randomized controlled trials showed that statins did not impact stroke risk in dialysis patients (114). Similarly, the Pravastatin Pooling Project, which included 4,491 patients with severe kidney disease, concluded that there was no statistically significant difference between statin and placebo groups in the prevention of stroke (102, 115).

Sodium-glucose cotransporter-2 inhibitors were initially developed to reduce hyperglycemia in diabetic patients, and seem to have beneficial cardiometabolic effects in patients with CKD, independent of diabetes (116). In the EMPA-REG OUTCOME trial, empagliflozin reduced non-fatal stroke risk by 14% when compared against placebo (HR = 0.86; 95% CI = 0.74–0.99), together with other primary cardiovascular endpoints (117). These vascular benefits in patients with declining kidney function appear to be largely independent from the effects on glycemia or hypertension, and warrant further investigation as preventive agents.

Lastly, a novel approach involves the use of anti-inflammatory therapies to reduce cardiovascular risk. Given the systemic pro-inflammatory status of CKD patients, efforts have specifically tested the benefits of anti-inflammatory compounds in this high-risk group. The CANTOS trial showed a reduction in vascular endpoints among patients with coronary artery disease receiving canakinumab, a monoclonal antibody against IL-1b (118). Furthermore, the RESCUE trial showed a reduction of inflammation and thrombosis biomarkers in subjects with CKD receiving a monoclonal antibody against IL-6, compared to placebo (119). Given evidence from human genetic and observational studies implicating IL-6 signaling in ischemic stroke risk (120, 121), anti-inflammatory approaches may represent a useful target for reducing stroke risk in CKD patients in the near future.

Regarding acute therapies, both intravenous thrombolysis with recombinant tissue plasminogen activator (IV-rtPA) and intra-arterial thrombectomy have been associated with worse overall outcome in patients with acute stroke and advanced CKD compared to patients with normal renal function (122). Increased bleeding risk and reduced efficacy of thrombolysis in patients with CKD have been suggested as mechanisms of unfavorable outcomes (123–125). Additional caution should be applied as these data are derived from studies of small sample size, and prediction of outcomes is complex in CKD patients as they tend to suffer from a higher burden of co-comorbidities. A recent systematic review of more than 53,000 patients clarified that impaired renal function independently associates with mortality after IV-rtPA administration, but has not been associated with a higher rate of hemorrhagic conversion (126). Similarly for endovascular procedures, limited data are available regarding safety in patients with CKD. Two studies showed that the presence of severe kidney impairment was a predictor of poorer functional recovery and higher mortality, but not through increased rates of hemorrhagic complications (127, 128). Given the paucity of data on safety and patient outcomes in CKD patients, the presence of CKD alone should not constitute a reason to defer IV-rtPA administration or endovascular thrombectomy.

Despite the lack of specific primary prevention of cerebrovascular disease in patients with CKD, the strength of the association between kidney disease and stroke supports development of rational strategies for noninvasive screening of kidney function, to fully capture individual risk for cerebrovascular events.

FUTURE DIRECTIONS

Given the prevalence of kidney dysfunction and its association with stroke, the impact on healthcare is massive and underlines the need for screening interventions and novel therapies. Elucidating mechanisms of shared pathobiology and risk between the kidney and cerebrovascular system is pivotal to developing new strategies to ameliorate both stroke and progressive kidney disease in patients at risk for these conditions. Genetic epidemiology in particular represents a useful means to help clarify the temporality and interactions among the hypothesized pathological mechanisms, with pleiotropy analyses demonstrating genes linking kidney and cerebrovascular damage, and MR analyses offering clues about the directionality of associations between kidney and brain pathology (129). Building on the works of ongoing population-based research and cohort studies, the construction of larger and more powerful genetic association studies may identify new mechanisms underlying the biological pathways of renal and cerebral SVD, leading to novel targets for disease prevention for patients with these prevalent and highly morbid conditions (130, 131).

AUTHOR CONTRIBUTIONS

SM and MKG: literature search and manuscript writing. CA: manuscript writing and review. All authors contributed to the article and approved the submitted version.

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REVIEW
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"Is It Removed During Dialysis?"—Cognitive Dysfunction in Advanced Kidney Failure—A Review Article

Kirsty Crowe[1]*, *Terence J. Quinn*[2], *Patrick B. Mark*[1,2] and *Mark D. Findlay*[1]

[1] Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, Glasgow, United Kingdom, [2] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

Cognitive impairment is independently associated with kidney disease and increases in prevalence with declining kidney function. At the stage where kidney replacement therapy is required, with dialysis or transplantation, cognitive impairment is up to three times more common, and can present at a younger age. This is not a new phenomenon. The cognitive interactions of kidney disease are long recognized from historical accounts of uremic encephalopathy and so-called "dialysis dementia" to the more recent recognition of cognitive impairment in those undergoing kidney replacement therapy (KRT). The understanding of cognitive impairment as an extra-renal complication of kidney failure and effect of its treatments is a rapidly developing area of renal medicine. Multiple proposed mechanisms contribute to this burden. Advanced vascular aging, significant multi-morbidity, mood disorders, and sleep dysregulation are common in addition to the disease-specific effects of uremic toxins, chronic inflammation, and the effect of dialysis itself. The impact of cognitive impairment on people living with kidney disease is vast ranging from increased hospitalization and mortality to decreased quality of life and altered decision making. Assessment of cognition in patients attending for renal care could have benefits. However, in the context of a busy clinical service, a pragmatic approach to assessing cognitive function is necessary and requires consideration of the purpose of testing and resources available. Limited evidence exists to support treatments to mitigate the degree of cognitive impairment observed, but promising interventions include physical or cognitive exercise, alteration to the dialysis treatment and kidney transplantation. In this review we present the history of cognitive impairment in those with kidney failure, and the current understanding of the mechanisms, effects, and implications of impaired cognition. We provide a practical approach to clinical assessment and discuss evidence-supported treatments and future directions in this ever-expanding area which is pivotal to our patients' quality and quantity of life.

Keywords: cognitive dysfunction, kidney failure, neurocognitive disorder, dialysis, dementia, cognitive impairment, uremia

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***Correspondence:**
Kirsty Crowe
kirsty.crowe@ggc.scot.nhs.uk

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INTRODUCTION

Cognitive impairment is increasingly prevalent in aging and multi-morbid populations. Chronic kidney disease (CKD) is also increasing in prevalence and after correcting for shared vascular risk factors within an aging multi-morbid population, advanced CKD is independently associated with cognitive impairment (1). Kidney replacement therapies (KRT) with dialysis or kidney transplantation carry a cognitive burden in themselves, from the lifestyle demands and healthcare interactions demands on patients through to marked physiological stressors and unique cardiovascular instability. The reciprocal relationship between cognitive impairment and CKD has been recognized for a long time, although a full understanding of this relationship and how to address it has only relatively recently become the focus of research activity.

In this article we provide an overview of the relationship of cognitive impairment and kidney failure—examining the past, present and looking to the future. After reflecting on the historical context of cognitive impairment in kidney failure, current epidemiological patterns, and presentation of cognitive impairment in people with kidney failure with replacement therapy (KFRT) will be discussed. The proposed mechanisms underlying the relationship between cognitive impairment and KFRT and the real-life patient implications of cognitive impairment will be considered. Methods of assessing cognitive impairment in the KFRT population and possible treatment and preventative strategies will be examined, followed by a discussion of future areas for research.

"HAS LONG BEEN KNOWN..."—THE HISTORY OF COGNITIVE IMPAIRMENT IN KIDNEY FAILURE

Nephrology as we know it now—a multifaceted specialty comprising immunology, dialysis, transplantation and hypertension—is a relatively young specialty. To put this in context, coinage of the word Nephrology and its recognition as a unique specialty is often attributed to the "Premier Congrès International de Néphrologie"—the first meeting of the International Society of Nephrology (2), held in 1960. Early a primary focus was, and remains, prevention and treatment of renal failure. In an aging and increasingly comorbid population the wider complications of kidney disease and its treatments are now claiming precedence (3).

However, it must be noted the effect of kidney disease on cognitive function is not a new observation as the "…*reciprocal action of the brain on the kidney and the kidney on the brain, has long been known.*" Written in 1839, in volume 31 of the Medico-Chirurgical review and Journal of Practice Medicine Dr. Thomas Addison describes this "new ground" in clinical observation (4). In his review he describes a variety of clinical presentations, including "…dullness of intellect..." and "…sluggishness of manner…" that affect those with renal disease. It seems likely Addison, an English physician and scientist, was describing uremic encephalopathy over a century before the birth of modern nephrology, see **Figure 1**.

Described in greater detail by Schreiner and Maher in 1961 (5), uremic encephalopathy is now fortunately a rarely witnessed complication of kidney failure at the point where dialysis is indicated. Presenting as lethargy, irritability, disorientation, hallucinations, and altered speech uremic encephalopathy can progress to tremor, myoclonus, seizures, and coma. Rarely, focal neurological signs such as hemiparesis can be present, and are unusually transient and can alternate from side to side (6). Although branded uremic encephalopathy and observation that the severity of symptoms parallels the degree of kidney dysfunction (and thus urea concentration), it remains unclear which toxin(s) are responsible for this clinical syndrome. Altered neurotransmitter function (7), acidosis (8), and elevated PTH (9) are amongst the suggested mechanisms. Diagnosis is clinical, and the continued treatment with dialysis resolves the majority of symptoms.

Although acute kidney injury is capable of causing similar cerebral dysfunction, and often labeled delirium of acute illness, modern nephrologists rarely witness such marked neurocognitive impairment attributable to the uremic encephalopathy of advanced kidney failure. However, such an insight was described in a recent case report from 2012 where a 27-year-old presented with advanced kidney transplant failure—serum creatinine 2443 umol/L and urea 67.6 mmol/L. A detailed neurocognitive assessment was serendipitously available due to ongoing research and its use demonstrated sequential improvement in executive function and attention with subsequent dialysis treatment, **Figure 2** (10).

Thus, with the advent of regular hemodialysis the neurotoxicity of kidney disease could now be alleviated as nephrologists provide respite. Describing the first two regular hemodialysis patients Scribner et al. highlight that sufficient dialysis led to improvement where *"neither patient has yet shown the relentless loss of weight and the mental deterioration which has been encountered in the past when less intensive dialysis therapy was employed*"(11). Dialysis was a success. For about a decade.

First described in 1972 (12) a syndrome of dysarthria, dyspraxia and speech problems leading to personality problems, seizures, dementia and death was emerging in patients on dialysis. Aluminum, a heavy metal, was suspected to cause this neurodegenerative disorder and in 1970 high serum aluminum levels were discovered and initially attributed to the use of aluminum hydroxide used as a phosphate binder (13). Coined "dialysis dementia," keen observation recognized an association with symptoms being "aggravated during and immediately following dialysis" (12) and geographical clustering led investigators to suspect an environmental factor. In 1976, a report from the Netherlands (14) described discrepancy of cases between two hemodialysis units. In the affected unit, high concentrations of aluminum were found in the dialysis water due to an eroded heating element. Evidence was growing to support aluminum in the water supply was culprit (15). However, the rare occurrence of faulty equipment did not explain the observed international outbreak. Two years later a report in the BMJ was

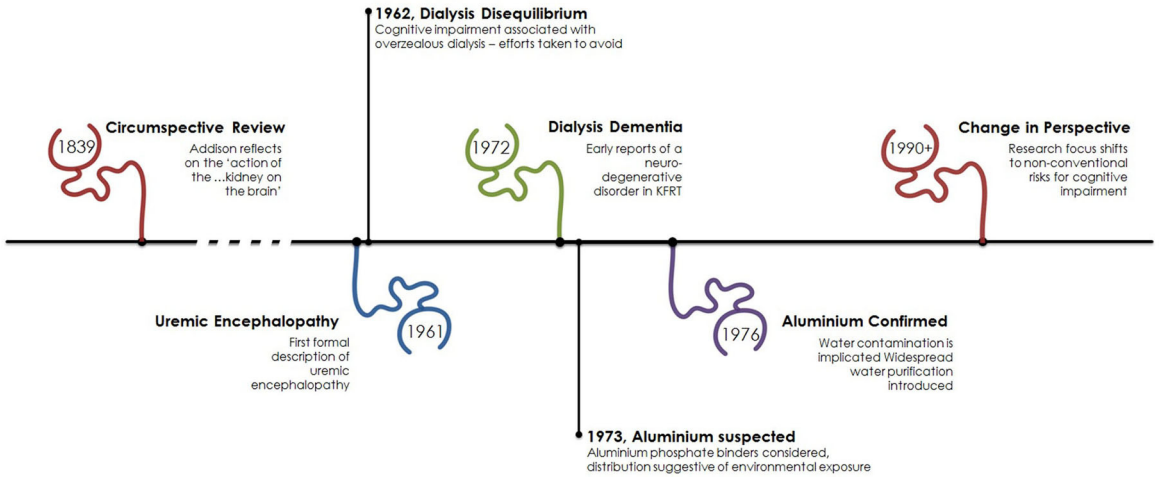

FIGURE 1 | Timeline of cognitive impairment in kidney failure. The association of cognitive impairment and kidney disease has been recognized for some time with early focus on the neurotoxic effect of kidney failure. Following the advent of dialysis the process of dialysis was responsible for cerebral dysfunction as a result of its own associated initially unrecognized neurotoxin, aluminum. From the early 1990s focus has turned toward other factors associated with kidney failure such as anemia and new dialysis-specific effects.

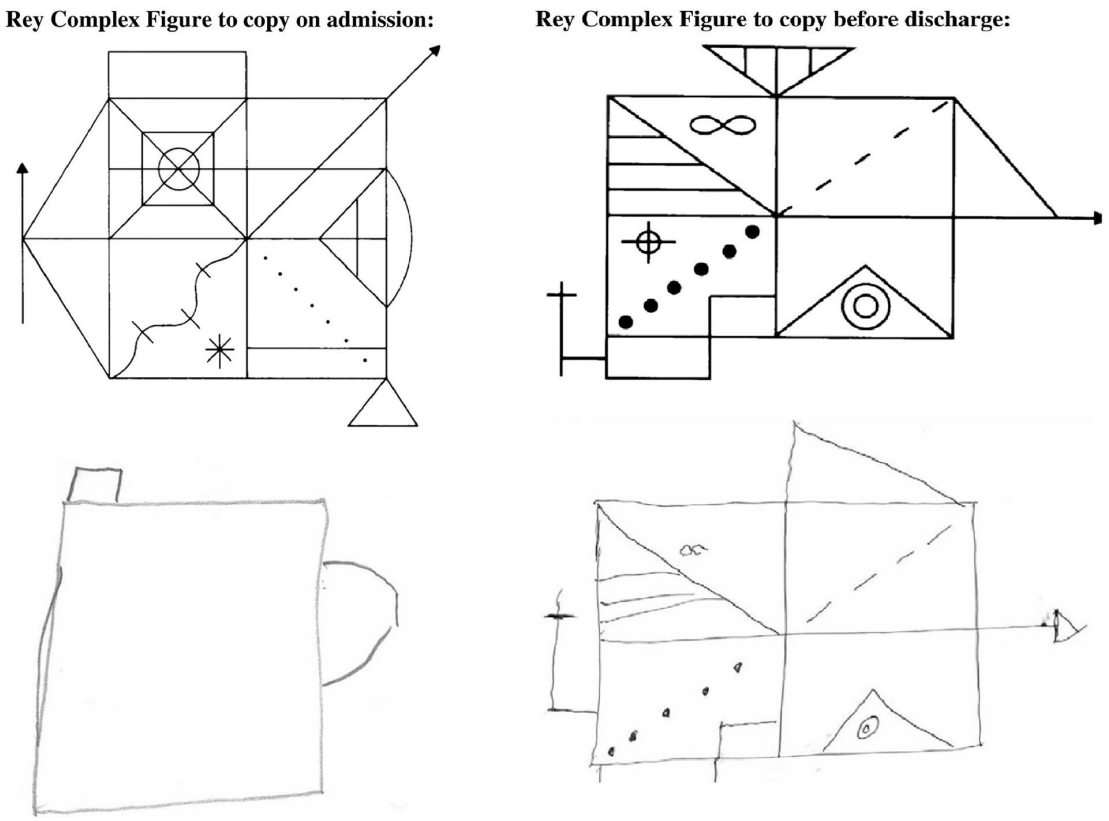

FIGURE 2 | Rey Complex figure testing before and after correction of severe kidney failure. This assessment captures multiple domains of cognitive function including memory, processing speed, and visuospatial construction ability. In this example the admission assessment, performed with a serum creatinine of 2,443 umol/L and blood urea of 67.6 mmol/L is compared to the discharge assessment (creatinine 629 umol/L, urea 17.8 mmol/L). Reproduced from Schneider et al. (10) under the Creative Commons Attribution License.

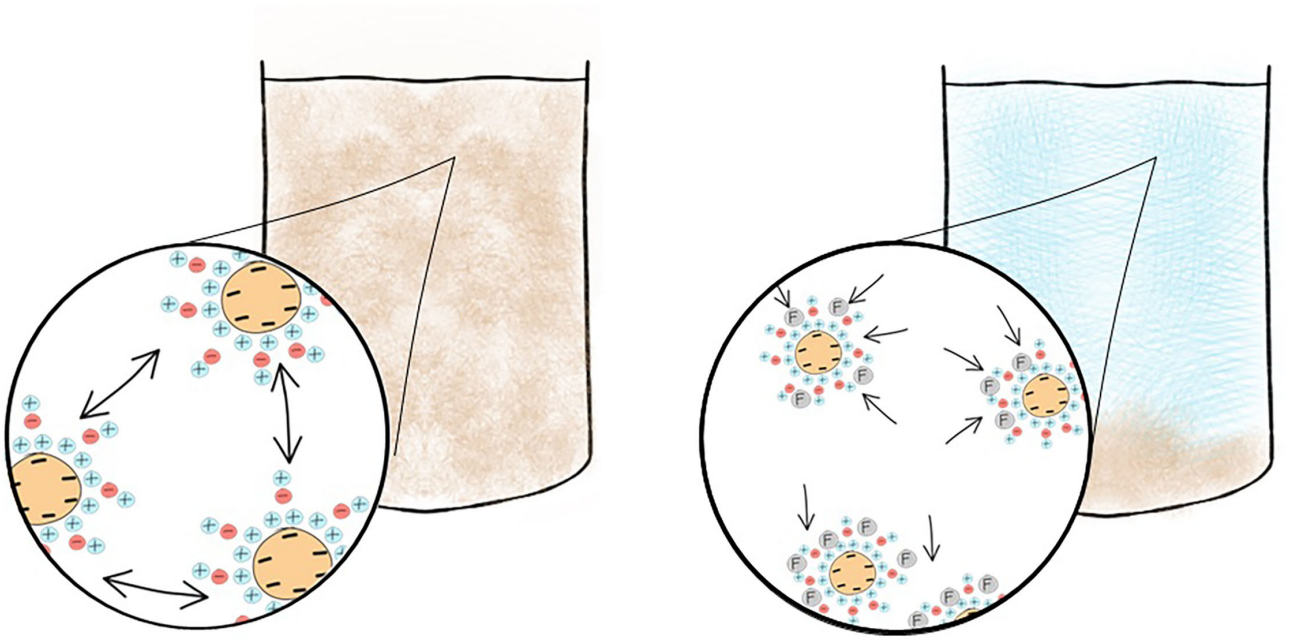

FIGURE 3 | Addition of a flocculant such as aluminum improves water clarity prior to public consumption. Colloidal suspensions persist when the particulate matter is too light to sink and their surrounding charge prevents the colloids from adhering to each other. The addition of a flocculant overcomes this causing the colloid to form flocs which will sediment within the body of water. Aluminum, a flocculant, is added to drinking water and now removed by reverse osmosis prior to use in dialysis preventing toxicity.

published from a group in Glasgow, Scotland demonstrating a correlation between local prevalence of dialysis encephalopathy and aluminum concentration in tap water (16) used for dialysis. Routinely, aluminum is added to drinking water to promote flocculation, a process where suspended particles clump together to improve clarity of the water, **Figure 3**.

In areas with soft water, such as the west of Scotland—where the use of reverse osmosis purification was not felt necessary to reduce calcium content prior to use—dialysis patients would be exposed to high levels of aluminum with each session. Since its recognition and focus on improving dialysis through strict water standards "dialysis dementia" is a thing of the past.

As the process of dialysis has become safer and more efficient and the population receiving dialysis more medically complex attention has turned toward recognizing cognitive dysfunction as a comorbidity in those with kidney failure and exploring the mechanisms which are responsible for it.

A COMMON BUT POORLY RECOGNIZED PROBLEM—EPIDEMIOLOGY

Cognitive impairment is common in kidney failure with replacement therapy (KFRT) (17). In order to discuss cognitive impairment, it is essential to consider a few definitions. For the purposes of clinical assessment, cognitive function is conveniently divided into individual domains. Commonly assessed domains include attention, memory, language, visuospatial perception, social cognition and executive function, which is the ability to plan and carry out complex tasks. These are the domains that are used to assess for the clinical syndrome of dementia in the latest iteration of the Diagnostics and Statistics Manual (DSM-5). Assessment tools exist to determine deficits in one or multiple domains (discussed later) and are used to assess the possible etiology, severity and consequences of cognitive impairment. The commonly labeled "mild cognitive impairment" (MCI), or strictly "mild neurocognitive disorder" in the DSM-5, is defined as a "moderate cognitive decline from a previous level in $\geq$1 cognitive domain," which is neither attributable to delirium nor another mental disorder and does not interfere with independence in daily activities. In contrast, dementia (or "major neurocognitive disorder") is defined by presence of "major decline," usually over two domains and which is sufficient to interfere with independence in everyday activities (18). Thus, it is the functional impact of the cognitive impairment that determines the eventual diagnostic formulation and emphasizes the importance of assessing not only cognitive domains but also how these impairments interfere with daily life.

Various factors influence the prevalence of cognitive impairment. Twelve modifiable risk factors which account for 40% of worldwide dementias include excessive alcohol use, smoking, physical inactivity, low social contact, diabetes, and hearing impairment (19). The single greatest factor in the general population is age (20, 21). Definitions of cognitive impairment and characteristics of included populations vary considerably between studies, and for this reason there is significant variation in reported prevalence. However, the authors of the COSMIC collaboration accumulated the results of 10 studies—collectively

20,987 participants—in an attempt to quantify this within a diverse geographical and ethno-cultural population. Using an MMSE score 24–27 they described a crude incidence of 12% in those with mean age range of 68.5–78.3 years (22).

So, how does this compare to the KFRT population? Executive function which encompasses higher cognitive processing such as planning, task prioritization and self-regulation, is the most commonly affected cognitive domain in kidney disease, reflecting the sub-cortical vascular impairment in this population (23, 24). There is a recognized linear relationship between GFR and prevalence of cognitive impairment. It is estimated that for every 10 ml/min/1.73m^2 decrease in GFR in those aged >55 years there is an 11% increase in prevalence of cognitive impairment (25). Further, as the eGFR falls below 45 mL/min/1.73^2 cognitive function declines substantially (26, 27), and cognitive decline accelerates more rapidly with eGFR below 30 mL/min/1.73^2 (28). At the point of KFRT the estimated prevalence of cognitive impairment ranges from 27 to 77% (17, 29). Many patients with KFRT are excluded from completing standard cognitive assessments due to physical disability from previous vascular events which results in underestimation of prevalence by excluding those with an established vascular burden (30). Additionally many studies attempting to ascertain the prevalence of cognitive impairment in these populations have missing data due to poor patient motivation for completing assessments, which can itself be a consequence of cognitive impairment.

In 2018 in the UK the median age of those receiving in-center hemodialysis was 67.4 years, having risen from 63.3 years, since 2000 (31). Therefore, in an ever-aging population, with such high burden of cognitive impairment nephrologists may become overwhelmed with concerns previously thought to be those of geriatricians. In a US publication from 2006, it was estimated that over 80% of a dialysis cohort ($n = 338$), mean age 71.2 years had cognitive impairment. They described 13.9% as having mild, 36.1% moderate, and 37.3% severe cognitive impairment. Most striking, in this same cohort only 2.9% had an existing clinical label of cognitive impairment (17).

Recognition of cognitive impairment is poor but perhaps this relates to the insidious onset throughout CKD stages and a potential recovery following initiation of dialysis? This does not appear to be the case. The authors of the Chronic Renal Insufficiency Cohort (CRIC) study recognized that the initiation of dialysis can induce a stepwise decline in cognitive function—specifically executive function. In their study they prospectively followed over 200 patients with CKD likely to progress to hemodialysis, or who had progressed to hemodialysis, over a 2-year period. Three groups of patients emerged, those who remained in CKD, those who transitioned to dialysis and those who were on dialysis at first cognitive assessment. A significant drop in executive function was noted in those who transitioned to dialysis during follow-up, with progressive decline at a rate similar to those on dialysis. The executive function of those who did not require dialysis declined at a slower rate than those on dialysis (32).

Increasing interest is being paid to the changes in cognitive function associated with the dialysis session itself, which has consequences for determining the optimal timing for undertaking cognitive assessments. Reports are somewhat contradictory. Improvements following dialysis have been reported by Williams et al. (33), Lux et al. (34), and Schneider et al. (35) who all report multi-domain cognitive function assessments immediately prior to dialysis and comparing this to cognitive function ∼24 h later. They demonstrate an improvement in multiple aspects of cognition, including memory, language, and executive function. However, one of the more revealing studies of the temporal relationship of dialysis and cognitive function was reported by Murray et al. (36). In this, they performed multi-domain cognitive assessment at multiple time points related to the dialysis treatment. Specifically, they tested 28 patients immediately before, 1 h into dialysis, 1 h after dialysis and ∼24 h later. With this method they demonstrated a significant intradialytic decline in all domains of cognitive function, demonstrating the highest scores immediately before or at 24 h after dialysis (36). Therefore, one conceptualization of the progression of cognitive dysfunction in those with kidney failure could be summarized as per **Figure 4**. In normal aging cognitive function will decline over years, with more rapid progression in those with kidney disease. Initiation of dialysis provides an acute decline in cognitive function with more rapid decline that may be explained by repeated dialysis, capably of inducing transient cognitive decline. However, a recent prospectively randomized study designed to circumvent the learning effect of neuropsychological testing found no difference in performance during the first or second half of dialysis compared with the day after dialysis (37). The small and relatively younger and less hypertensive hemodialysis cohort studied may have confounded results; however we acknowledge this further illustrates that the effect of the hemodialysis therapy on cognition is still not fully established.

As one ages, the brain undergoes several structural changes which may have an effect on cognitive function. Atrophy is the most common change. Rate of volume loss is usually 0.5% per year after the age of 40, but with considerable variation (38). Radiological evidence of cerebral atrophy can be considered normal aging after about age 50 (39). In disease states these changes can accelerate and lead to greater loss of function.

In people requiring KRT data have shown an association with greater prevalence of atrophy (40) and onset earlier in life than the general population—reported as occurring almost a decade earlier than would be expected (41). In KFRT, cerebral atrophy is associated with cognitive impairment, duration of dialysis (42), intradialytic hypotension (43), and cerebrovascular disease (44).

White matter hyperintensities, commonly believed to represent small vessel disease are twice as common in the dialysis population compared to the general population, with a prevalence of 52 vs. 22.4% in a cohort with mean age 55.9 years (45). Advanced MR imaging is capable of assessing white matter tract integrity, prior to the onset of white matter hyperintensities. Using diffusion tensor imaging an estimation of location, orientation and anisotropy (crudely, the "direction of flow" of water molecules within white matter tracts) is of particular interest and may signify areas at risk of vascular damage. In hemodialysis patients, deterioration in markers of diffusion imply a loss of tract integrity (46), and is associated

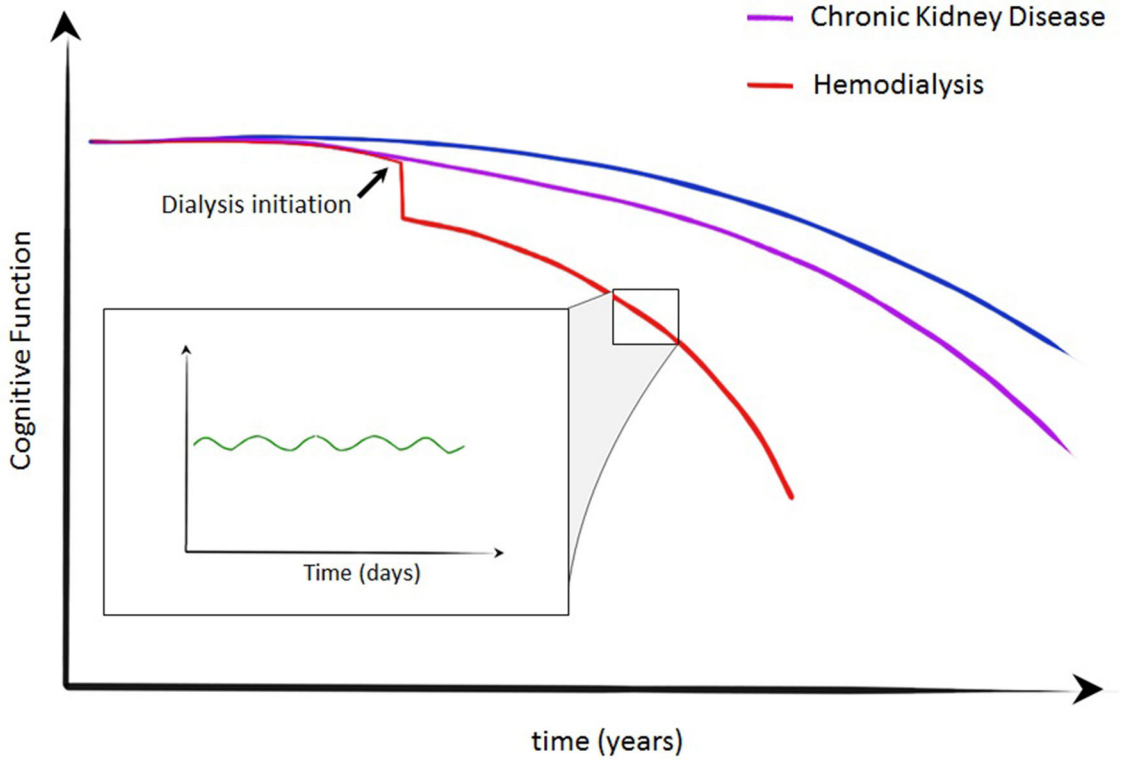

FIGURE 4 | Crude conceptualization of cognitive decline in normal aging, CKD and kidney failure requiring dialysis. A stepwise decline is described at the initiation of dialysis with more rapid decline in cognitive function in those on dialysis. During individual dialysis treatments, transient cognitive decline has been demonstrated—an insult likely to contribute to the trajectory of those on dialysis.

with cardiovascular instability during dialysis (47). This effect is mitigated by cooled dialysis (48), and renal transplantation (49, 50), and discussed later.

Therefore, in kidney failure requiring KRT cognitive impairment is common. Specifically, compared to age matched controls from the general population, severe cognitive impairment is more than three times more prevalent (17). It is poorly recognized, can accelerate with initiation of dialysis and may vary around the dialysis cycle. The urgent need to untangle the mechanisms of cognitive impairment in KFRT has gained increasing attention over the last two decades.

VASCULOPATHY: THE NEW ENCEPHALOPATHY?—MECHANISMS OF COGNITIVE IMPAIRMENT IN KIDNEY FAILURE

In this review we focus on cognitive impairment in those with kidney failure requiring KRT. However, to understand the multiple mechanisms responsible for cognitive impairment one must recognize that patients have progressed through stages of CKD accruing morbidity and complications which leads them to this point, where cognitive impairment is so highly prevalent. Once KRT is required, the process of dialysis brings unique insults implicated in the development of cognitive impairment. Although much evidence supports a vascular driven etiology of cognitive impairment in advanced CKD the process is likely multifactorial. We discuss the mechanisms of cognitive impairment unique to those requiring KRT by broadly dividing each into traditional risk factors—factors associated with cognitive decline in the general population—and non-traditional risk factors—those unique to the physiological stressors of KFRT, **Figure 5**.

Traditional Risk Factors for Cognitive Decline

Age

Age is the single biggest risk factor for cognitive impairment in the general population (20, 51, 52). The prevalence of cognitive impairment increases with age; approximately doubling for each decade over the age of 60 years; with an estimated prevalence of 6.7% from age 60, 10.1% from 70 and 25.2% from, age

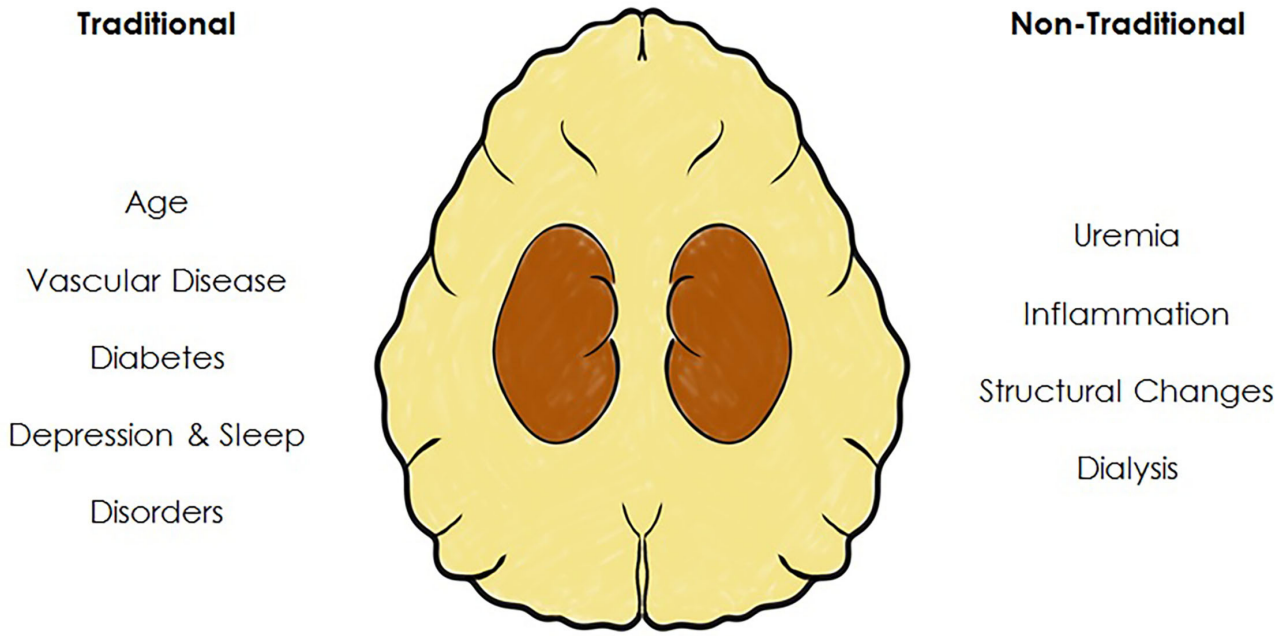

FIGURE 5 | Factors associated with cognitive impairment in kidney failure. In addition to an increased burden of risk factors traditionally associated with cognitive impairment, those receiving KRT have additional factors unique to KFRT.

80 onwards (21) in the general population. Age is also a recognized association for cognitive impairment in the dialysis population (32). With an aging dialysis population the prevalence of cognitive impairment is high and likely to rise. However, it is worth noting in KFRT the prevalence is notably high even at a relatively young age—reaching ∼10% in those aged 21–39 years (29). The rate of cognitive decline with age is highly variable between individuals. However, when comparing those on dialysis to a matched cohort of patients with CKD (GFR <30 mL/min/1.73^2) not only is cognitive function lower at baseline in those on dialysis, but cognitive function declines more rapidly over a period of 2 years (53).

Cerebrovascular Disease

Cerebrovascular disease is a driving force capable of producing mild cognitive impairment and vascular dementia—the second most common cause of dementia in the general population after Alzheimer's disease (54). Compared to the general population, cerebrovascular disease is 10 times more common in those on KRT (55). Although cognitive impairment may complicate a presentation of stroke, a more insidious onset can occur through development of small vessel disease or silent infarction (56). Compared to age-matched controls those on dialysis are five times more likely to have silent cerebrovascular disease than the general population (57). In contrast to Alzheimer's disease which—in its early stages—presents predominantly with memory loss, vascular cognitive impairment classically presents with progressive loss in attentional processes and executive function (58).

As stated, the burden of cerebrovascular disease in kidney failure has led many authors to believe cerebrovascular disease plays a pivotal role in the etiology of KFRT-related cognitive impairment. Multiple supporting factors consolidate this theory. Primarily, similar to those with vascular dementia the finding of reduced executive function is the most frequently reported cognitive impairment in dialysis patients (59–61). Further, in the stages preceding KRT higher levels of albuminuria—a recognized cardiovascular risk marker—are associated with worse executive function and white matter hyperintensities on MRI (62, 63). Finally, administering more intensive dialysis—thereby improving solute clearance—does not improve cognitive function (64).

Cardio-Metabolic Disease

The presence of diabetes, hypertension, and cardiac failure are all associated with cognitive impairment (65–67) and all found in abundance in those with renal disease. To put this in context, data from the US and European renal registries demonstrate that the most common cause of need for KRT is diabetic kidney disease (68, 69). Further, the prevalence of hypertension in the dialysis

population is significantly higher than the general population (70)—a factor often commented on when age and sex matched cohorts are compared. The relationship between cardiac and renal disease is firmly established, with cardiac disease listed as the most common cause of death in people needing KRT (71–73). A recent systematic review has summarized the magnitude of cognitive impairment in those with cardiac failure—with a prevalence of 43% (74). Although also assumed to be vascular, the pathophysiology of this remains elusive.

Depression

Cognitive impairment is a diagnostic criterion of major depressive disorder (18). However, even following treatment for the mood disorder, cognitive impairment can persist (75, 76). Usually presenting as self-reported memory loss, and often notably lacking in participant effort on testing, depression can present with marked memory disturbance a condition previously called "pseudodementia" (77).

Depression is common in KFRT and poorly recognized (78). Reported world-wide prevalence of depression in people requiring KRT is 13.1–76.3%, considerably higher than the estimate for the world's population at 3.38%, from a 2020 World Health Organization report (79). Diagnosing depression is difficult due to the overlap of symptoms brought by kidney disease such as anorexia, sleep disturbance, fatigue, and psychomotor retardation. Therefore, greater focus should be given to symptoms such as dysphoria, anhedonia, worthlessness/guilt, suicidal ideation, and cognitive dysfunction. Although increasingly recognized as clinically important, outside of research, regular screening for depression is not considered routine in the clinical care of those with kidney failure (80). Depression is associated with a wide range of cognitive impairment including impaired attention, decision making, memory and social cognition (81). The combined use of both cognitive behavioral therapy (CBT) and the SSRI sertraline are recommended in treating symptoms of depression—extrapolated from evidence from in the general population (82). There are data to support use of CBT in kidney failure (83) but attempts to identify a beneficial antidepressant to improve mood are yet to be conclusive (84, 85). Further, it remains unclear if cognitive function would be improved in people requiring KRT.

Sleep Disorders

The need for sleep varies significantly between individuals, with the average sleep length of 7–8.5 per day (86). The effect of sleep deprivation is all too familiar in medicine. Acutely, those at the end of a night shift may have been aware of altered cognitive function and all are likely to have witnessed patients with delirium worsened by sleep deprivation. Sleep deprivation can be classified as acute or chronic and partial or complete. In the general population sleep deprivation is associated with a number of cognitive deficits including attention, working memory, long-term memory executive function, and decision making (86). Recovery from sleep deprivation is possible if normal sleep regulation can resume. However, the recovery from chronic deprivation can take longer (87). Therefore, those with chronic partial sleep deprivation due to underlying chronic illnesses are unlikely to experience recovery unless provided with a treatment that results in significant alleviation of disease burden.

Sleep disturbances including insomnia, fragmented sleep or reduction in total sleep time are common in people on KRT (88). The prevalence is high, estimated at 44–95% of patients (89). Compared to age and sex matched healthy controls sleep quality is worse in those on dialysis (90). The underlying mechanisms for poor sleep are unclear. Likely hypotheses include physical factors such as daytime somnolence, sleep apnea, restless legs syndrome (91) and individual patient experience (92) such as worry and dialysis related disruptions. Alterations in brain neurochemistry are also thought to contribute. In animal models of CKD, serotonergic neurons which influence sleep-wake patterns and memory show increased activity (93). Serotonergic neurons are also recognized to contribute to depression and anorexia in CKD. The actions of neurotransmitters in kidney disease remain an area of great interest and complicated by such functional overlap. This may partly explain why observational studies have revealed association between sleep deprivation and cognitive impairment in the first year of dialysis (94) and depression in those on maintenance dialysis (95). The mechanisms underlying sleep and neurodegeneration is an active area of research and the most promising explanations center around the glymphatic system and clearance of potential toxins while sleeping (96). The detailed interaction of kidney disease and neurochemistry is beyond the scope of this review and well described elsewhere (93). Thus, a potential synergy between kidney disease and the consequences of poor sleep seems biologically plausible.

Non-traditional Risk Factors for Cognitive Decline

Uremic Toxins

Advanced CKD is associated with a high burden of toxic metabolites, many of which are not routinely measured in clinical practice. In the list of uremic solutes held by the European Uraemic Toxins Work Group several distinct "uremic toxins" are recognized to have a neurological or central nervous system pathological effects (97). As described earlier, the process of dialysis can improve cognitive dysfunction in the acute setting in those with high levels of uremia. However, the persistence of cognitive impairment following dialysis initiation, and the failure of increased dialysis clearance to improve cognition (64) implies if cognitive dysfunction is toxin driven, then such neurotoxic substances are ineffectively or incompletely removed by the process of dialysis.

In health an intact blood brain barrier may provide protection, however this barrier is dysfunctional in advanced CKD (98). Particular interest has been given to neuropeptide-Y—implicated in neurodegenerative conditions such as Alzheimer's and found in higher concentrations in those with cardiovascular disease and advanced CKD—and markers traditionally associated with mineral bone disease in CKD—Klotho and FGF-23(93). Higher serum concentrations of neuroactive mediators capable of crossing the blood-brain barrier can lead to cerebral osmotic dysregulation. Recent data have demonstrated a

significant fall in such neurochemical concentrations following transplantation (49).

Inflammation

Inflammation has been implicated in studies of neurovascular dysfunction (99). The resultant endothelial dysfunction can promote vascular leakage, protein extravasation and, as mentioned, contribute toward blood-brain barrier dysfunction.

CKD (100) and the process of dialysis are pro-inflammatory states (101) associated with a high cardiovascular disease burden. In an observational study higher levels of hsCRP, fibrinogen and IL-1b were associated with cognitive impairment (102). There are no studies which support treating inflammation to improve cognitive function.

Dialysis Modality

More recent developments have pointed toward an association with the process of dialysis itself. Dialysis is capable of altering cerebral blood flow which is associated with altered cognitive function (103). Polinder-Bos et al. demonstrated with PET-CT imaging an intradialytic decline in cerebral blood flow, associated with ultrafiltration rate and volume, temperature and pH (104). The hypothesis was that recurrent intradialytic decline in cerebral blood flow could predispose to cerebral ischemic injury. In 2019, our group demonstrated real-time intradialytic decreases in cerebral arterial flow correlating with worsening cognitive function (103). Receiving a kidney transplant produced an improvement in cognitive function and had a positive effect on markers of cerebral diffusion.

Kidney transplantation is clearly the gold standard, consistently improving neurochemistry, cerebral blood flow, white tract integrity and cognitive function. However, where dialysis is necessary, the use of peritoneal dialysis appears "protective" to cognitive function (105). In a well-designed study Neumann et al. explored the effect of peritoneal dialysis over hemodialysis on cognitive function. One must appreciate that by nature of the treatments, patients who opt for one form of dialysis or the other are inherently different, since peritoneal dialysis requires greater patient engagement and education to succeed. Therefore, in an attempt to overcome this, propensity score matching was utilized by Neumann et al. to create matched cohorts of hemodialysis and peritoneal dialysis treated patients with KFRT. Matching for age, education level, employment status, and comorbidity they created two groups of ∼100 participants and performed tests of executive function, attention and self-reported cognitive function at baseline and 12 months. Although in this study both groups demonstrated an improvement in cognitive function at 1 year—the improvement was more marked in those on peritoneal dialysis (105).

As shown, the mechanisms underpinning cognitive impairment in kidney failure with replacement therapy are complex and multifactorial. Vascular burden, cerebral alterations, and the recurrent vascular insult from dialysis all have a plausible role. Exploring modifiable factors is essential to developing strategies to reverse or limit the burden of cognitive impairment. However, before the introduction of new treatments or alteration to existing, one must ask—what are the implications of cognitive impairment and why does this matter?

"DIALYSIS BLURS THE MIND" –PATIENT IMPLICATIONS OF COGNITIVE DYSFUNCTION IN PATIENTS REQUIRING DIALYSIS

As previously mentioned, cognitive impairment in people requiring KRT is under-recognized by physicians. An understanding of the experiences of our patients and the "real-life" implications of cognitive dysfunction is essential to improve assessment and patient-centered care. "Brain fog" is a recognized experience amongst patients on dialysis and a hot topic of conversation on patient-led forums (106). Self-reported scores of concentration and memory impairment in KFRT patient populations are associated with measures on objective executive function testing (107). One study examined stage 5 CKD patients' self-recognition of concentrating ability and memory and found it was significantly associated with their dialysis modality choice (107). The conscious perception of an individual to their cognitive decline may have a negative impact on their self-efficacy and subsequent engagement with aspects of healthcare which require more functional independence.

Impaired health literacy is associated with cognitive decline (107). There is an increasing emphasis on the facilitation of patient-led decision making and self-management for long-term conditions with associated better patient outcomes. This shift from physician-driven paternalistic models of care clearly has the potential to be undermined by the burden of multi-domain cognitive impairment in patients with KFRT if not supported adequately. The relationship between cognition, affective disorders and complex decision making has been relatively under-studied in KFRT (107). This is despite the cognitive demands of abstract KRT planning decisions and, once established on dialysis or even having undergone transplantation, the cognitive adaptability that is necessary to engage with a dynamic chronic health condition and the unavoidable healthcare activity burden associated with it. Cognitive impairment has been identified as a key factor contributing to decisions to withdraw from dialysis therapy (108). Ensuring patients with cognitive impairment can exert their autonomy and engage in complex advance care planning decisions is clearly challenging.

Cognitive impairment in people requiring KRT has been associated with a decreased quality of life (109). The psychological impact of "machine dependency" in hemodialysis treatment has been well-documented and inadequate education and preparation for dialysis contributes to the associated psychological stress. Cognitive impairment may impact on successful kidney replacement therapy education (110). Furthermore, as previously discussed, affective disorders are more prevalent in patients with cognitive impairment, and depression is associated with poor outcomes in hemodialysis patients in terms of lower quality of life, non-adherence to treatments, increased requirement for healthcare intervention

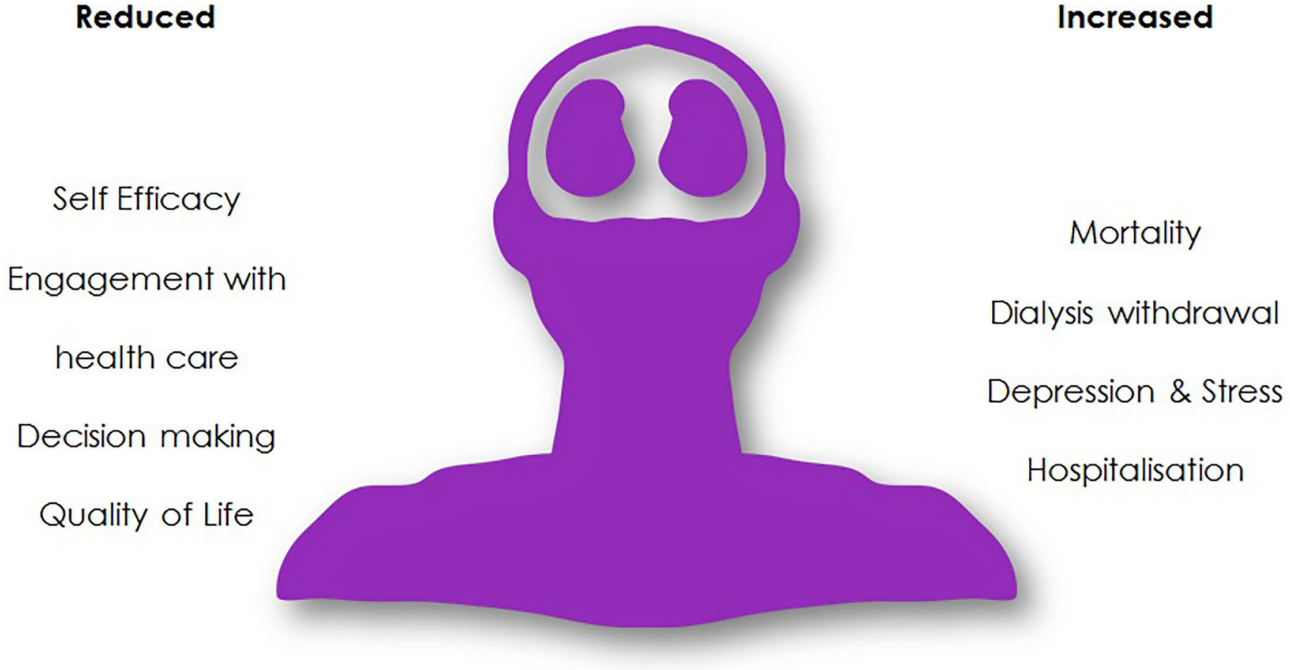

FIGURE 6 | Patient implications of cognitive impairment.

and increased mortality (110, 111), Despite the vulnerability of this population, the response of hemodialysis patients with concurrent depression and cognitive impairment to pharmacological treatment for affective symptoms has not been well-evaluated (111).

Cognitive impairment has been associated with significantly higher mortality in the hemodialysis population (109). One study suggested the higher mortality is related to the impact of executive dysfunction on the complex decision making required to engage with chronic disease management (112). The management of kidney failure carries a significant burden for patients in terms of polypharmacy, restrictive lifestyle choices related to diet and fluid intake, and time spent in hospital settings. Hemodialysis patients with cognitive impairment have an increased risk of hospitalization, increased length of hospital stay and utilize a greater number of healthcare resources, including dedicated healthcare staff time (109, 113). Cognitive impairment can manifest as disruptive behavior and non-concordance with treatments (109, 110). Medication non-adherence in hemodialysis populations has been estimated as high as 58.2% in those with cognitive impairment, in comparison to 25% in the non-cognitively impaired general population (110, 111). Adherence to treatment can be taken into consideration during assessment for suitability of future kidney transplantation therefore this has potentially significant implications.

Considering the implications for patients on KRT with cognitive impairment beyond the healthcare setting, a US based study found independent correlation with self-reported functional dependence in activities of daily living with cognitive impairment, and specifically with impairment in the domain of executive functioning. Functional dependence was noted in 70% of patients with cognitive impairment in this study (114). The mechanisms driving this association are speculative, including the shared relationship cognitive impairment and functional dependence have with frailty and cerebrovascular disease. The impact of cognitive decline in engaging with social interactions and physical exercise which are protective factors for functional independence likely contributes (114). Furthermore, there is a small amount of data that suggests the cohort of patients with cognitive impairment in context of CKD is at significant risk of unsafe driving. Inability to drive would have a significant impact on functional independence. There is a paucity of research, and guidelines for patients and health professionals are vague despite the potential implications for patient safety (115).

Cognitive impairment in the context of KRT clearly has significant implications for patients and their healthcare providers, **Figure 6**. Healthcare rationing decisions on the basis of cognitive impairment have been previously highlighted given the expense associated with KRT and the perceived benefits to a cognitively impaired population (113). Identifying individuals with cognitive impairment is important to enable appropriate adaptations to their care to be made. Strategies for reducing the progression of cognitive impairment in this cohort are clearly welcomed.

TABLE 1 | Cognitive testing in advanced chronic kidney disease.

Cognitive test scenario	Considerations	Potential cognitive tests	Renal testing "equivalents"
Informal assessment	• Usual practice • Poor accuracy (insensitive and non-specific)	Judging cognition based on clinic consultation	Palpation for pedal oedema
Cognitive Triage	• Very brief (<5 mins) • Acceptable • Minimal training • Blunt assessment	• Single screening questions • Four point AMT • Mini-Cog	Dipstick urinalysis
Multi-domain screen	• Brief (<20 mins) • Training required • Global assessment only	• MMSE • MoCA • RUDAS	Laboratory urea and electrolytes
Multi-domain assessment	• Often >60 mins • Needs specialist expertise • Detailed assessment	Neuropsychological battery	Renal biopsy
Diagnostic formulation	• Clinically relevant • Multiple consultations • Needs specialist expertise and ancillary tests	Multidisciplinary clincial diagnosis of dementia	Multidisciplinary clinico-pathological diagnosis of glomerulonephritis

MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; RUDAS, Rowland Universal Dementia Assessment Scale.

DETERMINING DYSFUNCTION—COGNITIVE ASSESSMENT IN CLINICAL PRACTICE

When considering cognitive problems in people living with renal disease, a common question is "what is the best cognitive test?" Unfortunately, there is no simple answer to this question, any more so than there is a simple answer to the question "what is the best method of assessing for kidney disease?" The optimal approach to assessment is dependent on multiple factors, some related to the test and some related to the context of the testing. Here, we offer practical advice and clinical applications that should allow for a more informed approach to cognitive testing within a renal service.

An important first step is to be clear on the purpose of testing. Cognitive testing can operate at many different levels, from very brief tools that can be performed at scale and offer a form of cognitive "triage," to neuropsychological batteries that detail function across the many differing cognitive domains but that are probably only appropriate for specialist assessment services. In **Table 1** are listed potential cognitive test scenarios, suitable tests and some renal medicine "equivalents."

In clinical practice, testing that operates at the triage or screening level is likely to be the most pragmatic. Even here the choice of test is not straightforward, with a vast array of cognitive screening tests available and frequent new tests described in the literature (116). Certain practical considerations can help "narrow the field." Does your service have the approvals or finance to use a copyrighted test? Traditionally popular tools such as Folstein's Mini Mental State Examination (MMSE) (117) now have copyright enforced and as a result many are looking for free to access alternatives. Does the test require training and is the training freely available? The introduction of mandatory training for the Montreal Cognitive Assessment (MoCA) (118) will raise standards and consistency in the use of the test, but the cost of the training has lessened the appeal of the test for many. The population to be tested also needs some thought, for example, are test versions available that are language and culture appropriate? The Rowlands Universal Dementia Assessment Scale (RUDAS) is a screening tool specifically designed to minimize educational and cultural biases.

Finally, the properties of the test itself should be considered. The classical test metrics of validity, reliability and responsiveness are detailed in academic texts, but often it is other aspects of the test that determine the practical clinical utility such as the feasibility of applying the test within a given clinical setting or the acceptability of the test to the patient and the person performing the testing. A thirty-minute global cognitive screen may have perfect psychometric properties but simply not be possible to administer within the constraints of an over-booked outpatient clinic or in a busy emergency department. The existing requirement for long and frequent healthcare attendances for patients on hemodialysis may limit additional attendance out with hemodialysis sessions for cognitive assessments. The common co-morbidities that occur in patients with renal disease may have impairments that complicate testing. For example, the visual impairment from diabetic eye disease, or aphasia from a stroke will all necessitate an adapted approach. As previously mentioned, there is concern regarding the systematic bias introduced into cognitive impairment epidemiology literature in KFRT populations due to the unsuitability of selected cognitive tests for those with physical disability from cerebrovascular disease and peripheral vascular disease.

If after all these considerations there is a still a choice between differing test options, then the accuracy of the test can help decide the preferred tool. When considered as a singular concept, the accuracy metrics of common screening tools are often fairly similar (117, 118). However, test accuracy is comprised of the two complementary measures of sensitivity and specificity and the relative balance of these two will differ between tests (119).

Here again, the rationale for the test needs to be considered. If the intention is to capture everyone with potential cognitive issues, even at the cost of erroneously labeling people as having cognitive impairment (false positives) then sensitivity should be preferred. If the intention is only to select those who truly have cognitive issues, even at the risk of missing some people with impairments (false negatives) then specificity should be preferred. For initial cognitive screening, sensitivity tends to be favored, as all those who screen "positive" should have further assessment that discriminates true cases from false positives. Although there are no guidelines stating the optimal screening test to identify cognitive impairment or dementia in the KFRT population, some validation studies have identified that the Montreal Cognitive Assessment (MoCA) tool is one of the more sensitive for detecting executive dysfunction and thus cognitive impairment in the KFRT population (23, 30). The importance that people living with renal disease ascribe to cognitive testing and potential false positive and false negative scenarios is an area ripe for further research.

IMPROVING THE OUTCOMES—MANAGEMENT OF COGNITIVE IMPAIRMENT IN KFRT

Evidence based treatments for cognitive impairment in patients with kidney failure have proven elusive to date. There are a number of challenges to overcome in establishing therapies for cognitive impairment in this population. First, as cognitive impairment is multifactorial in etiology a single agent is unlikely to address the multiple pathological mechanisms involved. Establishing the optimal assessment to use as the end point in clinical trial of possible interventions is required. Some trials use radiological changes on brain imaging (48), whilst others use cognitive assessment tools such as MoCA (120). As multiple observational studies have demonstrated correlations between cerebral perfusion and either radiological changes associated with cognitive impairment in the population or makers of cognitive performance (103, 104, 121), it may be reasonable to use a measure of cerebral perfusion as a surrogate end point in early phase clinical trials of an intervention for cognitive impairment. However, for definitive trials a clinical endpoint would usually be required before license approval.

The randomized controlled trials that have been performed or are ongoing in this area can be categorized into three groups of interventional strategies; trials of interventions around hemodialysis treatment aimed at minimizing hemodynamic instability on hemodialysis, "lifestyle" interventions which aim to assist cognitive performance and finally "conventional" clinical trials of an investigational medicine (or supplement), aimed at improving cognition vs. placebo or no medicine.

In one of the larger randomized controlled trials (RCT) in this area, performed in 73 patients requiring hemodialysis randomized to "cool" dialysate (0.5°C below core body temperature) compared to 37°C, cool dialysate was associated with minimal changes on brain MRI on follow up, compared to progressive changes in brain composition such as increased fractional anisotropy and reduced radial diffusivity on follow up imaging over 6 months (48). The authors attribute this to better hemodynamic stability on dialysis. The implications of this intervention on cognitive function was not assessed in this trial but will be addressed in the ongoing e-CHECKED trial (122), whilst the larger MY-TEMP cluster randomized controlled trial will assess the effect of cool dialysate on hard outcomes such as survival and cardiovascular events including stroke (123).

In older adults in the general population, both exercise and cognitive training have been demonstrated to have some impact as non-pharmacological intervention to prevent cognitive decline (124, 125). In this setting, it appears that exercise training protects executive function (126). Moreover, exercise training can also be delivered during dialysis, often using cycling, and has also a wide range of potential benefits including greater cardiovascular and vascular health (127). Cognitive training has been shown to have beneficial impact on multiple domains of cognitive function, including executive function, memory, abstraction, and verbal reasoning in older adults (128)—although evidence of persistence of effect or translation to improvements in function is lacking. In one small RCT (20 patients requiring hemodialysis) both intradialytic pedal exercise and cognitive training, using stimulatory games on a handheld tablet pilot study were associated with less cognitive decline in psychomotor speed and executive function when compared to routine care over 3 months (120). The investigators will follow this up with a larger 2 $\times$ 2 factorial trial to assess whether which of these interventions perform best in isolation or in combination (129).

It is harder to find any high-quality clinical trials of pharmacological interventions to improve cognition in this population. One small crossover study ($n = 39$) of valerian as a supplement in hemodialysis patients showed some benefit in the MMSE after valerian therapy (130). However, the generalizability of these findings is questionable, with a very high incidence of literacy in the group studied and it is unclear if the investigators excluded patients with advanced cognitive impairment at baseline.

Observational data has shown that treatment of renal anemia with erythropoiesis stimulating agents (ESA) increases cerebral perfusion and oxygen consumption, which is likely to be associated with improved cognition (131). However, any potential benefit of over overzealous correction of renal anemia with these agents may be mitigated by an increased stroke risk with higher hemoglobin observed in placebo controlled and/or carefully performed randomized controlled trials of anemia correction in patients with chronic kidney disease (132–134). The recent PIVOTAL trial has demonstrated that proactive iron may be a more appropriate method of treating renal anemia in patients requiring hemodialysis to improve cardiovascular outcomes with no excess risk of stroke (135). However, the effect of this approach on cognition of cerebral perfusion is unknown.

Renal transplantation remains the optimal intervention for restoring quality of life and improving life expectancy in appropriately selected people with kidney failure requiring dialysis. In small observational cohort studies of either cognitive assessment or neuroimaging in patients with kidney failure who undergo kidney transplantation, several cerebral benefits of

TABLE 2 | Evidence, cerebral effects, and cognitive effects of treatment strategies to improve or slow cognitive decline in KFRT.

	Evidence	Summary of Cerebral findings	Summary of cognitive effects
Lifestyle			
Physical exercise (120, 138)	Randomized controlled trials of cycling, treadmill and exercise classes over 3–12 months.	Improved cerebral blood flow	Improvements in executive function, memory, delayed recall and self-reported cognitive function.
Cognitive Training (120)	Randomized trial data of intradialytic tablet-based games	Not assessed	Improvements in psychomotor speed and executive function
Medicinal			
Supplements (130)	Cross-over study of valerian supplementation on MMSE score and EEG findings, $n = 39$.	No changes in EEG between groups	Improved MMSE scores in those taking valerian
ESA to correct anemia (131, 139)	Observational data. Use of ESA and effect on cerebral perfusion, oxygen consumption, event related potential and cognitive attention	ESA improves cerebral perfusion and oxygen consumption. Electrophysiology parameters improved with greater Hct (mean 42.8 vs. 31.6%).	Attention improved with higher Hct. The risk of ESA use overshadows potential benefit.
Kidney replacement therapy			
Cooled dialysis (48)	Randomized control trial data, $n = 73$. Measured brain diffusion parameters over 1 year in those receiving dialysis 0.5°C below body temperature.	Diffusion markers stable in those with cooled dialysis.	Cognitive function not assessed. Will be assessed in the pending e-CHECKED trial (122)
Renal transplantation (49, 50, 103)	Observational data using cognitive assessment and cerebral imaging before and after transplantation.	Improved diffusion parameters, normalization of neurotransmitters and neural networks as assessed by functional MRI.	Improvements in general cognitive status, psychomotor speed, attention, memory, and abstract thinking have all been reported

MMSE, mini-mental state examination; EEG, electro-encephalogram; ESA, erythrocyte-stimulating agent; Hct, Hematocrit; e-CHECKED, Evaluation of the Effect of Cooled Hemodialysis on Cognitive Function in Patients Suffering With End-stage Kidney Disease; MRI, magnetic resonance imaging.

transplantation have been observed. Transplantation has been shown to normalize concentrations of neurochemicals such as choline and myoinositol as assessed by magnetic resonance spectroscopy over 12 months (49). Similarly, in another cohort study pre- and post- kidney transplantation a variety of neural networks assessed by functional MRI including dorsal attention network, the central executive network, the auditory network, and the visual network recovered post transplantation, whereas others such as the default mode network and the sensorimotor network did not recover completely at 6 months after kidney transplantation (136). Finally, in other studies neuropsychological testing scores improved following kidney transplantation (137). All the studies around effect of kidney transplantation on cognition are limited by small sample size and biased by the fact that only the "fitter" patients with kidney failure are likely to considered kidney transplant candidates and hence these observations may not be generalized to all patients with kidney failure, **Table 2**.

It may be that by the time patients with progressive CKD require dialysis, the consequences of accelerated cerebrovascular disease make any decline in cognition difficult to reverse. Other interventions to improve cardiovascular outcomes such as statins which have been effective in multiple populations, have failed to demonstrated benefits in this population for this reason (140). The primary focus should be preventing cognitive decline earlier in the course of CKD. Once established on KRT, the main goal is to ensure that hemodialysis does not further exacerbate cerebral injury. Consideration may be given to the dialysis modality including using peritoneal dialysis or with hemodialysis with longer (often nocturnal) hemodialysis with less intense ultrafiltration (141) or more frequent short hemodialysis to minimize hemodynamic upset associated with hemodialysis treatment.

DISCUSSION AND FUTURE DIRECTIONS

The burden of cognitive impairment in the KRT population and the consequences for patients and the services caring for them is substantial. Yet, despite the growing research interest, much is still unknown about the epidemiology, natural history, and mechanisms driving the impaired cognition in this population. The contribution of hemodialysis therapy to the onset and acceleration of cognitive decline has only recently been partially described. Although early data is suggestive that cognitive function has the potential to be preserved through alterations to the dialysis process, there remains no robust or universally applied intervention demonstrated to be effective. However, kidney transplantation has once again demonstrated its benefits beyond correction of renal function.

Research into the epidemiology and natural history of cognitive impairment in KFRT would benefit from universally agreed methods of cognitive assessment with appropriate adjustments made to limit systematic bias from participant exclusion and drop-out. Research using such assessments should be in the context of larger multi-center longitudinal studies. Furthermore, undertaking studies with a KRT population under the age of 65 may help differentiate cognitive impairment

related to kidney failure and hemodialysis, vs. the accelerated effects of aging. It is well-established that cognitive decline is multi-factorial in this population, and patients requiring KRT have often had years of progressing through CKD stages accumulating various risk factors. The duration of renal disease rather than simply the severity of CKD stage may influence cognition (93). We propose there should be greater focus in determining how to optimally predict cognitive decline, including identifying reliable disease biomarkers, and conducting mechanistic research on earlier CKD cohorts to enable trials of earlier preventative treatments prior to irreversible brain pathology.

Cognitive screening of KRT populations would likely bring to attention a significant number of patients with undetected cognitive impairment, and there needs to be further research into management options for these patients. Randomized controlled trials of potential treatments associated with hemodialysis therapy such as dialysate cooling and intra-dialytic exercise are now forthcoming in this area. These will hopefully help guide nephrologists in appropriately adjusting hemodialysis treatments. There are further potential areas for research to be considered such as impact of hemodialysis vascular access modality and optimal ultrafiltration targets on cerebral perfusion, the role of high flux vs. hemodiafiltration on medium sized solute removal, and whether proactive iron replacement or optimizing CKD-Mineral Bone Disease can optimize cognitive function. Further consideration of methods to preserve native renal function and whether this can impact on the natural history of cognitive decline should be considered. The impact of pharmacological therapy used for dementia in the general population and for affective disorders which can impact cognitive function also needs to be ascertained in the KRT population. As previously discussed, comparable study end-points for cognitive impairment require to be established—whether by cognitive domain neuropsychological testing, or radiological studies.

Improved detection and awareness of cognitive impairment in people requiring KRT will enable care planning discussions to be appropriately adjusted and likely will require significant service delivery change. Further research defining the health behavior patterns of this population and the impact of healthcare activity on engagement and influence on poor prognosis in this patient group is needed. More research that includes patient-derived outcome measures is welcomed.

AUTHOR CONTRIBUTIONS

KC, TQ, PM, and MF contributed to the conception and design of the review article, wrote sections of the manuscript and contributed to manuscript revision, and approved the submitted version. MF created **Figures 1**, **3**–**6**. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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The Similarities and Differences Between Glomerular vs. Non-glomerular Diagnoses on Intelligence and Executive Functions in Pediatric Chronic Kidney Disease: A Brief Report

Stephen R. Hooper[1], Rebecca J. Johnson[2], Marc Lande[3], Matthew Matheson[4], Shlomo Shinnar[5], Amy J. Kogon[6], Lyndsay Harshman[7], Joann Spinale[8], Arlene C. Gerson[9], Bradley A. Warady[2] and Susan L. Furth[6]*

[1] Department of Allied Health Sciences, School of Medicine, University of North Carolina-Chapel Hill, Chapel Hill, NC, United States, [2] Department of Pediatrics, Children's Mercy Kansas City, School of Medicine, University of Missouri-Kansas City, Kansas City, MO, United States, [3] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, United States, [4] Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD, United States, [5] Department of Neurology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, United States, [6] Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [7] Department of Pediatrics, University of Iowa Stead Family Children's Hospital, Iowa City, IA, United States, [8] Department of Pediatrics, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States, [9] Department of Pediatrics, Johns Hopkins Medical School, Baltimore, MD, United States

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***Correspondence:**
Stephen R. Hooper
Stephen_hooper@med.unc.edu

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Pediatric chronic kidney disease (CKD) appears to be a heterogeneous group of conditions, but this heterogeneity has not been explored with respect to its impact on neurocognitive functioning. This study investigated the neurocognitive functioning of those with glomerular (G) vs. non-glomerular (NG) diagnoses. Data from the North American CKiD Study were employed and the current study included 1,003 children and adolescents with mild to moderate CKD. The G Group included 260 participants (median age = 14.7 years) and the NG Group included 743 individuals (median age = 9.0 years). Neurocognitive measures assessed IQ, inhibitory control, attention regulation, problem solving, working memory, and overall executive functioning. Data from all visits were included in the linear mixed model analyses. After adjusting for sociodemographic and CKD-related covariates, results indicated no differences between the diagnostic groups on measures of IQ, problem solving, working memory, and attention regulation. There was a trend for the G group to receive better parent ratings on their overall executive functions ($p < 0.07$), with a small effect size being present. Additionally, there was a significant G group X hypertension interaction ($p < 0.003$) for inhibitory control, indicating that those with both a G diagnosis and hypertension performed more poorly than the NG group with hypertension. These findings suggest that the separation of G vs. NG CKD produced minimal, but specific group differences were observed. Ongoing examination of the heterogeneity of pediatric CKD on neurocognition, perhaps at a different time point in disease progression or using a different model, appears warranted.

Keywords: glomerular disease, non-glomerular disease, executive functions, CKiD study, hypertension

INTRODUCTION

It is now known in both adult and pediatric literature that one potential health-related problem pertaining to chronic kidney disease (CKD) is the disruption of neurocognitive functioning. Hooper et al. (1–3) found that these neurocognitive difficulties are present even in children and adolescents with mild to moderate CKD, with lower performance being noted in IQ, attention regulation, and parent ratings of executive functions. Mendley et al. (4) reported specific difficulties in the area of attention regulation, particularly with longer disease duration and the presence of nephrotic proteinuria. In a comprehensive review of available pediatric findings, Chen et al. (5) also documented an array of neurocognitive difficulties, including executive dysfunction, in children and adolescents with CKD. To date, however, few studies have examined the diagnostic heterogeneity in the CKD pediatric population from a neurocognitive perspective.

Additionally, there has been emergent scientific inquiry into the mechanisms that contribute to neurocognitive difficulties in pediatric CKD that include ischemic stroke (6), lead exposure (7), mineral bone disease (8), depression (9), genetic abnormalities (10), and brain abnormalities (11). Two major suspected contributors to neurocognitive dysfunction in pediatric CKD are nephrotic proteinuria (i.e., urine protein:creatinine $\geq$2) (1) and hypertension (12, 13). Nephrotic proteinuria has been associated with lower neurocognitive functioning in cross-sectional studies in this population (1) and an independent correlate of CKD progression in children and adolescents with NG CKD (14); however, few studies, if any, have addressed the interaction of type of kidney disease and nephrotic proteinuria. Similarly, the presence of hypertension in pediatric CKD has been shown to be related to lower non-verbal IQ (12) and executive dysfunction, particularly set-shifting capabilities (13). While Harshman et al. (15) did not show a direct relationship between hypertension, bicarbonate, and executive functions, they did find a significant interaction between high bicarbonate and blood pressure variability with respect to parent ratings of overall executive functions. Here, higher blood pressure variability was associated with poorer parent ratings of executive functioning in the low and normal bicarbonate groups, and higher blood pressure variability was related to better parent ratings of executive function in the high bicarbonate group. As with nephrotic proteinuria, however, there have been no studies in pediatric CKD that have examined the interaction between hypertension and type of CKD.

Glomerular vs. Non-glomerular Diagnoses

There is significant diagnostic complexity regarding the various causes for CKD in the pediatric population and a variety of strategies to attack this problem (e.g., cluster analysis, latent class modeling), but a straightforward translational approach is to begin with a clinical sorting of the various CKD diagnoses. One strategy for addressing this heterogeneity from a clinical perspective is to organize the various CKD diagnoses into glomerular vs. non-glomerular diagnoses.

Glomerular (G) diagnoses include such conditions as focal segmental glomerulosclerosis, hemolytic uremic syndrome, and systemic immunological disease such as systemic lupus erythematosus. Non-glomerular (NG) CKD diagnoses include conditions such as aplastic/hypoplastic/dysplastic kidneys, reflux nephropathy, obstructive uropathy, and congenital urologic disease. In general, children and adolescents in the NG diagnostic groups tend to be younger in terms of their age of CKD onset than the G diagnostic groups, have CKD for a greater percentage of their life given the younger age of onset, and show slower rate of CKD progression when compared to their G diagnoses counterparts. Additionally, children and adolescents with NG-CKD are more likely to be born prematurely and have a low birth weight than their peers with glomerular diagnoses. They also tend to be smaller in terms of their height and weight (16). Warady et al. (16) prospectively evaluated the progression of CKD in children and adolescents with mild to moderate CKD to either renal replacement therapy or to a 50% decline in GFR. These investigators noted that patients with NG vs. G diagnoses had differential rates of progression to the designated outcomes, and evidenced somewhat overlapping predictors of outcomes. Specifically, those with NG diagnoses had a shorter time frame to the targeted outcome with the presence of urinary protein-creatinine ratio >2 mg/mg, hypoalbuminemia, elevated blood pressure, dyslipidemia, male sex, and anemia, whereas those with G diagnoses reached the targeted outcome more quickly, in the presence of urinary protein-creatinine ratio >2 mg/mg, hypoalbuminemia, and elevated blood pressure.

While it may be tempting to predict that children and adolescent with G diagnoses may perform more poorly than children and adolescents with NG diagnoses on the neurocognitive measures, due in large part to their faster rate of disease progression, to date, few, if any, studies have examined the difference between these clinical groups on neurocognitive functioning. Several studies have examined these outcomes in targeted G and NG groups. For example, despite the overall findings provided by Hooper and colleagues (3) and Chen et al. (5) in their reviews of the CKiD findings and CKD literature to date, respectively, Hartung et al. (17) found that their small sample of children and adolescents with Autosomal Recessive Polycystic Kidney Disease (ARPKD), considered a NG disease, showed little in the way of neurocognitive impairment when compared to those with other forms of CKD. Similarly, Knight et al. (18) demonstrated that children and adolescents with lupus nephritis, considered a G disease, evidenced similar levels of neurocognitive function to their peers with other forms of glomerular CKD. In fact, Knight et al. (18) showed that these children and adolescents actually performed better than the comparison group on measures of attention regulation and problem solving.

Current Study

The primary aim of this study was to examine the neurocognitive similarities and differences in IQ, attention regulation and related executive functions between children and adolescents with G vs. NG diagnoses. In conjunction with the significant, but subtle neurocognitive findings for the overall sample, and the

relatively positive findings on the neurocognitive findings for a G condition [Lupus Nephritis (18)] and a NG condition [ARPKD (17)], we are asserting a null finding for the primary research question. It is hypothesized that children and adolescents with NG diagnoses will perform at a similar level as children and adolescents with G diagnoses across all cognitive measures. A second exploratory research question addressed the possible presence of an interaction between diagnostic grouping and two key CKD-related variables on the neurocognitive outcomes: nephrotic proteinuria and hypertension.

METHODS

Participants

The sample included all of the available visits from participants enrolled in the NIDDK-funded CKiD Study. The CKiD Study comprises 54 clinical sites in the United States and Canada. Children and adolescents with mild to moderate CKD, ages 6 months to 16 years of age, are enrolled across sites to participate in the CKiD protocol examining issues of progression, growth, cardiovascular health, and neurocognition (19). The sample did not include children on any renal replacement therapies. All sites functioned under their university/site institutional review board with respect to recruitment and all other aspects of this study.

Measures

Neurocognitive measures were conceptualized to assess overall intellectual abilities as well as targeted executive functions. Specific measures assessed IQ (Wechsler Abbreviated Scale of Intelligence Full Scale IQ), inhibitory control [Conners' Continuous Performance Test-II (CPT-II) Errors of Commission], attention regulation (CPT-II Variability), problem solving [Delis-Kaplan Executive Function System (D-KEFS) Tower Task Total Achievement Score], working memory (Digit Span Backwards Task from the age-appropriate Wechsler Intelligence Scale), and parent ratings of overall executive functioning (Behavior Rating Inventory of Executive Function Global Executive Composite).

In addition to subdividing the sample into G and NG diagnostic groups, additional sample description variables and targeted covariates were collected on nearly all participants at study enrollment (∼96%). Sociodemographic variables included sex, race/ethnicity (for sample description only), maternal education (high school or less, some college, college or more), and chronological age at study entry. CKD-related variables included the presence of an abnormal birth history—a combined variable comprising low birth weight, prematurity, and small for gestational age, U25eGFR at study entry, (20) nephrotic proteinuria (uP/C >2), duration of CKD, age of CKD onset (i.e., ages 0–1, 2–5, 6–12, and 13 years of older), hypertension (blood pressure stage 2 or 3), (21) anemia (hemoglobin <5% threshold for chronological age, sex, race), and any history of seizures (Present/Absent).

Data Analyses

Neurocognitive data from all available visits on participants enrolled in the CKiD Study were employed in the data analyses such that the available data on each of the measures ranged from 1,197 on the D-KEFS Total Achievement Test to 2,058 for the parent-rated BRIEF Global Executive Composite. To address the primary and secondary research questions, a series of linear mixed model regressions were conducted for all of the neurocognitive outcomes. Each linear mixed model included the G/NG diagnostic group, the targeted sociodemographic and CKD-related covariates, and interactions terms for G/NG X nephrotic proteinuria and G/NG X hypertension. For models where the interactions were not significant, the interaction terms were removed, and the simple linear mixed models were examined for the presence of differences between the CKD groups on the neurocognitive outcomes.

TABLE 1 | Sample description at first available visit by glomerular vs. non-glomerular diagnostic groupings.

Characteristic	Median [IQR] or *n* (%)		*p*-value
	Glomerular Dx ($n = 260$)	Non-glomerular Dx ($n = 743$)	
Male sex	136 (52%)	495 (67%)	<0.0001
African-American race	79 (30%)	138 (19%)	<0.0001
Hispanic ethnicity	40 (15%)	103 (14%)	0.55
Maternal education			
High School or Less	113 (45%)	260 (36%)	
Some college	56 (22%)	204 (28%)	0.03
College or More	84 (33%)	266 (36%)	
Age, years	14.7 [11.5, 16.3]	9.0 [5.0, 13.3]	<0.0001
Abnormal birth history	69 (27%)	223 (30%)	0.28
U25eGFR, ml/min|1.73 m²	57.6 [42.5, 74.5]	47.3 [34.6, 61.5]	<0.0001
Nephrotic proteinuria, uP/C >2	60 (24%)	55 (8%)	<0.0001
CKD duration, years	4.0 [1.8, 8.1]	8.5 [4.7, 12.7]	<0.0001
Age of CKD onset			
0–1	49 (19%)	702 (95%)	
2–5	46 (18%)	11 (1%)	<0.0001
6–12	106 (42%)	18 (2%)	
13+	52 (21%)	7 (1%)	
Hypertension	54 (22%)	180 (27%)	0.11
Anemia	95 (37%)	148 (21%)	<0.0001
Seizures	44 (17%)	67 (9%)	0.0005

RESULTS

Sample Characteristics

The sample included a total of 1,003 children and adolescents with mild to moderate CKD that were subdivided into those with glomerular diagnoses and non-glomerular diagnoses. As can be seen in **Table 1**, the glomerular group comprised about a quarter of the study participants ($n = 260$) when compared to the non-glomerular group ($n = 743$). When compared to the NG group, the G group was older ($p < 0.0001$), had significant fewer males ($p < 0.0001$), more African-Americans ($p < 0.0001$), and a similar number of participants who identified with Hispanic ethnicity ($p = 0.55$). The G group also had mothers with less education

TABLE 2 | Median performance at first available visit on intelligence and executive function measures by diagnostic grouping.

Neurocognitive measures	Median [IQR]	
	Glomerular Dx (n = 260)	**Non-glomerular Dx (n = 743)**
WASI-II full scale IQ	96.5 [86, 107]	98 [85, 107]
CPT errors of commission	50 [41, 57]	53 [47, 60]
CPT variability	48 [40.5, 58]	51 [43, 60]
D-KEFS tower total achievement	10 (8,11)	10 (8,11)
Wechsler digit span reverse	10 (7,11)	9.5 (7,11)
BRIEF global executive composite	52 [44, 60]	53 [45, 62]

WASI-II Full Scale IQ has a Mean = 100, SD = 15, higher scores reflect a more intact performance. CPT and BRIEF have a Mean = 50, SD = 10, with higher scores reflecting a more impaired performance. D-KEFS and Wechsler scores have a Mean = 10, SD = 3, with higher scores reflecting a more intact performance.

TABLE 3 | Linear mixed model showing the model adjusted main effects for CKD diagnostic grouping on the parent-completed behavior rating inventory for executive function global executive composite (n = 2,058 visits).

Predictor	Parameter estimate (95% CI)	p-value
Glomerular Dx	−2.17 (−4.52, 0.17)	0.07+
Male sex	2.39 (0.91, 3.87)	0.002**
Maternal education: some college	−0.30 (−2.07, 1.47)	0.74
Maternal education: college or more	−3.25 (−4.90, −1.60)	0.0001***
Age, per year	0.05 (−0.07, 0.16)	0.45
Abnormal birth history	1.12 (−0.43, 2.66)	0.16
U25eGFR, per 10% decline	−0.02 (−0.18, 0.13)	0.75
Percent of life with CKD, per 10%	−0.15 (−0.48, 0.18)	0.38
Nephrotic proteinuria	0.57 (−0.91, 2.06)	0.45
Hypertension	−0.09 (−1.11, 0.93)	0.86
Anemia	−0.20 (−1.25, 0.85)	0.71
Seizures	1.91 (−0.11, 3.94)	0.06+

****$p < 0.001$; **$p < 0.01$; +$p < 0.10$.*

($p < 0.03$). While the two groups were similar on the presence of an abnormal birth history ($p = 0.28$) and hypertension ($p = 0.11$), the G group demonstrated higher U25eGFR ($p < 0.0001$), a greater percentage of individuals with nephrotic proteinuria ($p < 0.0001$), shorter CKD duration ($p < 0.0001$), a generally older age of CKD onset ($p < 0.0001$), higher rates of anemia ($p < 0.0001$), and a history that included seizures ($p < 0.0005$) than the NG group.

Diagnostic Grouping and Neurocognitive Outcomes

As can be seen in **Table 2**, median scores for all of the neurocognitive variables across both groups were in the average range for chronological age. Upon initial examination of these unadjusted results, the neurocognitive scores across all of the measures did not appear to be significantly different between the two groups.

TABLE 4 | Linear mixed model showing the model adjusted main effects for CKD diagnostic grouping on conners continuous performance test-II errors of commission (n = 1,640 visits).

Predictor	Parameter estimate (95% CI)	p-value
Glomerular Dx	−2.31 (−4.68, 0.06)	0.06+
Male sex	−2.31 (−3.76, −0.86)	0.002**
Maternal education: some college	−1.10 (−2.81, 0.62)	0.21
Maternal education: college or more	−3.05 (−4.67, −1.43)	0.0002***
Age, per year	−0.10 (−0.25, 0.05)	0.18
Abnormal birth history	−0.42 (−1.93, 1.09)	0.58
U25eGFR, per 10% decline	0.01 (−0.16, 0.18)	0.93
Percent of Life with CKD, per 10%	0.22 (−0.11, 0.55)	0.19
Nephrotic proteinuria	1.34 (−0.42, 3.1)	0.13
Hypertension	−0.94 (−2.33, 0.46)	0.19
Hypertension × Glomerular Dx	4.43 (1.54, 7.31)	0.003**
Anemia	−0.92 (−2.15, 0.32)	0.14
Seizures	1.71 (−0.26, 3.69)	0.09+

****$p < 0.001$; **$p < 0.01$; +$p < 0.10$.*

When adjusted for the targeted covariates, the linear mixed model regressions revealed that the diagnostic groupings of glomerular vs. non-glomerular disease did not seem to affect measures of IQ (n = 2,009, p = 0.85), attention variability (n = 1,637, p = 0.19), problem solving (n = 1,197, p = 0.85), or working memory (n = 1,277, p = 0.41). None of the interactions involving diagnostic grouping and hypertension and diagnostic grouping and nephrotic proteinuria were significant.

In contrast, as can be seen in **Table 3**, there was a trend for the diagnostic groupings to be different on the BRIEF Global Executive Composite (n = 2,058, $p < 0.07$). Specifically, for the BRIEF Global Executive Composite, a parent rating of overall executive capabilities, the glomerular group performed better than the non-glomerular group, with scores being ∼2.35 points higher (i.e., worse ratings) and reflecting a small effect size (Cohen's d = 0.23–0.24). The interactions between diagnostic grouping, hypertension, and nephrotic proteinuria were not significant.

There also was a strong trend for the glomerular group to perform better than the non-glomerular group on the measure of inhibitory control, the CPT-II Errors of Commission (n = 1,640, $p < 0.06$); however, as can be seen in **Table 4**, there also was a significant interaction present between the diagnostic grouping and the presence of hypertension ($p < 0.003$). This interaction negates the main effect and indicates that those with a glomerular diagnosis and hypertension will score 4.43 points worse on this measure. To determine the effect size, the effect of having a non-glomerular disease and being hypertensive (0.94) is removed from the parameter estimate of 4.43 (4.43–0.94 = 3.49), resulting in a small effect size being present (Cohen's d = 0.34). The interaction between diagnostic grouping and nephrotic proteinuria was not significant.

DISCUSSION

The primary question for this study pertained to the neurocognitive similarities and differences between children adolescents with G vs. NG diagnoses in order to address potential heterogeneity of pediatric CKD. Targeted neurocognitive outcomes included measures of intelligence, attention regulation, and related executive functions. Consistent with our null hypothesis, findings from this study revealed more similarities than differences between the G and NG groups, with IQ, attention regulation, problem solving, and verbal working memory being within the average range and unremarkable between the groups after controlling for a number of targeted sociodemographic and CKD-related factors. There was a trend for the groups to differ on a measure of inhibitory control and parent ratings of overall executive functions, with the G group performing more poorly in both instances. Additionally, there were few interactions between the groupings, nephrotic proteinuria, and hypertension on the neurocognitive outcomes. There was one significant interaction uncovered between the glomerular diagnostic group and hypertension indicating that this combination of factors contributed to poorer performance on CPT-II Errors of Commission, i.e., less inhibitory control. Consequently, while there were more similarities than differences on the neurocognitive measures, there was some sense that the G diagnostic group may be a bit more vulnerable to cognitive disruption than the NG group. Although our U25eGFR measure was not a significant predictor of neurocognitive functioning in any of the models, these findings would be consistent with the faster rate of disease progression in the glomerular diagnoses and the potentially associated neurocognitive impairment with increasing severity.

Findings revealed little in the way of neurocognitive differences between the G and NG diagnoses in children and adolescents with mild to moderate CKD, but they do suggest the potential ongoing examination of the heterogeneity of the pediatric CKD population with respect to neurocognitive functioning. In particular, the focus on the presence of hypertension and pre-hypertension should continue to be explored, particularly with respect to its impact on specific executive functions. Lande et al. (12, 13) found hypertension to not only contribute to lower non-verbal abilities, but also to set-shifting functions whereas Harshman et al. (15) found a significant interaction for high bicarbonate and blood pressure variability on parent ratings of executive functions. Further, findings from available neuroimaging studies show concerns for the vascular beds surrounding the white matter in structural imaging studies, (11, 22, 23) regional cerebral blood flow, (24) and blood flow abnormalities in both resting state (25) and working memory during fMRI (26). While these studies did not specifically examine G vs. NG diagnostic groupings, the findings do implicate the need for ongoing examination of the cardiovascular system with respect to the neurocognitive functioning in pediatric mild to moderate CKD. This also may have implications for pharmacological treatments for hypertension (Angiotensin-Converting Enzyme Inhibitors-ACES, Angiotensin Receptor Blockers-ARBS) in the pediatric CKD population with G diagnoses. While we did not find evidence of an interaction between type of kidney disease, as defined by G vs. NG diagnoses, and nephrotic proteinuria, it will be important for the impact of this factor to be tracked over time as kidney disease progresses, with perhaps a continued focus on the more rapidly progressing G diagnoses.

Additionally, it may be that the use of the dual classification of G and NG diagnoses, which is broad in nature, simply does not capture the complexities inherent in the cognitive dysfunction documented in CKD, and another type of classification strategy may be more useful in separating out those with and without neurocognitive risk. For example, Verbitsky et al. (10) reported that CKiD Study participants with genomic disorders demonstrated lower intelligence and executive dysfunction after controlling for a host of other factors. Differences also were detected with respect to the presence of anxiety and depression symptoms in those with genetic conditions and, indeed, children and adolescents with CKD and associated depression also have shown neurocognitive difficulties (9). Consequently, despite the relative lack of differences using the G vs. NG groupings in the current study, additional strategies exploring the heterogeneity of mild to moderate pediatric CKD could yield different results.

In addition, a number of other interesting possibilities could be contributing to these relationships or lack thereof. First, we wondered how repeated hospitalizations may have impacted the findings. While this is a worthwhile consideration, given the mild to moderate level of severity in our sample there actually were few repeated hospitalizations with nearly all of the sample having their health care in outpatient settings and none of them yet receiving any type of renal replacement therapy (e.g., transplant, dialysis). Furthermore, we would note that this is one of the reasons for including percent of life with CKD as a predictor in our model. A second area for ongoing exploration involves the potential relationship between age of onset and eGFR. This interaction was not included in our model due to the small correlation between variables (Rho = 0.19), so there was little need to include this in our modeling; however, it does not negate it possible influence with ongoing disease progression. A third, related possibility pertains to the relationship between age of onset and change in eGFR. This is an intriguing question as it goes to the core of whether cognitive abilities change in relationship to disease severity. For our sample, there was no correlation ($p = 0.64$) between a subject's age at CKD onset and their observed CKD progression (i.e., slope of U25eGFR over time in the study); thus, not a factor that should influence our current findings. Finally, our findings did show an independent contribution of both sex and maternal education wherein the groups differed. While these variables were automatically adjusted in the model to address the G vs. NG comparisons on the neurocognitive outcomes, the findings do raise some questions about not only how sex and lower education may impact neurocognitive outcomes. In our sample, sex produced mixed findings wherein males performed worse than females on the GEC, but better than females on the CPT-II Errors of Commission. In each instance, the effect sizes were small. In contrast, higher maternal education was related to better performance across groups on both the parent-rated

GEC and the CPT-II Errors of Commission, suggesting possible protective factors of higher maternal education with respect to cognitive outcomes in pediatric CKD. Taken together, these factors provide the basis for future studies examining these key variables in the neurocognitive functioning of children and adolescents with CKD.

In summary, the groupings of G vs. NG diagnoses did not show a major differential impact on the presence of intellectual capabilities or targeted executive functions in our sample of children and adolescents with mild to moderate CKD, but those with G diagnoses did show a trend for lower overall executive functions and lower inhibitory control. Further, the glomerular X hypertension interaction also suggested that this combination of factors could lead to poor inhibitory control even after controlling for a variety of covariates. Whether the current findings will be maintained in the presence of CKD progression remains to be determined, but current knowledge supports the need for ongoing neurodevelopmental monitoring beginning with the earliest time of CKD detection. The complicated pathway of CKD toward renal replacement therapies also will demand more sophisticated types of analyses involving various interactions of key CKD-related variables with respect to the appearance of neurocognitive impairment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of North Carolina at Chapel and at each participating site. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SH conceptualized the research, drafted the article, and worked with all authors on its completion. RJ, ML, SS, AK, LH, and JS assisted in the editing of the various drafts of the manuscript. MM contributed to the data analyses and interpretation of the findings. AG contributed to the conceptualization of the study and assisted in the editing of the various drafts of the manuscript. BW and SF conceptualized the overall CKiD design and assisted in the editing of the various drafts of the manuscript. All authors contributed to the article and approved the submitted version.

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Hypertension and Cognitive Impairment: A Review of Mechanisms and Key Concepts

Michelle Canavan[1,2]* *and Martin J. O'Donnell*[1,2]

[1] Health Research Board (HRB), Clinical Research Facility, National University of Ireland, Galway, Ireland, [2] Galway University Hospital, Galway, Ireland

Cognitive impairment, and dementia, are major contributors to global burden of death and disability, with projected increases in prevalence in all regions of the world, but most marked increases in low and middle-income countries. Hypertension is a risk factor for both Vascular Cognitive Impairment and Alzheimer's disease, the two most common causes of dementia, collectively accounting for 85% of cases. Key end-organ pathological mechanisms, for which hypertension is proposed to be causative, include acute and covert cerebral ischemia and hemorrhage, accelerated brain atrophy, cerebral microvascular rarefaction and endothelial dysfunction, disruption of blood-brain barrier and neuroinflammation that affects amyloid pathologies. In addition to the direct-effect of hypertension on brain structure and microvasculature, hypertension is a risk factor for other diseases associated with an increased risk of dementia, most notably chronic kidney disease and heart failure. Population-level targets to reduce the incidence of dementia are a public health priority. Meta-analyses of blood pressure lowering trials report a significant reduction in the risk of dementia, but the relative (7–11%) and absolute risk reductions (0.4% over 4 years) are modest. However, given the high lifetime prevalence of both conditions, such relative risk reduction would translate into important population-level reductions in dementia globally with effective screening and control of hypertension. Optimal blood pressure target, especially in older adults with orthostatic hypotension, and antihypertensive agent(s) are uncertain. In this review article, we will detail the observational and interventional evidence linking hypertension with cognitive impairment, summarizing the mechanisms through which hypertension causes cognitive decline.

Keywords: hypertension, cognitive impairment, dementia, neurocognitive syndrome, vascular cognitive impairment and dementia (VCID), blood pressure lowering

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Dearbhla Kelly,
Trinity College Dublin, Ireland

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Alessandro Biffi,
Massachusetts General Hospital and Harvard Medical School, United States

***Correspondence:**
Michelle Canavan
michelle.canavan@hse.ie

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INTRODUCTION

Hypertension causes acute and chronic injury to the brain, accelerates brain atrophy and engages neuroinflammatory processes, each of which contribute to cognitive impairment and major neurocognitive syndromes (dementia) (1). In addition to a "direct-effect" of hypertension on brain structure and microvasculature, hypertension is a risk factor for other syndromes related to end-organ damage, which are also associated with an increased risk of dementia, most notably chronic kidney disease and heart failure (**Figure 1**).

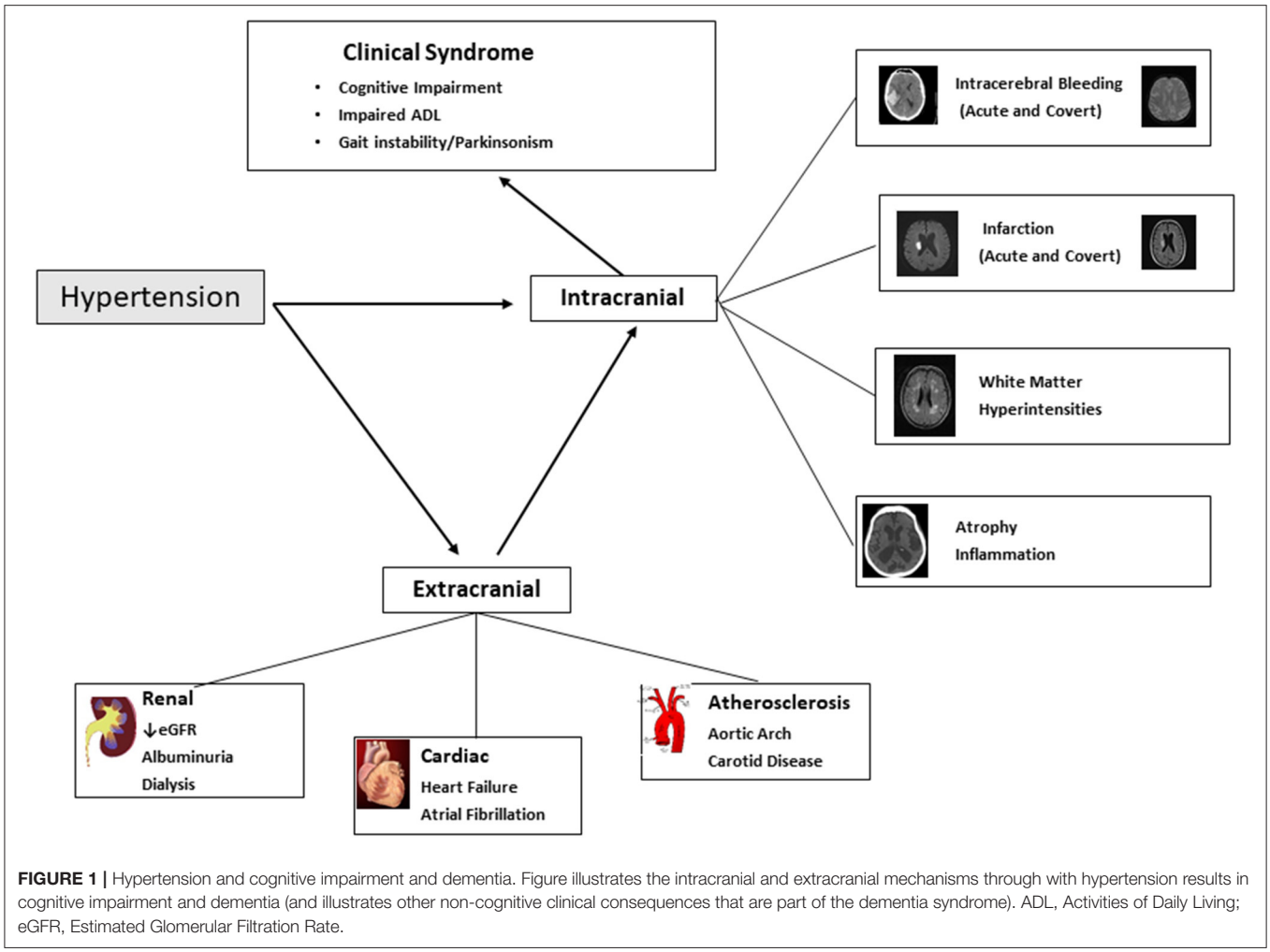

FIGURE 1 | Hypertension and cognitive impairment and dementia. Figure illustrates the intracranial and extracranial mechanisms through with hypertension results in cognitive impairment and dementia (and illustrates other non-cognitive clinical consequences that are part of the dementia syndrome). ADL, Activities of Daily Living; eGFR, Estimated Glomerular Filtration Rate.

Hypertension is a risk factor for both Vascular cognitive impairment and Alzheimer's disease, the two most common etiologies of dementia which commonly co-exist, and collectively account for 85% of cases of dementia (2). At present, there are no widely available effective treatments that favorably alter the natural history of cognitive decline and dementia, placing enhanced emphasis on the importance of primary prevention (3).

Identification and treatment of hypertension is considered an important target for population-level reduction in global burden of dementia (4). Although there have been improvements globally in detection of hypertension, levels of treatment and control are variable with one study quoting control rates of 23% for women and 18% for men in 2019 with worse rates in low to middle income countries where there is increasing prevalence of hypertension. Unequal access to medications, universal health-care and low levels of implementation of targeted public health measures may account for the low rates of control which will ultimately increase the burden of hypertension related conditions including ischemic heart disease and heart failure, chronic kidney disease and dementia (5).

However, while mid-life hypertension increases the relative risk of life-time dementia by 20–54%, use of antihypertensive therapy is associated with a more modest reduction in risk of dementia, with recent meta-analysis of trials reporting 7–11% relative risk reduction (6) (**Figure 2**). Nonetheless, such a relative risk reduction in prevalence of dementia among individuals with hypertension constitutes a considerable reduction in absolute frequency of dementia globally, given the high lifetime prevalence of both conditions (7).

In the following review article, we will detail the observational and interventional evidence linking hypertension with cognitive impairment, summarize the mechanisms through which hypertension causes cognitive decline, and explore some of the key unanswered questions in the field.

EPIDEMIOLOGY

Hypertension Is a Risk Factor for Cognitive Impairment and Dementia

Prospective cohort studies mostly report a positive association of hypertension and risk of cognitive impairment and dementia (8–12), with the strongest association between mid-life hypertension and risk of future cognitive decline and incident dementia. A recent meta-analysis of observational studies, including data

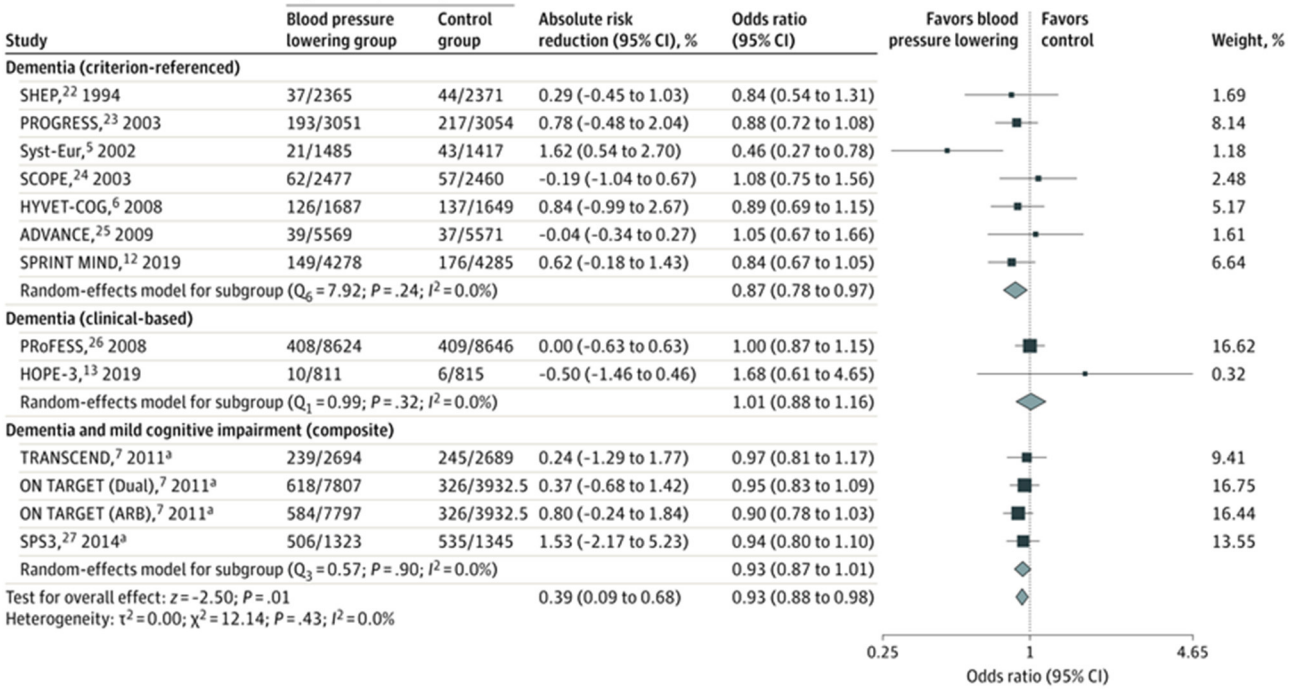

FIGURE 2 | Meta-analysis of blood pressure lowering randomized controlled trials. The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. Diamonds represent the combined effects and the vertical dotted line represents the line of no association. [a]Composite of dementia and cognitive impairment [Hughes et al. (6), reproduced with permission].

from 135 prospective cohort studies (three of which employed nested designs) with over 2 million individuals, reported a significant association of mid-life history of hypertension (RR 1.20; 1.06–1.35), elevated systolic blood pressure (RR 1.54; 1.25–1.89) and diastolic blood pressure (RR 1.50; 1.04–2.16) with risk of dementia. In that analysis, an increased risk emerged with systolic blood pressure over 130 mmHg (1). Among participants in later life, they did not report an overall association of hypertension with dementia risk, but did find a significant association for progression from mild cognitive impairment to dementia (RR 1.41; 1.00–1.99). In contrast to mid-life blood pressure, the risk of dementia emerged with systolic blood pressure over 180 mmHg (RR 1.45; 1.03–2.06). In older age groups, there was an apparent protective effect of diastolic blood pressure with dementia (RR 0.77; 0.59–1.00 for diastolic blood pressure of 90 mmHg or greater), likely reflecting the emergence of competing blood pressure mechanisms (e.g., orthostatic hypotension) (see below). A feature of these, and other analyses was apparent heterogeneity by ethnicity, with higher risks in older adults reported among black populations, compared to other ethnicities (13).

Population Attributable Fraction (Hypertension and Dementia)

Livingston et al. reported the PAF associated with common risk factors, based on meta-analytic estimates from observational studies, and reported a PAF of 5.1% (2.9–3.6%) and weighted PAF of 2.0% (0.6–0.9%) (14). In contrast, the reported PAF for acute stroke is estimated to be 49–64% (15, 16). However, PAF estimates for dementia were based on a prevalence of hypertension of 8.9%, which is expected to be an underestimate. The 10/66 Dementia Research Group (n = 12,865) (14) reported the cross-sectional association of mid-life hypertension, reporting a PAF of 18.6% for China, 25% for South America and 10.4% for India. These estimates are based on self-reported hypertension, and PAF would be larger when accounting for undiagnosed hypertension.

Given these considerations, it is anticipated that the PAF related to hypertension, especially in regions where rates of identification and control are low, particularly LMICs, will be where the largest burden of dementia will be borne. Moreover, the PAF does not account for the intermediary risk factors (e.g., atrial fibrillation) and chronic diseases (e.g., chronic kidney disease and heart failure), which also contribute to the global burden of cognitive impairment and dementia (17). Determining the PAF related to hypertension for dementia is also affected by outcome ascertainment of dementia which varies hugely between studies and sometimes focuses only on cognitive test scores which may not reflect the level of functional decline which is the core part of diagnosis in real world clinical practice.

PATHOPHYSIOLOGY (MECHANISMS AND MEDIATORS OF RISK)

As detailed in **Figure 1**, there are a myriad of causal pathways through which hypertension can contribute to adverse structural and functional consequences on the brain, leading to development and progression of cognitive decline.

Structural Changes in the Brain

Key end-organ pathological mechanisms, for which hypertension is proposed to be causative, include acute and covert cerebral ischemia and hemorrhage, accelerated brain atrophy, cerebral microvascular rarefaction and endothelial dysfunction, disruption of blood-brain barrier and neuroinflammation that affects amyloid pathologies (18) (**Figure 1**).

Cerebral Ischemia

Acute ischemic stroke and transient ischemic attack (TIA) are associated with an increased risk of cognitive impairment and dementia. A meta-analysis of population-based studies reported a rate of 7.4% (within 1 year) in population-based studies of first stroke without a history of dementia, and prevalence of 41.3% (95%CI 29.6–53.1%) in hospital-based studies of recurrent stroke (19). Hypertension is also associated with covert brain infarction, i.e., present on neuroimaging but without an acute clinical presentation of stroke, which are most often (90%) discrete small infarcts located in white matter or subcortical structures in the brain (**Figure 1**).

Beyond infarction, hypertension may be considered as an accelerator of aging cerebral vasculature, especially for small vessel disease. Small vessel disease is also a risk factor for post-stroke cognitive impairment (20). The effect of hypertension on small vessels within the brain can related to endothelial damage, lipohyalinosis, fibrinoid necrosis, microaneurysms, and pericyte injury. In addition, hypertension can result in reduced blood flow through a process of rarefaction, which has been demonstrated in animal models in renal and cerebral vascular beds. One common manifestation is white matter hyperintensities (**Figure 1**), which involve the coalescence of hyperintense signals in the periventricular structures of the brain, and their presence is associated with an overall 2-fold increase in dementia (21), but risk is related to burden of hyperintensities (22). Moreover, severity of white matter hyperintensity is associated with loss of instrumental activities of daily living (e.g., looking after finances), meaning that individuals are more likely to be diagnosed with dementia, which requires the combination of cognitive deficits with attributable impairment in activities of daily living (23).

Cerebral Hemorrhage

Cognitive impairment is common after acute intracerebral hemorrhage, for which hypertension is the dominant risk factor, with prevalence ranging from 19 to 63% at 6 months after intracerebral hemorrhage (24). Similar to ischemic stroke, an important determinant of whether patients develop cognitive impairment is location and size of stroke. In addition to acute hemorrhage, covert cerebral microbleeds, small discrete areas of bleeding (<5 mm diameter) (**Figure 1**), are also a manifestation of small blood vessel disease, are associated with cognitive decline (25).

Brain Atrophy/Inflammation

Hypertension is a risk factor for presence and severity of brain atrophy, a key feature of neurodegenerative diseases. Elevated blood pressure is associated with brain atrophy, and increased number of neuritic plaques in neocortex and hippocampus and neurofibrillary tangles in autopsy studies (26, 27). Other mechanisms include oxidative stress with microvascular damage and inflammation. A proposed mechanism, which promotes inflammation is disruption of the blood brain barrier with microglia activation, and impaired glymphatic clearance of amyloid (28–30). These latter mechanisms likely account for the contribution of hypertension to accelerating Alzheimer's disease mechanisms.

Extracranial Mechanisms and Mediators

Chronic Kidney Disease

Hypertension is a major risk factor for chronic kidney disease. The prevalence of cognitive impairment in people with CKD ranges from 10 to 40% (31, 32), with the highest in those receiving haemodialysis where approximately half of patients undergoing dialysis have moderate to severe cognitive impairment (33). Both reduced estimated glomerular filtration rate and albuminuria are independent risk factors for development of cognitive impairment and dementia (34). The association of albuminuria and cognitive impairment is largely mediated through a common mechanism of vascular endothelial damage. Chronic uraemia is associated with loss of blood brain barrier integrity contributing to cerebral small vessel ischemia (35). In dialysis populations, additional contributors include fluctuating blood pressure during ultrafiltration, an inadequate autonomic response to this fluctuation, as well as cerebral stunning which can cause cerebral injury and hypo-perfusion (36, 37). Other mechanisms by which chronic kidney disease contributes to cognitive impairment include vascular calcification and arteriosclerosis (38). Chronic kidney disease is also a risk factor for acute and covert stroke, independent of hypertension, and has also been associated with increased beta amyloid production and impaired clearance of beta amyloid (39) (**Figure 1**).

There is some evidence of a shared natural history of disease (40), with hypertension playing an overlapping role in both chronic kidney disease and cerebrovascular disease. Both kidney (afferent arterioles) and brain (deep perforating) arterioles are exposed to high pressure, requiring them to maintain large pressure gradients which make them particularly prone to hypertensive injury and problems with autoregulation (Strain Vessel Hypothesis) (41). There is a long latent period between the damage to the kidney from hypertension and a decline in kidney function similar to the effect of prolonged hypertension on cognition and it may be accelerated by other cardiovascular events (42). In randomized controlled trials of blood pressure lowering, the relative risk reduction in renal outcomes is consistent with estimates for cognitive outcomes,

based on indirect comparisons of meta-analyses, and findings from the SPRINT trial (43, 44).

Extracranial Large Vessel

Large vessel atherosclerosis is associated with an increased risk of ischemic stroke and increased risk of Alzheimer's disease (45). In addition, hypertension also results in age-related stiffening of the elastic arteries in aortic arch and large vessels, which provide an important buffering role in dampening haemodynamic pulsatility (Windkessel effect), with hypertension resulting in the increased pulsatility pressure in brain. In older adults with hypertension, this increased pulsatile pressure results in greater strain on the cerebral microcirculation (46).

Cardiac Disease

Hypertension is an important risk factor for heart failure (RR 1.40; 1.24–1.59), with an estimated PAF of 10.1%, based on analysis of NHANES dataset (47). Heart failure is an independent risk factor for dementia, associated with a 28% relative odds increase in risk. Hypertension is also major risk factor for atrial fibrillation, which, in turn, is associated with an increased risk of cognitive impairment (48), mediated largely though the risk of thromboembolism. In a meta-analysis of 43 cohort studies, atrial fibrillation was associated with a 50% increase in relative odds of cognitive impairment or dementia (OR 1.5; 1.4–1.8).

Hypertension, Cognitive Domains, and Aetiological Subtypes of Dementia

While hypertension is reported to be a risk factor for Vascular Cognitive Impairment and Alzheimer's disease, there is considerably less convincing evidence of an association with Lewy Body Dementia and Frontotemporal dementia, which occur at lower frequency. In older populations, however, vascular disease commonly co-exists, making it difficult to discern the independence of association between hypertension and neurodegenerative subtypes.

As detailed, the principal mechanisms governing the association of hypertension and cognitive loss are related to vascular disease. Not surprisingly, therefore, hypertension is most strongly correlated with cognitive domains associated with Vascular dementia, but is also a risk factor for global cognition (RR 1.55; 1.19–2.03). For example, one meta-analysis reported a numerically stronger association of hypertension with impairment in executive function (RR 1.22; 1.06–1.41) than memory (RR 1.13; 0.98–1.30), which would be more consistent with Vascular cognitive impairment than Alzheimer's pattern impairment.

Another study reported increased risk in abstract reasoning and executive function loss, which has greater specificity for vascular cognitive impairment (49). People with chronic kidney disease and cognitive impairment also tend to have preferential deficits in executive functioning and processing consistent with the pattern seen in vascular cognitive impairment (50). The pattern of cognitive impairment observed with hypertension or vascular cognitive impairment is often differentiated from the pattern seen in clinical Alzheimer's disease based on preservation of memory function. However, evidence now emerging that hypertension is a risk factor for Alzheimer's Disease by exacerbating accumulation of Aβ in the brain makes it difficult to make a clean distinction and the reality in clinical practice particularly in older people is a mixed picture of both types.

DOES TREATING HYPERTENSION REDUCE THE RISK OF COGNITIVE IMPAIRMENT?

Recent metanalyses of cohort studies and meta-analyses of randomized controlled trials (13, 51, 52) show a modest benefit of lowering blood pressure on the development of dementia or cognitive impairment. The magnitude of the relative reduction in risk of dementia from blood pressure lowering in clinical trials ranges from 7 to 10% with similar risk reductions noted from observational studies (53). One meta-analysis, that included 96,158 participants from 14 trials, reported an absolute risk reduction of 0.4% (95%CI 0.1–0.7%) in incidence of dementia over a mean follow up of 4.1 years (OR 0.93; 0.88–0.98) (6) (**Figure 2**). Therefore, the effect size is modest for dementia at an individual-level, but expected to translate into an important population-level impact, with effective identification and treatment of hypertension. In meta-regression, mean age of population (trial-level) was not associated with different treatment effect size, which does not provide support for a differential effect by age.

The relative risk reduction in dementia (7%) associated with antihypertensive therapy is lower than reported for reduction of major cardiovascular events (20%), but similar to the effect reported for renal outcomes (5%) (54). These differential effects of blood pressure lowering on acute cardiovascular events, compared to chronic cognitive and renal outcomes, emphasize that the causative role of hypertension appears to differ by mechanism of disease. In general, large randomized controlled trials of blood pressure lowering are designed to detect treatment effects on incidence of acute events rather than clinical manifestations of vascular disease, which are not event-based. Another distinction is validity and reliability of the outcome measure. Cognitive outcome measures, included in blood pressure lowering trials, range from scores on cognitive testing to centrally adjudicated, criterion-based definitions of dementia. In the SPRINT-Mind trial, they employed a rigorous centrally adjudicated definition of dementia, and reported a 17% relative risk reduction in probable dementia. In one meta-analysis, antihypertensive therapy was also associated with a 13% risk reduction in dementia in clinical trials that employed a criterion-referenced definition of dementia, rather than a clinically defined definition (6). In each of the randomized controlled trials, the cognitive outcomes were secondary or tertiary, and sample size was not based on ability to detect difference in dementia outcomes. Larger trials to determine the effectiveness of multi-domain interventions, targeting a number of cardiovascular risk factors including hypertension, have been completed (55, 56). The largest trial to evaluate the clinical outcome of dementia was the Pre-DIVA trial (56), a cluster

randomized trial of older adults in General Practice. A nurse-led cardiovascular risk factor intervention resulted in greater uptake of antihypertensive therapy among those with untreated hypertension at baseline, compared to control (67 vs. 56%). The incidence of dementia after median follow-up of 6.3 years was not different between groups, but this trial was not designed to test the effectiveness of blood pressure lowering in a population.

The effect of blood pressure lowering on covert cerebrovascular disease has also been studied, with observational studies reporting the association of antihypertensive therapy with reduction in risk of developing white matter hyperintensities (57). In two recent RCT sub-studies, blood pressure lowering was associated with a reduction in the rate of progression of WMH. In the INFINITY (58) ($n = 199$) and SPRINT-Mind (59, 60) ($n = 670$) trials, blood pressure lowering was associated with a smaller percentage change in white matter hyperintensity volume, and, in the SPRINT-Mind trial, a greater decrease in brain volume, based on comparison of MRI brain imaging at baseline and follow-up.

There is an absence of clear information on what, if any, is the best antihypertensive medication class for prevention of dementia or cognitive decline. Randomized controlled trials reporting cognitive outcomes have employed diverse antihypertensive agents, including ACE inhibitors (61), diuretics (62), calcium channel blockers (63) and angiotensin receptor blockers (64). Two recent systematic reviews evaluating the effect of particular classes of antihypertensive drugs on cognitive outcomes did not report a larger benefit of any one class of antihypertensive drug over another (65, 66). However, these meta-analyses were underpowered to determine between-class effects of antihypertensive drugs. A recent Phase II trial ($n = 176$) reported superiority of candesartan vs. lisinopril in mean change in some neurocognitive tests over 12 months (67). However, there are no large randomized controlled trials comparing different antihypertensive agents with clinical syndrome of dementia or cognitive impairment as the primary outcome.

COGNITIVE IMPAIRMENT AND OTHER BLOOD PRESSURE PARAMETERS

Steep declines in blood pressure in later life, compared to mid-life, are associated with development of cognitive impairment (10, 68). This observation suggests that cerebral perfusion plays a significant role in development of dementia, and that the association between blood pressure and development of cognitive impairment is not linear and may well be *J* or even *U*-shaped and depends on age (69, 70). The Chinese Longitudinal Healthy Longevity survey reported that a systolic blood pressure range of 130–150 mmHg was associated with the lowest risk of cognitive impairment in adults over 80 years (71). The association of lower blood pressure and risk of dementia in older age may be due to reverse causation.

Orthostatic hypotension is a risk factor for dementia, associated with a 26% relative increase in risk. It is common in older adults and can affect cognition through a number of mechanisms. First, neurodegeneration of brain regions responsible for cognitive function may also be involved in regulation of cardiovascular activities leading to orthostatic hypotension cognitive impairment. Second, orthostatic hypotension can cause poor frontal lobe perfusion which can affect executive function. Third, low cerebral blood flow can cause subcortical infarction and ischemic demyelination (72).

Blood pressure variability (BPV) is increasingly being recognized as having a significant role in target organ damage (73). Several longitudinal studies have also reported that BPV is significantly associated with increased risk of cognitive impairment and dementia (11, 74–76). Higher BPV between sequential visits was associated with a higher long-term risk of dementia in the Rotterdam study which was most pronounced when BPV was measured 15 years before the diagnosis of dementia (77). Another study showed that increased day to day BPV is also associated with higher risk of dementia over 5 years but the long-term risk of dementia in relation to day to day BPV is unknown (76). The precise biological mechanism relating blood pressure variability with cognitive impairment is incompletely understood, but likely related to subclinical ischemic changes in brain, hypoperfusion and hypotension, endothelial dysfunction and inflammation all playing a role. Reverse causation may also have a role where there is BPV due to autonomic dysfunction associated with dementia syndromes (78).

In clinical practice, use of antihypertensive agents and regimens associated with least blood pressure variability and orthostasis may be more appropriate for older patients with hypertension (79).

CONCLUSION/FUTURE DIRECTIONS

Hypertension is an important modifiable risk factor for cognitive impairment and dementia. Evidence from randomized controlled trials suggests a 7–11% relative risk reduction in the incidence of dementia with antihypertensive therapy. While none of these trials included cognitive outcomes as the primary outcome measure, it is unlikely that large definitive trials will be completed, as antihypertensive agents are indicated for primary prevention of cardiovascular disease in individuals with hypertension. Future studies are needed to determine the optimal blood pressure target, especially in older adults and those with orthostatic hypotension. Additional research is also required to determine which antihypertensive agents, and regimens, are optimal for maintaining cognitive health. Of greater importance, however, is the need for improved detection and treatment of hypertension in the general public, which is expected to translate into meaningful gains in lowering the global burden of dementia.

AUTHOR CONTRIBUTIONS

MC and MO'D both conceptualized the paper, designed the figures and tables, and wrote sections of the first draft of the manuscript. Both authors contributed to subsequent manuscript revision and refinement, read, and approved the submitted version.

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REVIEW
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Disentangling the Relationship Between Chronic Kidney Disease and Cognitive Disorders

Dearbhla M. Kelly[1]* *and Peter M. Rothwell*[2]

[1] J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2] Wolfson Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom

Chronic kidney disease (CKD) is a rapidly rising global health burden that affects nearly 40% of older adults. Epidemiologic data suggest that individuals at all stages of chronic kidney disease (CKD) have a higher risk of developing cognitive disorders and dementia, and thus represent a vulnerable population. It is currently unknown to what extent this risk may be attributable to a clustering of traditional risk factors such as hypertension and diabetes mellitus leading to a high prevalence of both symptomatic and subclinical ischaemic cerebrovascular lesions, or whether other potential mechanisms, including direct neuronal injury by uraemic toxins or dialysis-specific factors could also be involved. These knowledge gaps may lead to suboptimal prevention and treatment strategies being implemented in this group. In this review, we explore the mechanisms of susceptibility and risk in the relationship between CKD and cognitive disorders.

Keywords: CKD, dialysis, hypertension, cognitive impairment, dementia, stroke

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Federal University of Mato Grosso do Sul, Brazil

***Correspondence:**
Dearbhla M. Kelly
dkelly28@mgh.harvard.edu

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INTRODUCTION

The global burden of chronic kidney disease (CKD) is rising with estimated prevalence rates of 11–13% (1), increasing to nearly 40% in persons aged 60+ years (2). Although its contribution to cardiovascular diseases is well-established (3), the significant impact of CKD on cognitive brain health is only beginning to emerge. CKD is strongly associated with both cognitive impairment and dementia, and these associations worsen with declining renal function (4). In this review, we will discuss the clustering of risk factors associated with dementia in this group as well as the potential role of novel renal-specific factors. We will endeavor to tease out the role of these putative risk factors and mechanisms as mediators, confounders, or epiphenomena.

KIDNEY-BRAIN AXIS

The kidney-brain axis refers to a relationship that exists under both physiological and pathophysiological circumstances. This relationship has been described as the "neglected kidney-brain axis" (5) because the critical interplay between these two organs that can lead to important neurological disease pathophysiology has only recently been recognized. The kidney and brain share similar anatomical and physiological features that render them vulnerable to the impact of traditional cardiovascular risk factors such as hypertension, diabetes, and smoking (6). Both organs share a low vascular resistance system, allowing continuous high-volume perfusion (7). Autoregulation allows constant blood flow despite fluctuations in blood pressure, to maintain

cerebral perfusion pressure in the brain and GFR in the kidney. The "strain vessel hypothesis" has been proposed as a possible mechanism for the relationship between renal and cerebrovascular diseases whereby juxtamedullary afferent arterioles in the kidney and cerebral perforating arteries are both exposed to high pressure and have to maintain large pressure gradients, rendering them uniquely susceptible to hypertensive injury (8). This hypertensive vascular injury is then clinically manifest as proteinuria and progressive GFR decline in the kidney, and as symptomatic stroke, silent cerebral small vessel disease and cognitive decline in the brain.

It has also been hypothesized that there may be inflammatory cross-talk between the two organs that may also contribute to the cerebrovascular and neuropsychiatric disease burden observed in patients with CKD (9). This cross-talk between the kidney and brain may include enhanced cytokine/chemokine release and production of reactive oxygen species (ROS) in AKI or CKD leading to neuroinflammation, cytokine interaction with pathogenic neurotrophic factors through a disrupted blood-brain barrier, and activation of the brain renin–angiotensin system (RAS) contributing to oxidative stress via angiotensin II. The cytokines/chemokine release in CKD activates immune cells, neurons, and glial cells in the brain creating a cascade with release of more inflammatory molecules, which locally interact with neurotrophic factors and with ROS, thus contributing to neuropsychiatric disorders.

EPIDEMIOLOGY OF COGNITIVE DISORDERS IN CKD

The prevalence of MCI in pre-dialysis CKD is reported as variably being between 25 and 62% (10, 11), compared to rates of 11–26% in the matched general population (10, 12). In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, each 10 mL/min/1.73 m^2 decrease in eGFR <60 mL/min/1.73 m^2 was associated with an 11% increase in prevalence of cognitive dysfunction (13). Haemodialysis patients are three times more likely to have severe cognitive impairment than age-matched non-dialysis patients with reported prevalence rates of 30–40% (14).

CKD is in fact one of the strongest risk factors for mild cognitive impairment (MCI) and dementia as demonstrated by a recent 6-year population-based longitudinal study in which the impact of CKD on risk of MCI and dementia was exceeded only by stroke and chronic use of anxiolytics (15). Even early stages of CKD are associated with cognitive impairment (16). In a pediatric study of 340 patients (ages 6–21) with mild–moderate CKD, a longer duration of CKD was associated with reduced attention and executive function, with a doubling of the odds of poor performance for every 4.6 years of disease exposure (17). However, in the Three-City (3C) Study, a longitudinal cohort of 9,294 adults aged 65 years and over, although the cross-sectional findings suggested that duration of disease was more relevant than the level of GFR; in the longitudinal analysis, rapid eGFR decline (>4 ml/min/1.73m^2/yr) was more strongly associated with cognitive decline and incident dementia (18). It may be the case that duration of CKD is particularly relevant in children and adolescents during periods of critical neurodevelopment (19).

In another recent, large population-based study, CKD was associated with a higher dementia risk [hazard ratio (HR), 1.71; 95% confidence interval (CI)], 1.54–1.91 in eGFR 30–59 ml/min and HR 2.62, 1.91–3.58 in eGFR<30 ml/min] compared with eGFR of 90–104 ml/min (20). In this study, both the severity of CKD and steeper kidney function decline were associated with dementia. It was found that as many as 10% (95% CI 6–14%) of dementia cases could be attributed to CKD, a proportion higher than that attributed to other dementia risk factors such as cardiovascular disease and diabetes.

As a measure of kidney function, proteinuria also appears to be more strongly associated with cognitive decline than low eGFR for reasons that are unclear (21, 22). This finding is however consistent with recently published meta-analyses data on the relationship between low eGFR, proteinuria, and stroke risk (23, 24).

The prevalence of dementia among haemodialysis patients is 8–37% with the risk increasing linearly with age (12, 25). Prevalence rates are broadly similar (4–33%) for patients on maintenance peritoneal dialysis (12, 26) but fall for kidney transplant recipients (7–22%) (27, 28). Although there may be a selection bias in terms of transplant candidates, improvements in cognitive scores in parallel with favorable structural and functional changes in white matter integrity have been described 1 year after kidney transplantation (29). However, these changes may not be sustained in frail recipients (27). Older adults on haemodialysis with a diagnosis of Alzheimer's disease or dementia have a >2-fold risk of mortality compared to those without these diagnoses (25).

MECHANISMS OF SUSCEPTIBILITY AND RISK

Mechanisms underlying the pathogenesis of MCI and dementia in CKD are poorly understood. Both vascular and neurodegenerative hypotheses have been proposed (**Figure 1**) (5, 30). In support of the vascular hypothesis, there is a high prevalence of cardiovascular risk factors, such as hypertension and diabetes mellitus, as well as a significant burden of both symptomatic and subclinical cerebrovascular disease (31). On the contrary, consistent with the neurodegenerative hypothesis, the accumulation of uraemic toxins can cause cerebral endothelial dysfunction and has been implicated in cognitive decline (32). However, this binary view of potential pathogenesis for CKD-related neurocognitive disorders is likely an over-simplistic summary of a multi-factorial process that likely includes elements of both hypotheses. We will outline the evidence for these cognitive risk factors, some of which are shared by the general population, and some of which are renal-specific.

Age and Sex Differences

The greatest risk factor for Alzheimer's disease (AD) is advanced age (33). Prevalence of AD shows a steep increase with age, from 0.6% in the group age 65–69 years to 22.2% in the group aged

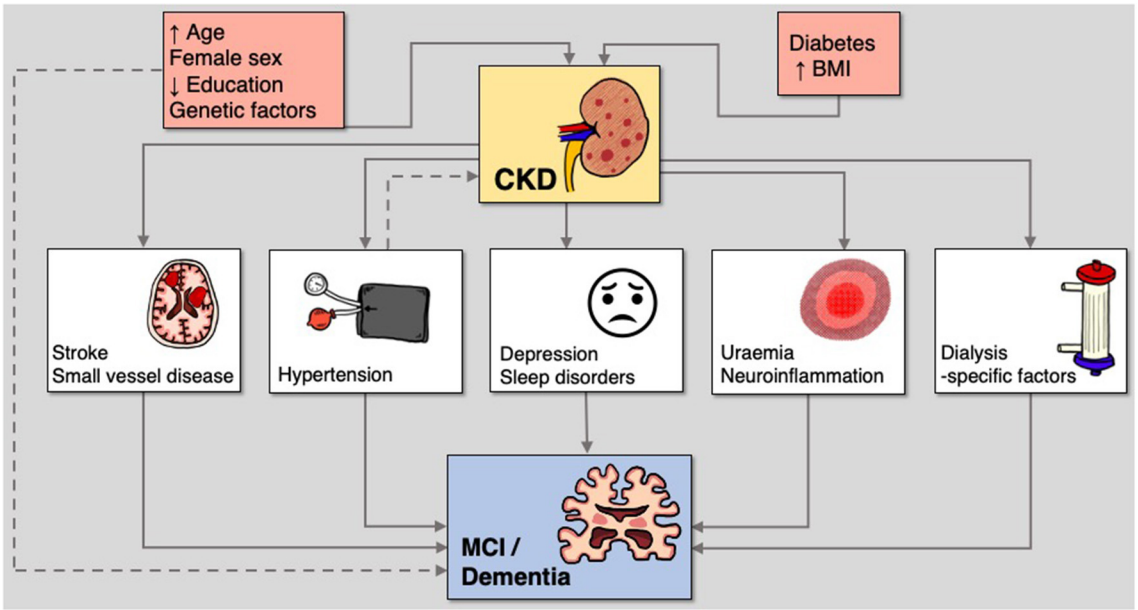

FIGURE 1 | Mechanisms of susceptibility and risk in the relationship between CKD and cognitive disorders.

90 years and older (34). Age also contributes to the etiology and progression of CKD. The aged kidney undergoes a range of structural and functional changes that can lead to disordered inflammation and renal fibrosis, rendering the kidney vulnerable to acute insults and increasing the risk of CKD progression (35). These changes may be part of a broader process of systemic persistent inflammation causing inflammatory aging known as "inflammageing". This condition is characterized by elevated levels of blood inflammatory markers (36), a high susceptibility to cerebrovascular disease and dementia (37, 38), and is exacerbated by uraemia and dialysis dependency (39).

There are also key sex differences in the prevalence of both dementia and CKD. A European meta-analysis found that the pooled prevalence of AD was 7.02 per 1,000 person-years in men and 13.25 per 1,000 person-years in women (40). Women account for approximately two-thirds of patients with AD and related dementias in both Europe and the US (41, 42). This disparity is thought to be attributable to women's greater longevity since risk of developing dementia increases with age and there may be a competing mortality risk for men that can confound HR estimation of dementia (43, 44). However, a recent study showed that incident midlife hypertension was associated with greater memory decline in women and suggested that such discrepancies in risk factor-disease associations could also potentially contribute to heterogeneity of AD disease prevalence in later life (45). Similarly, several other key vascular risk factors such as hyperlipidaemia, diabetes mellitus and atrial fibrillation also appear to be associated with greater risk of stroke in women compared to men which may contribute to downstream dementia burden (46). The proportion of women with pre-dialysis CKD is also higher than that of men, a difference that is also likely accounted for by the longer life expectancy of women, but nonetheless renders them especially vulnerable to accelerated "inflammageing" and the enhanced effects of vascular risk factors, and consequently, to diseases of brain aging such as stroke and dementia (47). Therefore, both age and sex could account for confounding and epiphenomenal association in the relationship between CKD and cognitive impairment.

Education Level

A low educational level is associated with an increased incidence of clinical AD or dementia (48). It has been suggested that education could delay the clinical expression of dementia symptoms by increasing the neocortical synaptic density (the "brain reserve" hypothesis) (49). Others have proposed that educational and occupational attainment provide a reserve against dementia, enabling this group to cope with advanced pathological changes of the disease more effectively by maintaining function longer (the "cognitive reserve" hypothesis) (50). However, it may also be the case that those with greater educational attainment and associated higher socioeconomic status may be exposed to fewer neurotoxins and have fewer cardiovascular risk factors that may contribute to vascular/neurodegenerative brain disorders (the "brain battering" hypothesis) (51).

Similarly, low educational and occupational levels have been associated with CKD and worse kidney outcomes (52). CKD risk, albuminuria, and reduced eGFR rates are all higher among participants with low educational level compared to those with high educational level. Exploratory longitudinal mediation analysis suggest that the association between education and CKD can partly be explained by diabetes and the modifiable risk factors, body mass index (BMI), waist-to-hip ratio (WHR), smoking, potassium and hypertension (53). Thus, low

educational attainment is another potential confounder in the association between CKD and cognitive disorders with some evidence of synergy as subtle GFR decline is associated with more rapid cognitive decline in those with lower educational levels (54). However, more recent data in the general population suggests that higher cognitive reserve may not diminish the adverse effects of covert vascular brain injury (55).

Hypertension

The causal relationships between hypertension, CKD and dementia are particularly complex as hypertension could be potentially both a confounder and mediator in the relationship between CKD and dementia.

Many observational studies report hypertension to be an important risk factor for dementia (56–58) and in a recent meta-analysis of randomized clinical trials, blood pressure lowering with antihypertensive agents compared with control was significantly associated with a lower risk of incident dementia or CI (59). The relationship between hypertension and cognitive decline may be mediated through cerebrovascular disease (60, 61) or via augmentation of neurodegenerative mechanisms. At autopsy, hypertensive older adults also have evidence of greater AD pathology in the brain, including neurofibrillary tangles and neuritic amyloid-beta (Aβ) plaques (62). Positron emission tomography studies have shown that the extent of Aβ deposition in the brain is positively associated with higher BP (63). The chronicity of past hypertension appears to be most important. Multiple studies have indicated that it is the occurrence of midlife hypertension and its persistence into late life that is one of the leading risk factors for late-life dementia (64, 65).

It follows then that since hypertension occurs in 67–92% of patients with CKD (66), that the adverse cognitive consequences could be accentuated in this group. However, although premorbid mid-life to late-life blood pressure is strongly associated with MCI and dementia in the general population, its role in dementia pathogenesis in CKD is unknown. A recent systematic review and meta-analysis of stroke risk in CKD suggested that most of the risk in this setting may be attributable to long-term blood pressure burden (23). Premorbid blood pressure may therefore also play a similarly central role in the etiology of cognitive dysfunction in CKD, though this has not been previously shown. In an analysis of 8,563 hypertensive adults in the SPRINT trial, they found that a $\geq$30% decline in baseline eGFR and incident eGFR $<$60 ml/min/1.73 m^2 were associated with an increased incidence of probable dementia and MCI, independent of the intensity of hypertension treatment (67). This highlights a potential synergy between hypertension and kidney disease in the pathogenesis of CI and dementia.

Stroke

Stroke is associated with an increased risk of subsequent dementia. In a large meta-analysis of symptomatic stroke patients, 10% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and more than a third had dementia after recurrent stroke (68).

There are also strong associations reported between CKD and cerebrovascular disease (30). Meta-analyses of cohort studies and trials indicate that reduced GFR is associated with a 40% greater risk of stroke and that proteinuria is associated with a 70% greater risk (69) even after adjusting for traditional cardiovascular risk factors. In terms of potential mechanisms, there is a high prevalence of shared vascular risk factors including hypertension, diabetes mellitus, and atrial fibrillation but "non-traditional" risk factors such as anemia, hyperuricemia, and mineral-bone disorders may also play a role (70).

Importantly, several of the predictors of post-stroke dementia (68) are common in the CKD population including older age (35), low educational attainment (52), premorbid disability, (71) and vascular risk factors such as diabetes mellitus and atrial fibrillation (AF) (72). In addition, CKD is associated with several stroke-specific factors (68) that are predictive of post-stroke dementia including higher stroke severity and greater risk of recurrence (73).

Small Vessel Disease

Cerebral small vessel disease (SVD) is a major etiologic factor in dementia (74). This may relate to a reduction in cerebral blood flow (75), and impaired cerebral autoregulation (76). SVD and AD pathology are thought to interact in important ways (77). Chronic cerebral inflammation due to vascular risk factors exposure and genetic modulators (apoE4) may lead to increase Aβ production while chronic SVD (arteriosclerosis, cerebral amyloid angiopathy) and vascular inflammation may drive inefficient perivascular and cell-mediated Aβ clearance (78).

SVD is highly prevalent in patients with CKD (79) and it is associated with all subtypes including white matter lesions (WML) (80), silent cerebral infarctions (SCI) (81), perivascular spaces (PVS) (82), and cerebral microbleeds (CMB) (83). Over half of all CKD or dialysis-dependent patients have evidence of SCI on imaging studies (84, 85). These associations may relate to the "strain vessel hypothesis" (8), shared cardiovascular risk factor burden (81), or perhaps genetic pleiotropy may play a role in younger populations (86). SCI in the presence of CKD has been associated with executive dysfunction (87). This pattern of cognitive change with prominent impairment of executive function and processing speed has also been observed in maintenance haemodialysis patients (88), consistent with cognitive deficits associated with cerebrovascular disease (89). It is therefore unclear whether CKD is a risk factor for dementia independent of either symptomatic or subclinical cerebrovascular disease.

Diabetes Mellitus and Obesity

A recent meta-analysis of over 2 million participants showed that individuals with type 2 diabetes are at ∼60% greater risk for the development of dementia compared with those without diabetes (90). Those with a younger age of diabetes onset and cardiovascular comorbidity are particularly at risk (91). Several mechanisms for the link between diabetes and dementia have been proposed including brain metabolic dysfunction as a driver for AD pathology (92), with impairments in insulin transport through the blood-brain barrier, insulin signaling, and resultant decreased cerebral glucose utilization (93). In addition, hyperglycemia may lead to neurotoxicity, vascular injury, and

accumulation of advanced glycation end products (94). Nearly one third of CKD is attributable to diabetic nephropathy (3) and even patients with mild-moderate stages of diabetic kidney disease have been found to have occult neurocognitive disorders (95), highlighting the role of diabetes as a potential confounding factor in this pathway.

Increasing evidence suggests that obesity, highly prevalent in the CKD population (96) and estimated to account for ∼20–25% of kidney disease worldwide (97), is also an independent risk factor for dementia. In an analysis of 6,582 participants from the English Longitudinal Study of Aging, individuals with baseline obesity had about a 30% increased risk of dementia even after adjusting for sex, baseline age, apolipoprotein E-ε4 (APOE-ε4), education, physical activity, smoking, marital status, hypertension and diabetes (98). Similar to diabetes though, excess adiposity is linked with a change in brain energy metabolism, the accumulation of brain lesions and brain volume loss leading to neurodegeneration (99).

Depression and Sleep Disorders

Approximately 25% of CKD patients report symptoms of a major depressive disorder (100) with high rates of under-treatment described (101). In particular, hemodialysis patients with a greater burden of depressive symptoms perform worse on tests of cognition related to processing speed and executive function, suggesting that depression could therefore be a potential mediating or contributing factor in the relationship between CKD and cognitive disorders (102).

Similarly, sleep disorders are highly prevalent in CKD with a spectrum of manifestations described including insomnia, sleep fragmentation, daytime somnolence, sleep apnoea, altered circadian rhythm, and restless legs syndrome (103). Sleep disorders are also highly linked to cognitive impairment and dementia and are often representative of underlying brain pathology (104). The glymphatic system is responsible for clearance of ∼60% of β-amyloid clearance and since this occurs primarily during sleep (105), which is altered during CKD, it has been proposed that glymphatic fluid transport may be suppressed in CKD, leading to an accumulation of potentially neurotoxic waste products (106).

Genetic Factors

The role of genetic factors in the pathogenesis of cognitive dysfunction in CKD has been largely unexplored (106). In younger patients, some rare genetic syndromes have been described that can cause both kidney disease as well as neurocognitive disorders including tuberous sclerosis (107), Fabry disease (108), and Bardet-Biedl Syndrome (109). In general, compared with noncarriers, children with genetic kidney disease score significantly poorer on all measures of intelligence, anxiety/depressive symptoms, and executive function (110).

A genetic cause has been described in 10% of adult patients with CKD (111), and this figure can rise to 37% of those with positive family history, many of whom have extra-renal features (112). However, it is not known whether there is a similar tendency toward neurocognitive disorders in this group. Several single-nucleotide polymorphisms (SNPs) associated with kidney disease (113) are in exons for genes that also expressed in the brain including in the striatum (SLC47A1, KLHDC7A and SLC25A45; from the Allen Brain Atlas database), cortex (EDEM3, PPM1J, and CERS2; from the Human Protein Atlas database) and the cerebellum and hippocampus (TSPAN9 and EPB41L5; from the Human Protein Atlas database). Furthermore, some are in genes linked to Alzheimer's disease (CACNA1S; WikiPathways database).

Two genome-wide association studies have also previously indicated genetic pleiotropy between kidney and cerebrovascular disease, particularly with large artery atherosclerotic and small vessel stroke (86, 114). In the most recent of these studies that leveraged large-scale data from international consortia, a locus at 2q33 showed pairwise associations between urinary albumin:creatinine ratio and both small vessel stroke and white matter hyperintensities (WMH), indicating that 2q33 may play a role across small vessel pathologies in both the kidney and brain through microalbuminuria, small vessel stroke, and WMH, and that there may be a shared common pathway among cerebral and renal manifestations of small vessel disease (114).

Uraemia and Neuroinflammation

The accumulation of uraemic toxins is proposed to cause cerebral endothelial dysfunction and contribute to cognitive disorders in CKD (32). High uraemic toxin concentrations of guanidine compounds such as creatinine, guanidine, guanidinosuccinic acid, and methylguanidine have been found in CKD patients in strategic brain regions for cognition, such as the thalamus, mammillary bodies, and cerebral cortex (115). Haemodialysis efficiently eliminates water-soluble toxins and improves acute uraemic encephalopathy, but is relatively ineffective for protein-bound or medium-sized toxins that may contribute to chronic cognitive dysfunction in patients with ESKD (106). Of particular interest is Neuropeptide Y, a polypeptide that has been implicated in some neurodegenerative and neuroimmune disorders (116), and that is also present in high levels in CKD (117).

Inflammation has also been suggested as a mediator of cognitive decline in CKD (118). The intensity of systemic inflammation, as indicated by elevations in multiple markers of inflammation, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor–α (TNF-α), and C-reactive protein (CRP), appears to increase as kidney function declines (119). Both cross-sectional and longitudinal studies have shown that that CRP and fibrinogen are independently associated with deterioration in some domains of cognitive function in patients with CKD (120, 121), though these studies are vulnerable to type 1 error from multiple testing.

Dialysis-Specific Factors

It is increasingly recognized that haemodialysis is associated with both acute and chronic brain injury (122, 123). Even in clinically stable patients undergoing intermittent haemodialysis, it can cause cerebral oedema via an increase in brain water content and from reverse osmotic shift due to urea (124) or other newly formed brain osmoles (125). Global cerebral blood flow has

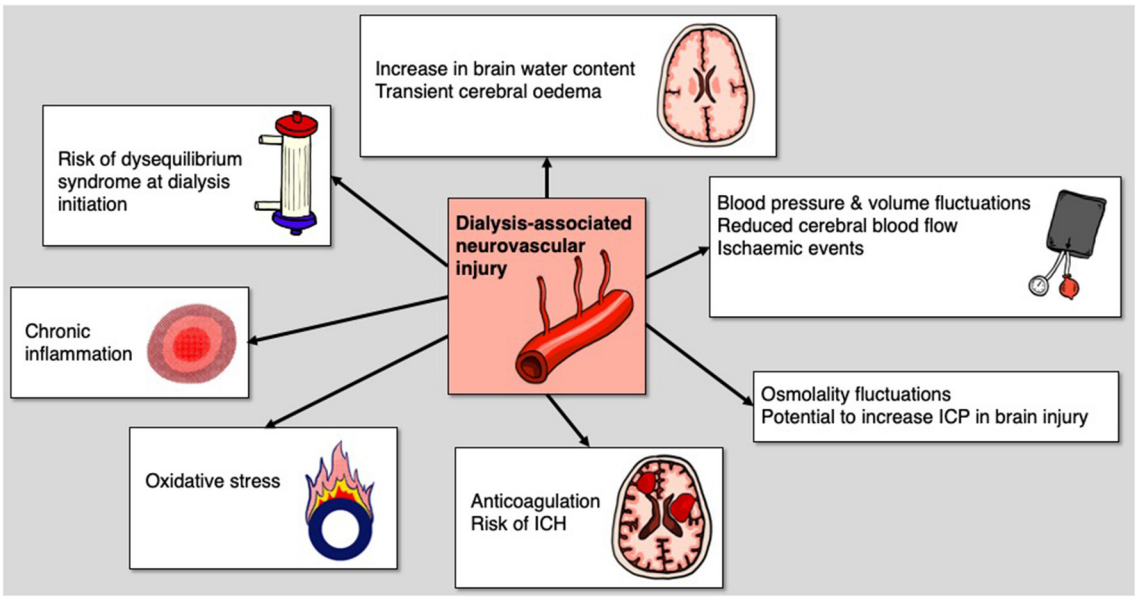

FIGURE 2 | The potential impact of dialysis-associated neurovascular injury on cognition.

also been shown to decline acutely by 10% during hemodialysis (126). Thus, in the setting of acute brain injury, there is a risk of secondary brain injury in what's now referred to as dialysis-associated neurovascular injury (DANI) (**Figure 2**) (122).

In the chronic setting, it has been shown that every 10 mmHg drop from baseline in mean arterial pressure during a dialysis session is associated with a 3% increase in ischaemic events (127). Nearly one-quarter of haemodialysis sessions feature cerebral ischaemic events and these intradialytic events correlate with decreased executive cognitive function at 12 months.

In a prospective cohort study of about 100 chronic haemodialysis patients, cerebral arterial mean flow velocity (MFV) was demonstrated to decline significantly during dialysis and this decline correlated with intradialytic decline in cognitive function (128). Decline in MFV also correlated significantly with progression of white matter burden and cerebrovascular disease at 12 months follow-up. Haemodialysis is thus capable of inducing transient "cerebral stunning," analogous to myocardial stunning, and may be a major mechanism of cerebral injury and accelerated cognitive decline in dialysis-dependent patients.

Beta-Amyloid Pathology

The role of beta-amyloid (Aβ) pathology in the relationship between CKD and cognitive decline in poorly understood. Serum Aβ levels have been shown to be significantly higher in CKD patients, possibly related to reduced renal clearance of Aβ protein from peripheral blood (129). Cystatin-C, a low-molecular weight protein that is used to estimate GFR, has also been demonstrated to colocalize with beta-amyloid in the brain (130).

However, there is some evidence from animal and small human studies that peripheral clearance of Aβ by dialysis could help to reduce the amyloid plaque burden in the brain (131). In one study, plasma Aβ levels before and immediately after peritoneal dialysis in 30 patients with newly diagnosed CKD and in APP/PS1 mice were measured. In both cases, plasma Aβ40 and Aβ42 levels were significantly reduced after dialysis. In the animal model, PD resulted in a decrease in Aβ levels in the brain interstitial fluid with reduced plaque deposition. Dialysis solution appeared to account for only 10% of Aβ removal suggesting that the remaining clearance was mediated by efflux transport of Aβ across the BBB and enhancement of endogenous clearance pathways. The dialysis-treated mice showed reduced levels of hyperphosphorylated tau in the brain, suggesting a slowing of neurodegeneration along with decreased inflammation. Attenuated cognitive decline was demonstrated by improved performance on the Y-maze and open-field tests.

Brain Aβ deposition also appears to be lower in maintenance haemodialysis patients (132). Clearance rates of both peptides during one haemodialysis session were 22% and 35% for Aβ42 and Aβ40, respectively (133). By inducing peripheral Aβ sink and stimulating Aβ efflux from the brain, it has been suggested that haemodialysis could be considered as an anti-amyloid treatment strategy.

CONCLUSIONS

CKD is strongly associated with MCI and dementia, and the pathogenesis is likely multifactorial, incorporating elements of both vascular disease as well as neurodegenerative processes. Patients with CKD appear to have a clustering of susceptibility and risk factors associated with dementia including lower cognitive reserve (advancing age, lower educational and occupational attainment), cardiometabolic risk factors (hypertension, diabetes, obesity, stroke), neuropsychiatric comorbidities (depression, sleep disorders) and renal-specific factors (uraemia, inflammation, intradialytic "cerebral

stunning"). From an epidemiological perspective, it remains challenging to disentangle independently causal associations from intermediate mediators, confounders, and epiphenomena. Further research is needed to fully elucidate the role of genetic factors and Aβ pathology in this relationship. In an aging population, targeting novel modifiable risk factors such as CKD and associated multimorbidity may help reduce the global burden of dementia.

AUTHOR CONTRIBUTIONS

DK drafted the manuscript for intellectual content. PR contributed to the format and revised the manuscript for intellectual content. Both authors contributed to the article and approved the submitted version.

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REVIEW
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Impact of Chronic Kidney Disease on Brain Structure and Function

Emily J. Steinbach[1] *and Lyndsay A. Harshman*[2]*

[1] Department of Radiation Oncology, Carver College of Medicine, University of Iowa, Iowa City, IA, United States, [2] Division of Nephrology, Dialysis, and Transplantation, University of Iowa Stead Family Children's Hospital, Iowa City, IA, United States

Chronic kidney disease (CKD) affects more than 37 million American adults. Adult-onset CKD is typically attributed to acquired comorbidities such as aging, type II diabetes, and cardiovascular disease. Conversely, congenital abnormalities of the kidney and urinary tract are the most common cause of CKD in children. Both adult and pediatric patients with CKD are at risk for neurocognitive dysfunction, particularly in the domain of executive function. The exact mechanism for neurocognitive dysfunction in CKD is not known; however, it is conceivable that the multisystemic effects of CKD—including hypertension, acidosis, anemia, proteinuria, and uremic milieu—exert a detrimental effect on the brain. Quantitative neuroimaging modalities, such as magnetic resonance imaging (MRI), provide a non-invasive way to understand the neurobiological underpinnings of cognitive dysfunction in CKD. Adult patients with CKD show differences in brain structure; however, much less is known about the impact of CKD on neurodevelopment in pediatric patients. Herein, this review will summarize current evidence of the impact of CKD on brain structure and function and will identify the critical areas for future research that are needed to better understand the modifiable risk factors for abnormal brain structure and function across both pediatric and adult CKD populations.

Keywords: chronic kidney disease, magnetic resonance imaging (MRI), pediatric chronic kidney disease, neurocognition and behavior, brain structural abnormalities, neuroimaging, disease and development

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***Correspondence:**
Lyndsay A. Harshman
lyndsay-harshman@uiowa.edu

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INTRODUCTION

Neurocognitive deficits have been well-described in both the adult and pediatric chronic kidney disease (CKD) and end-stage kidney disease (ESKD) populations (1, 2). These deficits are associated with longer duration of kidney disease (1, 3, 4), metabolic acidosis (5, 6), proteinuria/microalbuminuria (1, 7, 8), anemia (1, 9, 10), and hypertension (11, 12). Even subtle neurocognitive deficits have broad impacts on quality of life, as they contribute to poorer high school graduation rates and long-term underemployment in the adult CKD population (13). The cognitive complications of CKD may be linked to an aberrant "kidney-brain axis" whereby decreases in kidney function, CKD-associated sequelae (including cardiovascular disease), and concomitant inflammatory milieu all negatively impact the brain, leading to increased risk of cognitive impairment in parallel with CKD progression (14–16).

Unfortunately, our understanding of the neurobiology of cognition in CKD is limited because of a lack of concurrent neuroimaging and neurocognitive assessment. Neurodevelopment is a dynamic process occurring throughout the human lifespan, with the most rapid neurodevelopmental changes occurring in childhood and adolescence (17)—specifically, reductions in cortical gray matter (e.g., dendritic pruning) and concomitant white matter (myelin) deposition (18). Our understanding of normal developmental processes in the context of chronic

disease is limited. Use of magnetic resonance imaging (MRI) provides an opportunity to examine the brain structure, as it relates to CKD, in a noninvasive manner.

To reduce the burden of neurocognitive deficits within the CKD population, there is an urgent need for new approaches to patient care applied across CKD lifespan. Such approaches require understanding the effects of CKD progression and severity on both the adult and pediatric brain. In this review we will 1) address existing literature specific to the impact of CKD on brain structure and function and 2) discuss potential CKD-associated risk factors for abnormal brain structure and function in both pediatric and adult populations.

HOW DOES CKD IMPACT BRAIN STRUCTURE AND FUNCTION?

Neuroimaging in Adult CKD

More than 37 million adults in the United States are living with CKD and millions more are living with either undiagnosed CKD or with an increased lifetime risk of developing CKD. Diabetes and hypertension are the leading causes of CKD in adults, contributing to almost 66% of CKD cases in the United States (19). Cardiovascular disease remains the major cause of death for individuals with CKD.

Structural brain findings of adult patients with CKD–not receiving renal replacement therapy–have demonstrated the presence of cerebral atrophy, as well as decreased cerebral density in both white and gray matter. Poor kidney function has been associated with glomerular small vessel disease, and in the 2008 study by Ikram et al. (20) hemodynamic similarities were investigated between the kidneys and vascular beds of the brain by MRI. Here, impaired kidney function was associated with smaller brain volume, smaller deep white matter volume, and more white matter lesions (20). Other randomized trials, including the Systolic blood PRessure INterventional Trial (SPRINT), examined the effects of hypertension treatment on the structure of the brain in patients with and without CKD, with cognitive endpoints noted (21). The SPRINT study found that CKD patients who were on standard blood pressure treatments had increased risks of mortality and major cardiovascular events, demonstrated mild cognitive impairment, and showed small vessel ischemic disease (white matter lesions) by MRI.

White matter hyperintensities are noted more frequently within the adult CKD/ESKD population. These hyperintensities are often associated with increased cerebrovascular risk and may predict risk of stroke and dementia (22). Diffusion tensor imaging (DTI) is an MRI technique used to provide detailed images of the brain. MRI-DTI measures the rate at which water moves through the brain's white matter (23). While *macrostructural* MRI markers, such as white matter hyperintensities, correlate with reduced kidney function, loss of white matter *microstructural* integrity may be a more sensitive measure of white matter disease (24). White matter degeneration and white matter abnormalities may be attributed to several causes. First, the kidneys and brain share several perfusion pathways in which cardiovascular and hemodynamic deviances may damage both organs simultaneously. Other factors, including the hypertension seen in many CKD patients, may also play a role in the association between kidney function and white matter integrity (25). Finally, impaired kidney function can lead to increased circulating inflammatory factors. Proinflammatory factors decrease serum nitric oxide in the brain vasculature, and this could contribute to cerebral hypoperfusion, which, in turn, could lead to white matter damage as well (25).

Cerebral hypoperfusion has been implicated in neurodevelopmental disorders. Hemodynamic disturbances during CKD may play a role in the regulation of cerebral blood flow (26), potentially linking CDK to cognitive problems. An analysis based on the Rotterdam Study (27) found that lower estimated glomerular filtration rate (eGFR) is independently associated with lower cerebral blood flow (27). More recently, Lepping et al. (28) used arterial spin labeling to assess cerebral blood flow in a cohort of EKSD patients and age-matched controls. The authors' goal was identify kidney-associated brain changes following kidney transplantation. Here, after kidney transplant, cerebral blood decreased in ESKD patients to values comparable to controls. White matter integrity, as measured by fractional anisotropy and by mean diffusivity with MRI-DTI, also increased and decreased, respectively, post-kidney transplant (28). These measurements of white matter integrity taken after kidney transplant were comparable to controls. Taken together, these data suggest that proper kidney function is essential for regulation of blood flow to the brain and hemodynamic homeostasis.

Neuroimaging in Pediatric CKD

In contrast to adult CKD, congenital anomalies of the kidney and urinary tract are the leading causes of CKD among children ages birth to 4 years, whereas systemic diseases, infection, and glomerular disease (e.g., focal segmental glomerular sclerosis) become the leading causes of kidney failure in the older pediatric population (29). Up to half of all children with congenital CKD will experience a decline in kidney function so severe as to require dialysis and eventually, a kidney transplant (30). Thus, children with congenital anomalies of the kidney and urinary tract are faced with a lifetime of CKD and of potential detrimental impacts on the developing brain.

Neuroimaging studies in the pediatric population have focused mainly on children with moderate to severe CKD (including dialysis and transplant populations). The effect of kidney disease in these children introduces many confounding factors that affect brain function, such as uremia. Another limitation of imaging studies in older children is that these studies cannot provide direct information about the key stages of brain development that occur from birth to 4 years of age. These issues signal a critical gap in our understanding of the kidney-brain axis during periods of peak neurodevelopment.

Cystic kidney diseases are some of the leading causes of early-onset inherited kidney disorders. These diseases are often characterized by enlarged kidneys with multiple cysts and progressive kidney impairment. Autosomal dominant and autosomal recessive polycystic kidney disease, as well as Meckel's syndrome, are a few examples of renal ciliopathies seen in the

pediatric population. Cysts develop due to uncontrolled epithelial cell proliferation, growth, and altered cell polarity—events that occur downstream of abnormal cilia-dependent signaling. Due to the early onset of renal ciliopathy-induced CKD and concomitant development of severe hypertension, it is thought that ciliopathies are a risk factor for neurocognitive dysfunction secondary to CKD (31). The spectrum of neurocognitive deficits ranges from relatively benign (akin to that seen in polycystic kidney diseases) to more progressive deficits in neurocognition (such as that seen in Joubert syndrome). One cross-sectional, control-matched analysis, which involved the Chronic Kidney Disease in Children (CKiD) cohort, compared a group of autosomal recessive polycystic kidney disease patients with mild-to-moderate CKD patients with respect to intellectual functioning, academic achievement, attention regulation, executive functioning, and behavior (31). No differences were observed between these two disease cohorts; however, further investigation into the potential effects of renal ciliopathies on neurocognition in the pediatric population is needed.

The majority of published pediatric CKD studies evaluating volumetric brain structure have used computerized tomography (CT) imaging data obtained in a clinical setting, rather than quantitative MRI data obtained as a part of a specific research focus (19). Brain atrophy is well-described in the early pediatric nephrology literature (prior to 1990): up to 60% of patients had atrophy that was not clearly related to etiology of disease or CKD-associated sequelae such as hypertension (32). Qualitative CT imaging also provides evidence for global cerebral atrophy, silent white matter infarcts, and ventriculomegaly in advanced pediatric CKD (19). In other studies, lower cerebral density (33, 34) and ventriculomegaly secondary to brain atrophy (35) were found to be associated with the need for pediatric hemodialysis (especially duration), but not with peritoneal dialysis (36).

To date, there are only four published studies that have utilized quantitative, research-based MRI sequences to evaluate the brain in CKD (26, 37–40). Hartung and colleagues (41) used MRI to examine brain structure in 85 patients aged 8–25 with CKD, encompassing a mix of pre- and post-transplant patients (37). The authors reported subtle, cortical gray matter abnormalities; however, their findings were significant only in unadjusted models and did not persist in models adjusted for age and gender. In this study, observed volumetric brain differences were more prominent among the kidney transplant recipients compared to those with pre-transplant CKD. More recently, our group has observed significant reductions in overall cerebellar gray matter volume and unexpectedly, an increase in cortical (cerebral) gray matter volume among children ages 6–16 years old with early-stage CKD, relative to controls (39). The degree of cerebellar volume reduction was associated with estimated glomerular filtration rate (**Figure 1**). Volumetric reduction in the cerebellar gray matter was also associated with poorer performance in tests of executive function. The volumetric increase in the cerebral gray matter was associated with poorer mathematics performance (**Figure 2**).

CKD is a known risk factor for cerebrovascular disease, with white matter being particularly susceptible to the effects of altered vascular tone. Matsuda et al. (38) evaluated the impact of CKD on brain white matter within a cohort of 49 children, including 29 children with CKD of varying stages, ranging from pre- to post-transplantation. Diffusion tensor imaging was used to compare white matter microstructure in CKD patients compared to controls.

Patients with CKD were found to have abnormal white matter microstructure (specifically, within the anterior limb of the internal capsule), as reflected by decreased white matter fractional anisotropy and increased mean diffusivity and radial diffusivity. Within the sample, 21% of CKD participants had evidence of focal and multifocal white matter injuries compared to healthy controls. No neurocognitive data were obtained in this study; thus, the clinical significance of these white matter findings remains unclear.

Recently, our group identified global abnormalities in white matter microstructural integrity in CKD patients compared to controls. The global decrease in white matter fractional anisotropy was driven by regional reductions within the body of the corpus callosum, cerebral, cingulum (hippocampus), and posterior limb of the internal capsule (**Figure 3**). Despite these significant differences in white matter integrity, we found no significant association between the neurocognitive abilities of CKD patients and white matter fractional anisotropy. Likewise, there were no CKD-associated medical variables that emerged as predictors for decreased white matter integrity.

Cerebral blood flow, which is a reliable measure of cerebrovascular integrity, can be quantified using arterial spin labeling MRI. Based on data from the Neurocognitive Assessment and Magnetic Resonance Imaging Analysis of Children and Young Adults with Chronic Kidney Disease (NiCK) study cohort (41), Liu et al. (26) found, unexpectedly, that global cerebral blood flow is higher in children with CKD compared to healthy controls (41). These findings are in line with adult data showing increased global cerebral blood flow, again as determined using arterial spin labeling sequences (42). Since increases in cerebral blood flow are associated with reduced hematocrit level in children with CKD (26), it has been hypothesized that the higher cerebral blood flow reflects a physiological compensation for the chronic anemia typically associated with advanced CKD.

DISEASE OR DEVELOPMENT: DELINEATING RISK FACTORS FOR BRAIN ABNORMALITIES IN THE SETTING OF CKD

Cognitive deficit in CKD has been linked to a variety of mechanisms associated with decreased kidney function, including concomitant uremia, proteinuria, anemia, metabolic acidosis, and cardiovascular disease (43). These CKD-associated medical sequelae become more prominent in CKD stage 3 and beyond (eGFR $<$ 60 ml/min/1.73 m^2). Elevated blood urea nitrogen (uremia) is a CKD-associated comorbidity that often appears together with cognitive problems. Neurons, such as the noradrenergic and serotonergic neurons responsible for sleep/wake cycles and motor control, as well as the acetylcholinergic neurons responsible for memory, may be

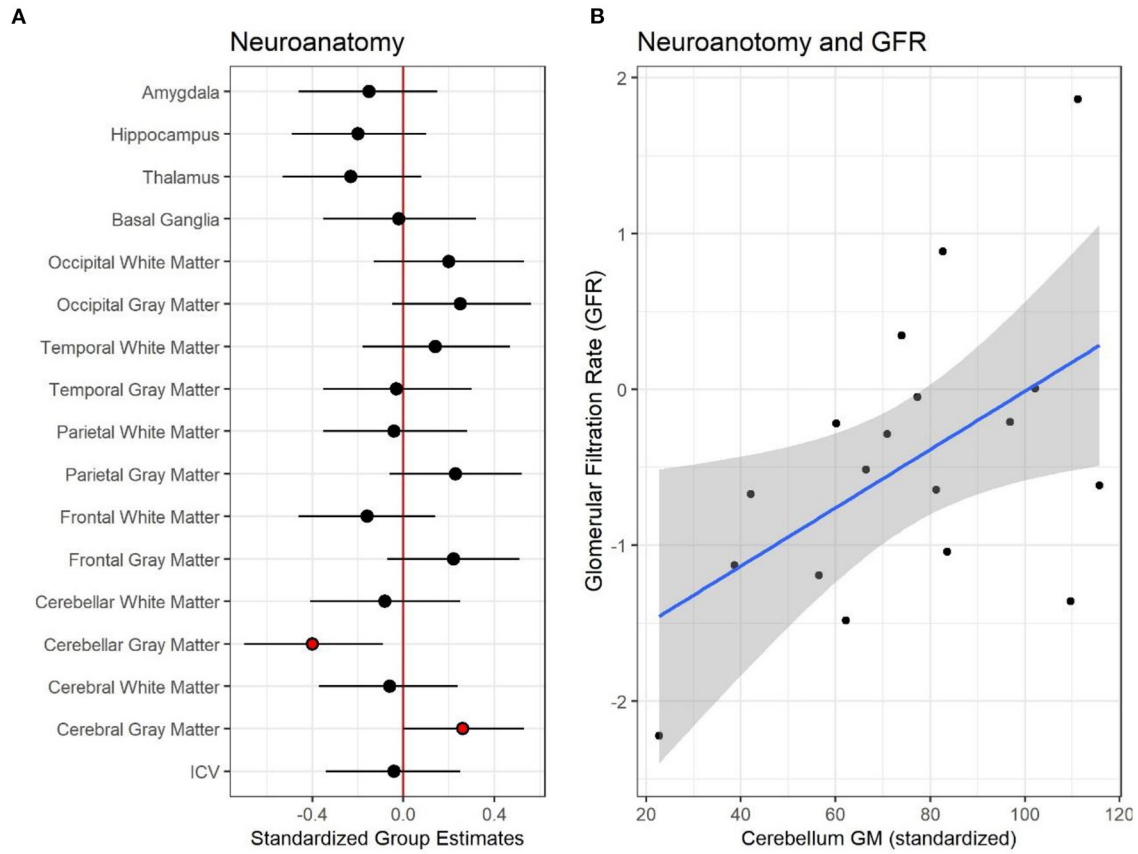

FIGURE 1 | Neuroanatomical differences between controls and patients with pediatric chronic kidney disease CKD. **(A)** Shows the standardized group estimates (x-axis) and 95% confidence limits of the estimates for each of the regions of interest (ROI) included in the analysis (y-axis). Estimates are adjusted for age, socioeconomic status (SES) and maternal education. The red (vertical) line marks 0, or no significant effect of group on ROI. Red circles mark significant group estimates. **(B)** Shows the relationship between estimated glomerular filtration rate, eGFR, (x-axis) and standardized cerebellum gray matter volume (y-axis) in the CKD group. Reproduced with permission from Solomon et al. (39).

particularly sensitive to high levels of uremic milieu (44). Alterations in the monoaminergic neurons may contribute to the transient development of cognitive impairment that is seen in patients with advanced CKD requiring dialysis (44). Although uremia is commonly invoked as a primary etiology for cognitive deficit in CKD, a clear neuroimaging correlate to link changes in the brain with symptomatic uremia is lacking. One recent case series evaluated MRI scans from patients with clinically documented uremic encephalopathy and showed bilateral basal ganglia lesions in the majority of images (45). However, since no neurocognitive phenotype was described in this study, no inference can be drawn as to whether the lesions noted were associated with cognitive deficit.

Metabolic acidosis may play a direct role in cognitive impairment in adults with CKD. Animal data suggest that metabolic acidosis perpetuates neuronal dysfunction by upregulation of excitatory synapses on gaba-aminobutyric acid-ergic neurons (44, 46). The SPRINT-MIND [Systolic Blood Pressure Intervention Trial Memory and Cognition IN Decreased Hypertension (21)] cohort assesses adults with hypertension and includes adults with CKD. Data from this study showed that decreases in serum bicarbonate were independently associated with lower performance on tests of executive function (5). Harshman et al. (6) evaluated the impact of metabolic acidosis in relationship to blood pressure variability in pediatric CKD patients using the CKiD cohort. The researchers found that the effect of increased blood pressure variability on executive function was attenuated in the setting of higher serum bicarbonate levels.

Hypertension (HTN), a CKD-associated comorbidity, can affect the severity and course of cerebrovascular disease. Consequently, HTN is a potentially modifiable risk factor for cognitive defects in both pediatric and adult CKD populations. As noted previously, the SPRINT study is the largest intervention study to date looking at the effect of intensive blood pressure control on cardiovascular outcomes among persons at high risk for cardiovascular disease. The SPRINT trial demonstrated a role for intensive systolic blood pressure control (goal of $<$120 mm Hg) in the reduction of probable dementia within an adult CKD subgroup (21). Importantly, data from the SPRINT-MIND

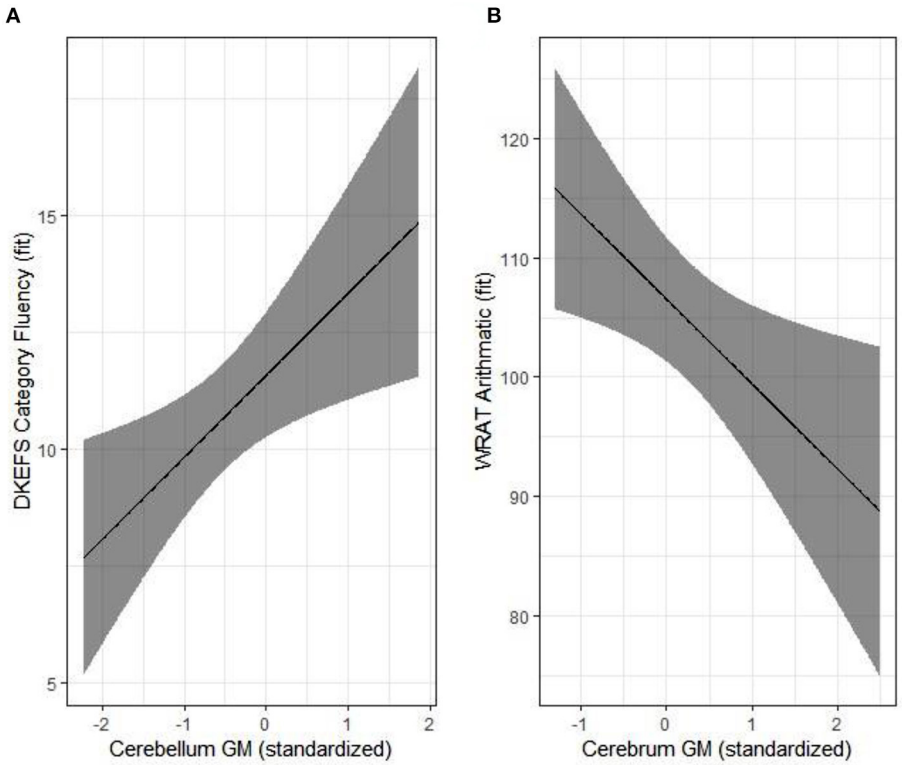

FIGURE 2 | Structure-function relationships in the pediatric chronic kidney disease (CKD) group. Significant associations are illustrated for cerebellum gray matter and category fluency **(A)** and cerebrum gray matter and arithmetic **(B)**. Results were adjusted for age, parental SES and maternal education. Reproduced with permission from Solomon et al. (39).

sub-analysis found no detrimental effect of intensive lowering of systolic blood pressure on brain perfusion or volumetric structure (47).

The neurocognitive deficits in the adult CKD population exacerbate comorbidities and contribute to a lower quality of life. The most frequently impaired cognitive domains in the adult CKD population include executive function, orientation, and attention (48). Multiple studies have reported increases in cognitive impairment with increasing age; however, even the younger kidney transplant candidate in the adult population has a relatively high burden of cognitive impairments compared to the average adult. The conclusions from Chu et al. (48) suggest that transplant centers consider screening kidney disease patients for global cognitive impairment throughout their clinical care regardless of age (48).

The association between hypertension, CKD, and cognition has received a significant amount of focus within the prospective CKiD cohort study. Lande et al. (12) evaluated data from children with mild to moderate CKD who have elevated blood pressure [i.e., systolic or diastolic blood pressure > 90th percentile for age (49)]. Children with elevated blood pressure were more likely to have lower nonverbal IQ than normotensive children. Within the analysis, it was also noted that the blood pressure index (i.e., the subject's blood pressure divided by the 95th percentile blood pressure for that subject's gender, age, and height) correlated inversely with nonverbal IQ, and this relationship was maintained even after controlling for demographic and disease related variables.

The neurocognitive deficits in the pediatric CKD population have also been assessed through batteries such as the Penn Computerized Neurocognitive Battery (50). This test revealed that children and young adults with CKD have lower accuracy in tests of complex cognition compared to their age-matched peers, as well as deficits in verbal reasoning, nonverbal reasoning, and spatial processing. Patients with CKD also had lower accuracy for attention but were found to have faster response times, possibly indicating greater impulsivity.

While unlikely to be the underlying cause of adult cognitive impairment, genetic factors may influence the pathogenesis of cognitive dysfunction in pediatric CKD patients. Both single-gene variants and copy number variants have been implicated as potential factors influencing cognitive deficit in pediatric CKD. Genomic differences associated with pediatric CKD were analyzed as part of the CKiD study (51); the aim was to determine whether genetic factors (in addition to, or perhaps rather than, renal impairment) were responsible for the subtle neurocognitive differences seen in pediatric CKD. Children with CKD-associated genomic disorders were found to score significantly poorer on all measures of intelligence and executive function compared to noncarriers (52).

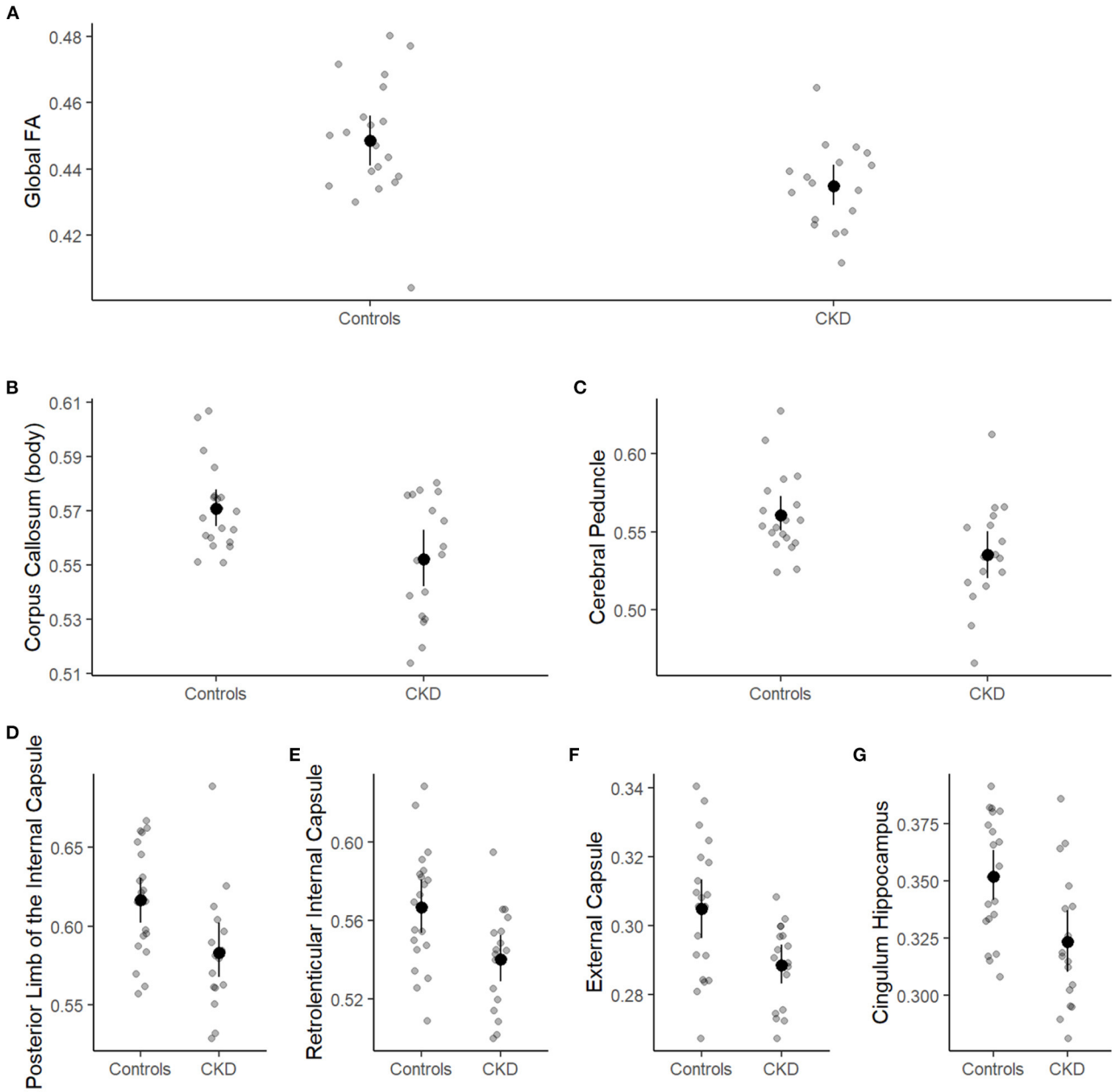

FIGURE 3 | Group differences in global and regional white matter fractional anisotropy. Patient group (case or control) is shown on the x-axis and white matter fractional anisotropy on the y-axis. Individual observations are represented by small, gray circles. Means and 95% confidence limits of the means are shown for each group. **(A)** Shows the global fractional anisotropy, and **(B–G)** show white matter fractional anisotropy for the corpus callosum, cerebral peduncle, posterior limb of the internal capsule, retrolenticular internal capsule, external capsule, and cingulum hippocampus, respectively.

Variation in the klotho gene has been associated with both an accelerated aging phenotype as well as development and progression of CKD (53, 54). Klotho is expressed in the brain, with high levels of mRNA expression in the choroid plexus, hippocampus, and cerebellar Purkinje cells (55, 56). The klotho gene is also highly expressed in the kidney, where Klotho acts as a coreceptor for fibroblast growth factor 23 (FGF23) in regulating calcium and phosphorus homeostasis (57). Homozygous klotho knockout mice and CKD subjects have similar phenotypes, suggesting that klotho dysfunction may contribute to CKD progression (54, 58). Additionally, Klotho-deficient mice demonstrate an accelerated aging phenotype characterized by neurodegeneration and cognitive deficits (59, 60). In both CKD patients and in mice lacking Klotho function, plasma FGF23 levels increase (61). Limited preclinical suggests that elevation of FGF23 is associated with abnormalities of

hippocampal neural networks. While previous studies evaluating the effect of FGF23 on cognition have been equivocal in adults, data from the CKiD cohort suggests that a higher plasma FGF23 level is associated with higher cognitive impairment and lower performance in tests of executive function (55, 62).

Recent evidence suggests that there is crosstalk between the kidney and brain, and that this "kidney-brain axis" is sensitive to cellular oxidative stress and chronic inflammatory processes (14). The crosstalk, mediated by reactive oxygen species and inflammatory markers, may contribute to the high prevalence of cognitive impairment observed during the progression of CKD. Emerging data suggests that the metabolic interactions of the "kidney-brain axis" are likely mediated—at least in part–by the activities of hormetic processes and a phenomenon dependent on the severity of disease (63, 64). Oxidant-induced inflammatory pathways could be promising therapeutic targets for the protection of neurocognitive function in developing children who have CKD.

NEUROIMAGING IN CKD: WHERE DO WE GO FROM HERE?

In contrast to adult CKD populations, there is a paucity of systematic, quantitative neuroimaging studies in young children with CKD. The reasons for this are multiple. Certainly, there are clear challenges to obtaining quality images from non-sedated, young children. Furthermore, published pediatric CKD neuroimaging studies have relied on patient samples with heterogenous disease stage and etiology, making it difficult to pinpoint mechanisms of neurocognitive deficits across the lifespan. Additionally, there has been a stark lack of attention to the impact of CKD on early brain development: to date, only one neuroimaging study has been published that evaluated the brain in very young CKD patients (children younger than 8 years of age) (39).

The value of incorporating neuroscience-oriented analyses into pediatric CKD research is that this combined approach provides the clinical-translational tools needed to identify potential neurobiological mechanisms that bring about neurocognitive deficits in CKD children. This means moving beyond the use of clinical scans to describe brain structure in pediatric CKD; by their nature, these scans can highlight only a limited range of the potential neurobiological mechanisms. Multisite collaborations are necessary to address limitations related to small sample sizes and heterogeneity of neuroimaging research in pediatric CKD. And for these multisite neuroimaging initiatives to be effective, collaboration between nephrologists and neuroscientists is essential as well.

Neuroimaging research in the field of CKD requires tandem assessment of cognition and kidney disease sequelae, in order to identify patients who are at risk for neurocognitive deficits and also to learn how early brain changes relate to CKD progression. In comparison to the pediatric literature, the adult CKD-brain literature is robust and incorporates a comprehensive approach to the study of the brain. This should serve as an example for the field of pediatric nephrology to embrace when designing future CKD-brain studies. Neurocognitive difficulties emerge in early childhood, during early CKD, and signal a need for a greater understanding of how the developing brain is affected by this life-long, chronic disease process. Thus, longitudinal neurological assessment into adulthood is essential, and must continue through the period when CKD progresses to the point of requiring dialysis and/or kidney transplant. Future neuroimaging research is necessary to elucidate the neurobiological underpinnings of cognitive deficits in CKD.

AUTHOR CONTRIBUTIONS

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Cognitive Impairment Early After Initiating Maintenance Hemodialysis: A Cross Sectional Study

Melissa Schorr[1,2], *Mariah Zalitach*[3], *Cindy House*[3], *Janice Gomes*[3,4], *Conor J. Wild*[5], *Fabio R. Salerno*[3,6] *and Christopher McIntyre*[1,3,6*]

[1] Division of Nephrology, Department of Medicine, London Health Sciences Centre, London, ON, Canada, [2] Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada, [3] The Lilibeth Caberto Kidney Clinical Research Unit, London Health Sciences Centre, London, ON, Canada, [4] Department of Pathology and Laboratory Medicine, University of Western Ontario, London, ON, Canada, [5] Brain and Mind Institute, University of Western Ontario, London, ON, Canada, [6] Department of Medical Biophysics, Western University, London, ON, Canada

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Anand Viswanathan, Massachusetts General Hospital and Harvard Medical School, United States

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Anne Murray, Hennepin Healthcare, United States

***Correspondence:**
Christopher McIntyre
cmcint48@uwo.ca

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Background: Abnormalities in cognitive function are almost universal in patients receiving hemodialysis (HD) and are associated with worse quality of life, impaired decision making, increased healthcare utilization and mortality. While cognitive impairment in the HD population is increasingly recognized, it is unclear how quickly it develops after starting HD.

Methods: This was a cross-sectional study of a cohort of low dialysis vintage HD patients (<12 months). We used the validated Cambridge Brain Science (CBS) battery of web-based tests to evaluate cognition compared to age- and sex matched controls across three cognitive domains: verbal processing, reasoning and short-term memory.

Results: Forty-nine HD patients were included in this study; 43 completed the full battery of tests. The average scores for HD patients were consistently below the age and sex-matched controls. Fifty-five percent of HD patients had cognitive impairment in verbal skills, 43% in reasoning and 18% in short-term memory.

Conclusions: There is a high prevalence of CI evident early after starting HD, with the largest deficits seen in reasoning and verbal processing. These deficits may be attributable to the HD treatment itself. Further studies are needed to characterize the natural history of CI in this patient population and to test interventions aimed at preventing or slowing its progression.

Keywords: hemodialysis, cognitive impairment, Cambridge Brain Sciences, memory, verbal, reasoning, cognitive domains

INTRODUCTION

Neurological disorders including ischaemic brain injury, cognitive impairment (CI) and dementia are becoming increasingly recognized in hemodialysis (HD) patients (1–3). Abnormalities in cognitive function are almost universal in this patient population (4, 5). Mild CI and dementia—in particular, vascular dementia—are significantly more prevalent in HD patients than the general population (6–9).

Etiology of CI

There are a number of factors that may contribute to CI and dementia in CKD and ESRD including accumulation of uremic toxins, cerebral vascular dysfunction, chronic inflammation, anemia and white matter injury in addition to established risk factors such as advanced age and depression (10–13). Compared to patients with chronic kidney disease (CKD) or undergoing peritoneal dialysis (PD), CI appears to be more common in HD patients, suggesting unique contributing factors in these patients (14–16).

Relevance of CI

Impaired cognitive function is associated with depression (17), non-adherence (18) and a worse quality of life (19). It may result in poor self-care, impaired ability to make informed decisions and increased healthcare utilization (19–21). CI has also been associated with increased mortality in HD patients (1, 22, 23).

Testing for CI

In an American study by Drew et al., the performance of established screening tests for CI was evaluated in the HD population. The best performing test was the Montreal Cognitive Assessment (MoCA), a 30-question test administered by trained healthcare professionals (https://www.mocatest.org/) (24). This test predicted CI with high sensitivity and moderate specificity (a score of $\leq$21 had a sensitivity of 86% and specificity of 55% for severe impairment), however, it requires trained healthcare personnel to administer it (24).

An alternate tool is the Cambridge Brain Sciences (CBS) neurocognitive test which is a web-based battery of 12 tests that comprehensively evaluates cognition. The details of each test have been well-described elsewhere (25, 26). This tool can be self-administered with automated scoring and obviates the need for trained personnel. There is a well-established database of healthy controls available for matching, and the tool has been widely validated and used in clinical research (26–28). It has been used internationally among a culturally diverse populations including in individuals with structural brain abnormalities as well as neurodegenerative diseases (25, 26, 28–30).

To the best of our knowledge, however, the CBS has not been previously used in the HD patient population.

Objectives

The objectives of this cross-sectional study are (1) to use the CBS tests to measure CI within the first year of HD and (2) to describe the patterns of CI early after starting HD. The CBS battery to patients who have been on maintenance hemodialysis for $<$12 months and compare their scores to a database of age- and gender-matched controls.

MATERIALS AND METHODS

We conducted a cross sectional study of new start hemodialysis patients at eight hemodialysis centers in Southern Ontario associated with London Health Sciences Center. The study was approved by our local research ethics board (Western REB, study identification number 111721).

We included adult patients ($\geq$18 years of age) who had been on maintenance hemodialysis for a minimum of 30 days but $<$12 months. Patients were excluded if they had a pre-existing diagnosis of dementia, new or pre-existing diagnosis of neurological disease known to affect cognitive function (e.g., head trauma, intracranial hemorrhage, traumatic brain injury, or intracranial malignancy), impaired vision or significant upper extremity weakness precluding use of a computer, inability to communicate in English or were unable to, or declined to provide informed consent. They were also excluded if they had been on hemodialysis for longer than 12 months.

Patients were screened for eligibility using electronic medical records as well as paper charts and dialysis records. Eligible patients were approached during hemodialysis and written informed consent was obtained prior to commencing the study. Demographic and clinical data were collected from electronic medical records and dialysis run sheets from the date of assessment (if the patient completed the tests during dialysis) or the dialysis run prior to the date of assessment (when the patient completed the assessment on the day following dialysis).

Patients completed cognitive assessment using a study tablet during hemodialysis or using a personal computer or tablet if the tests were completed at home after dialysis or on the day following dialysis. Investigators assisted patients by creating a personalized login and password on the CBS study webpage. As part of the CBS battery, there are standardized sets of written and pictorial instructions and a short instructional video preceding each test. Patients were provided with as much time as they needed to review the instructions prior to beginning each test. Each test was completed in sequence until the entire battery of 12 tests was finished or they were unable to continue due to testing-related fatigue.

Statistical Analysis

Patients were defined as having cognitive impairment on a given test if their raw score was 1.5 standard deviations (SD) below age- and sex-matched controls derived from the CBS normative database (25). We then compared patients' cognitive performance with available data from healthy age and sex-matched control data by converting raw scores into *z*-scores. To determine patients' scores on each of the three cognitive domains (reasoning skills, short-term memory, and verbal processing), the z-score for each individual test was multiplied by a value that reflected the contribution of that test to each cognitive domain (i.e., factor loading) as established by Hampshire et al. (25). Patients' overall score on each cognitive domain was therefore the sum of the weighted (factor loaded) scores for that domain across all 12 tests. The resulting scores are designed such that the healthy population mean on each cognitive domain is 0 and the SD is 1.0. For patients who did not complete all 12 tests, we replaced missing scores with their expected values given the observed test scores and the known correlation structure among the tests in the population. The correlation structure between the 12 tests in the CBS battery was derived from a sample of 44,600 individuals (25). This conditional-mean replacement method has been shown to be most accurate when calculating principal component analysis scores in the presence of missing data (31). We then calculated a

z-score for each patient on each of the three cognitive domains based on the abbreviated CBS and compared this score to the z-scores calculated based on the complete CBS battery.

Study patients were defined as having CI if they had a *z*-score <-1.5 in at least one of the three aforementioned cognitive domains. They were then stratified into two groups according to absence vs. presence of CI. Demographic and clinical variables were reported using descriptive statistics, expressed as frequency and percentage for categorical variables and mean ± SD for continuous variables. Comparisons between categorical and continuous variables were performed using Fisher's exact test and Mann-Whitney's *U*-test, respectively. An alpha < 0.05 was used as a cut-off to determine statistical significance.

RESULTS

Eighty-five of one-hundred thirty eligible patients who were within their first year of hemodialysis treatment in Southwestern Ontario were approached to participate in this study. We ultimately had 43 participants complete the full battery of tests and 6 complete part of it. Twenty-two declined participation and 10 withdrew from the study (**Figure 1**).

Baseline characteristics for the included patients and details of their hemodialysis are summarized in **Table 1**. The majority (35/49, 71%) of patients enrolled were from satellite dialysis units—units outside of major tertiary centers. The average age was sixty-three, 53% were female and all participants were caucasian. Approximately half had diabetes and the majority (95%) had hypertension. The most common etiology of renal disease was diabetes. The average dialysis vintage (duration of hemodialysis therapy prior to undergoing cognitive assessment) was 6 months (minimum 2 months; maximum 11 months). The average ultrafiltration rate (UFR) was 6.5 ml/kg/h although there was a wide range from 0.35 to 20 ml/kg/h.

Ten participants (20%) had issues completing the tests including fatigue, frustration and technological issues.

Of the 43 patients who completed the full battery, nine (18%) did not meet criteria for cognitive impairment on any test; the average participant had scores qualifying for cognitive impairment in 3.7 tests (SD). The average scores for patients on dialysis were consistently below those of their age and sex-matched controls although only three tests had average z-scores consistent with cognitive impairment (**Table 2**). The majority (82%) of patients had cognitive impairment on at least one test and 35% had impairment on at least two (**Table 3**). **Figure 2** shows individual participant as well as cohort average scores for each of the 12 tests.

Across all three cognitive domains, 23 (47%) patients qualified as having CI in one cognitive domain, 15 (31%) in two, 2 (4%) as having CI in all three (**Table 3**). **Figure 3** shows individual test performance in each domain: as a whole, HD patients performed worse than healthy age and sex-matched controls. 9/49 patients (18%) qualified as having significant Short-Term Memory impairment (mean *z*-score -0.41 ± 1.24) compared to the normal population. In the domain of Reasoning, 21/49 (43%) of HD patients had *z*-scores showing significant impairment, (*z*-score -1.37 ± 1.16). HD patients had the poorest performance in Verbal domain with 27/49 (55%) meeting criteria for cognitive impairment (z-score -1.47 ± 0.97).

We investigated whether any differences in cognitive scores were evidenced after stratifying our study sample by major comorbidities (diabetes, hypertension, cerebrovascular disease, heart failure, ischaemic heart disease, atrial fibrillation, vascular disease, mental health conditions, and obstructive sleep apnea), but no significant differences were found (data not shown). Minor and non-statistically significant differences were evident after stratifying for hypertension, however, the groups were significantly unbalanced with 46/49 patients having hypertension. Similarly, no significant correlations between dialysis parameters (HD vintage, UF rate, lowest systolic blood pressure and time on dialysis) were detected in this population all characterized by having been established on dialysis for only a relatively short period (data not shown).

DISCUSSION

The results of our study show a high prevalence of CI within months of starting HD. Nearly half of our participants exhibited scores qualifying for CI in one domain, and a third with scores consistent with CI in two domains. CBS appears to be a meaningful and easily administered form of comprehensive cognition testing.

The majority of patients in our study were from satellite dialysis units; these patients are generally healthier and more independent than those being treated in tertiary care centers. The degree of CI that was seen in our results likely underestimates its prevalence in the general in-center HD population. This is supported by previous literature showing that CI affects in-center hemodialysis patients more so than other dialysis populations (13).

The pattern of CI observed in this study showed that reasoning and verbal processing skills were less preserved compared with short-term memory. To clarify, "reasoning skills" included visuospatial processing, deductive reasoning, and planning. Significant CI in the reasoning and verbal domains were seen in 43%, and 55% of participants respectively, compared with 18% showing impaired short-term memory. These results are partially in line with previous findings. Murray et al. explored cognitive performance (memory, executive function, language) in a sample of 338 HD patients with standard neuropsychological testing: although only 2.9% had a known history of CI, the authors found that only 12.7% patients did not exhibit any CI. Furthermore, the authors found that memory and executive function were impaired in 35–41% cases, respectively, as opposed to 11% having impaired verbal domain (4). This might reflect lower dialysis vintages; in a study where dialysis vintages were higher (median 57 months), memory and language were most severely impaired in those with mild cognitive impairment and attention and visuospatial functions were more severely impaired in those with severe cognitive impairment. Further, this study showed a correlation between higher dialysis vintage and major

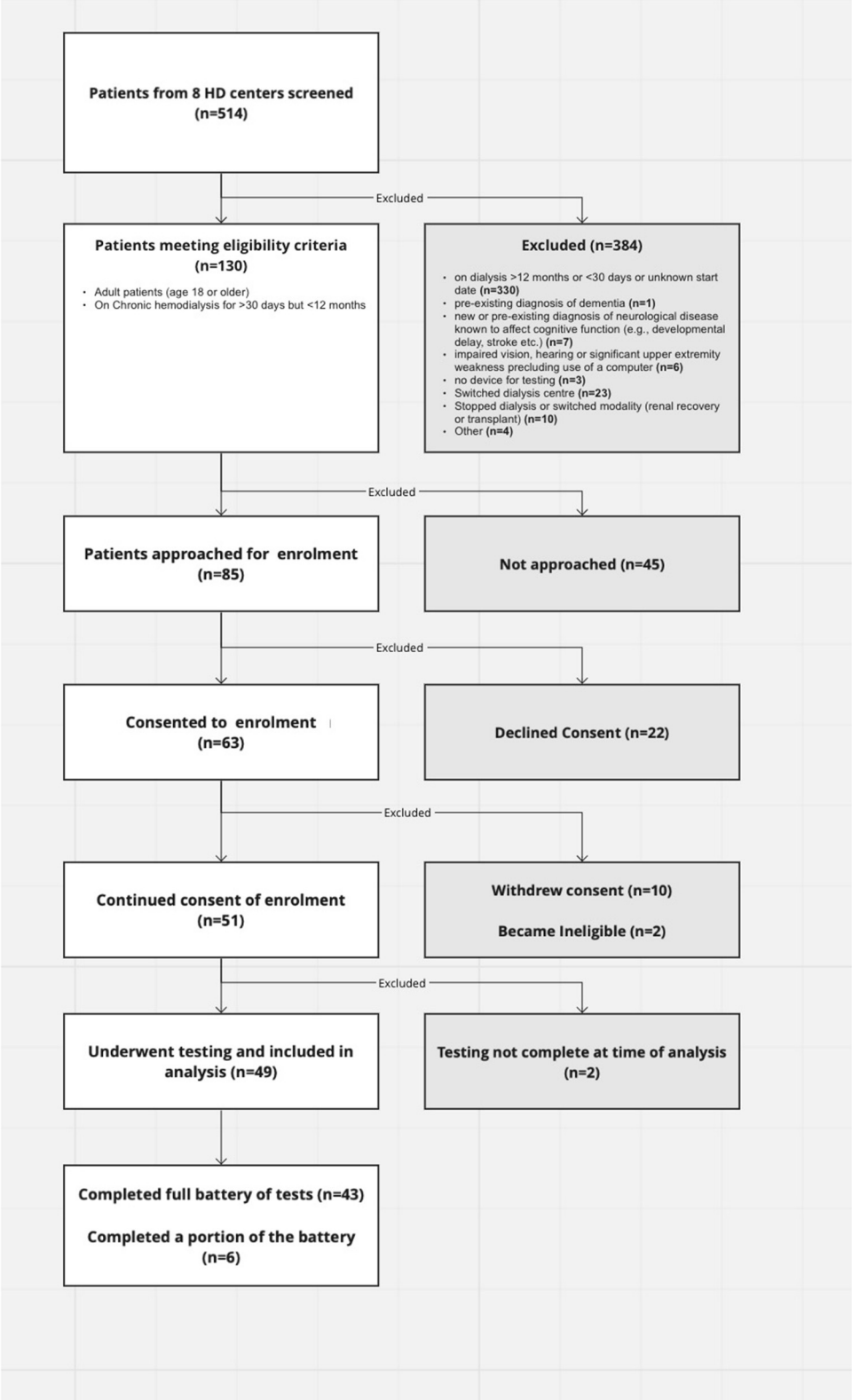

FIGURE 1 | Flow chart of participant enrollment and testing.

TABLE 1 | Patient demographic and clinical characteristics.

Characteristic	*n* (%), or mean (±SD)
Female sex	26 (53%)
Age	62.6
Comorbidities	
Hypertension	46 (94%)
Diabetes	25 (51%)
TIA/stroke	8 (16%)
Mental health	8 (16%)
Sleep apnea	15 (31%)
HF	11 (22%)
CAD/IHD	22 (45%)
Atrial fibrillation	8 (16%)
Vascular disease	5 (10%)
Etiology of renal disease	
Diabetes	18 (37%)
Hypertension	7 (14%)
GN	7 (14%)
Obstructive/reflux/structural	6 (12%)
PCKD	2 (4%)
Drug or other	9 (18%)
Dialysis details	
HD vintage	6.1 months (±2.8) [mean (SD)]
Lowest systolic BP	117 (±19.9) [mean (SD)]
Average UF rate	5.85 ml/kg/h (±3.83) [mean (SD)]
Duration of treatment	211.2 min (±27.6) [mean (SD)]
Location of hemodialysis	14 (29%)—tertiary care center 35 (71%)—satellite unit
Cognitive testing location	
Testing completed at/during hemodialysis	19 (39%)
Testing completed at home	30 (61%)

TABLE 2 | Cognitive performance of HD patients relative to age and sex-matched controls.

Cognitive test[domain tested*]/domain	Mean *z*-score (SD)	Statistics (*t*-test, *p*-value)
CBS cognitive test		
Feature match[a,b,c]	−1.47 (0.98)	$t(47) = -10.28$, $p < 0.0001$
Odd one out[a,b]	−0.64 (1.17)	$t(45) = -3.67$, $p = 0.0007$
Polygons[b,c]	−1.02 (0.87)	$t(47) = -8.04$ $p < 0.0001$
Rotations[b,c]	−1.58 (0.82)	$t(45) = -12.93$, $p < 0.0001$
Spatial planning[a,b]	−0.52 (1.04)	$t(45) = -3.35$, $p = 0.0016$
Monkey ladder[a]	−0.52 (1.46)	$t(47) = -2.36$, $p = 0.0227$
Paired associates[a]	−0.55 (0.87)	$t(45) = -4.24$, $p = 0.0001$
Spatial span[a]	−0.86 (1.31)	$t(47) = -4.50$, $p < 0.0001$
Token search[a]	−0.37 (1.01)	$t(44) = -2.43$, $p = 0.0193$
Digit span[c]	−1.20 (0.90)	$t(43) = -8.74$, $p < 0.0001$
Double trouble[a,b,c]	−0.97 (0.84)	$t(46) = -7.83$, $p < 0.0001$
Grammatical reasoning[b,c]	−1.57 (0.98)	$t(45) = -10.75$, $p < 0.0001$
Cognitive domain		
Reasoning skills	−1.37 (1.16)	$t(49) = -8.27$, $p < 0.0001$
Short-term memory	−0.41 (1.24)	$t(49) = -2.32$, $p = 0.0250$
Verbal processing	−1.47 (0.97)	$t(49) = -10.61$, $p < 0.0001$

**Each task can test more than one cognitive domain; the main cognitive domain(s) tested are noted here.*
[a] Short term memory.
[b] Reasoning.
[c] Visual.

cognitive impairment (32). Although results from this study are challenging to compare due to different cognitive testing methodologies, both studies show significant impairment in executive function, which is typically associated with cerebral small vessel disease and leukoaraiosis: indeed, executive function relies on deep white matter connectivity. In support of this finding, brain diffusion tensor imaging magnetic resonance has shown evidence of white matter ischemic injury associated with intradialytic hemodynamic instability (33). Another study of older Chinese HD patients and found a high frequency of CI with attention and visuospatial domains the most impaired. This was a larger study including over 600 participants and found age, education level, history of stroke, hypertension, dialysis vintage and single-pool Kt/V to be contributing factors to CI (32). Another risk factor is reduced cerebral venous oxygenation which has been demonstrated to occur in HD patients and correlated with reduced performance on cognitive testing (12). A second study also demonstrated reduced deep regional cerebral venous oxygenation in HD patients as well as reduced cognition although the two did not correlate. This may be a result of different testing approaches as the first study used the MoCA and the second used the mini mental status exam (MMSE) which has been shown to be a less effective test of cognition in this population (24).

To the best of our knowledge, this was the first use of the CBS in hemodialysis patients. While many validated measures of cognitive function have been used in the CKD and ESRD populations (24, 34), most tests require the time and presence of trained personnel for administration and scoring and require in-person testing. These human resources are not routinely available in tertiary care centers, much less in the satellite dialysis units. Further, patients on dialysis are often limited in terms of mobility, fatigued by their dialysis treatment and rely on pre-booked

transportation. This means staying late or returning to a hospital setting for testing is difficult; treatment-related fatigue may limit ability and willingness to complete tests. In this study, although some participants had difficulties, the majority had no problem completing the tests. Toward the end of our study, based on our participant feedback, the CBS was able to adjust their testing to allow patients to save their progress and resume testing within a 72-h period. The timing of testing is an important consideration, although the current evidence remains ambiguous. One study suggests improvement in CI as quickly as 1 h post HD, and better cognition both a day prior and following HD treatment (35). Another study demonstrated decreased evoked potential latency for 24 h post HD treatment with progressive increase thereafter; it also demonstrated best performance on CI testing at 24 h post treatment (36). In a third study, HD and control participants underwent cognitive testing twice (the day prior to and immediately following dialysis for the HD patients). This

TABLE 3 | Participants with scores consistent with cognitive impairment in each domain and total number of domains.

	***N* (%) with scores consistent with cognitive impairment**			
Reasoning skills	22 (45%)			
Short-term memory	10 (20%)			
Verbal processing	27 (55%)			
	Cognitive impairment across domains			
	None	**One domain**	**Two domains**	**Three domains**
N (%)	9 (18%)	23 (47%)	15 (31%)	2 (4%)

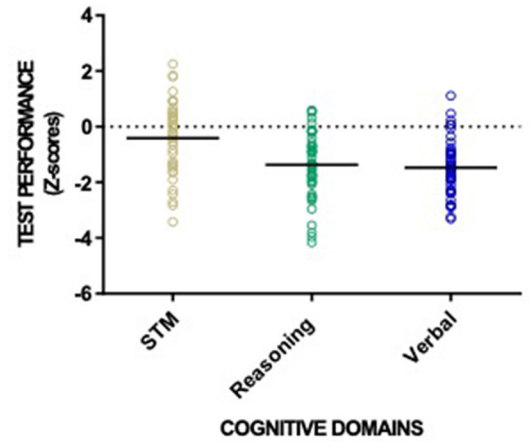

FIGURE 3 | Patient performance categorized into the three CBS cognitive domains: reasoning skills, short-term memory and verbal processing. Individual patient (circles) and cohort (solid line) performance presented as z-scores with healthy normal mean = 0 and standard deviation =1.

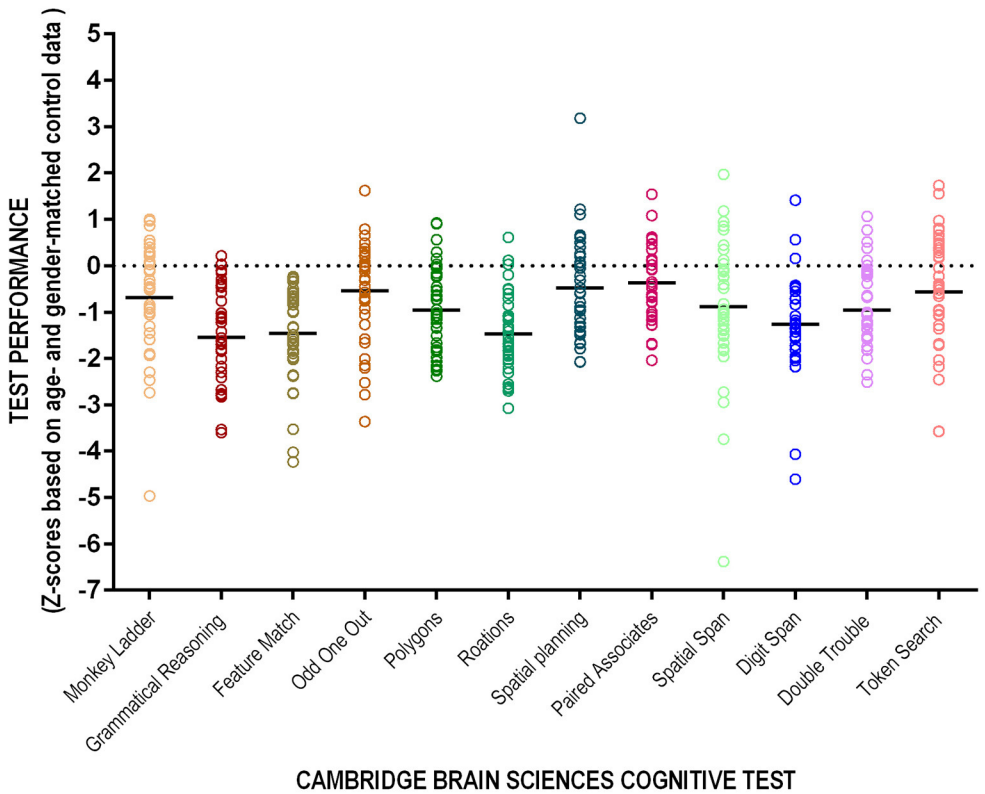

FIGURE 2 | Performance on the 12-test CBS. Individual patient (circles) and cohort average (solid line) presented as *z*-scores corrected for age and sex.

study found increased CI in the HD group compared to controls however, on the individual level, they found stable performance on cognitive testing overtime (37). Of the patients who completed testing in our study, 27 (>60%) did so in the interdialytic period. Considering most participants in our study tested during the interdialytic period and still demonstrated CI, this may be under-representing the degree of CI that occurs during the HD period. This may, however, be a more relevant time to assess as patients spend more of their time in the interdialytic period compared to time on HD therapy. An issue with the current evidence is that it is all based on small sample sizes. The question of when the best time to test for cognitive function in HD is important and needs answering based on a large study that measures cognitive performance over multiple time points.

Additionally, as the CBS compares study scores to matched controls using z-scores, we are better able to attribute CI to hemodialysis rather than to age-related risk. The CBS is therefore a potentially promising tool to screen for, diagnose and monitor CI in this patient population. The web-based platform and automated scoring allows for inclusion of patients who otherwise might not have the opportunity for in-person cognitive assessment and follow-up.

This study has several limitations. This was a cross-sectional study and does not allow attribution of causality based on any observed relationships. A few of the included patients had comorbidities that may impact CI including history of TIA or stroke, obstructive sleep apnea (OSA) and mental health disorders such as anxiety and depression. However, these are also common comorbidities in the HD population that should be taken into consideration when assessing cognition - HD therapy may be a contributing factor to these comorbid conditions. In a cross-sectional study in Saudi Arabia, nearly 20% of HD patients had anxiety at 25% depression (38). In another study, nearly 85% of hypertensive HD patients had depression (39). The prevalence of anxiety has been estimated at up to 52% in HD patients (40). Sleep apnea is also far more prevalent in the HD population than the general population with multiple studies suggesting a prevalence of >50% (41–43). The high prevalence of these conditions is important and may contribute to CI in this population and therefore, patients with these comorbidities should be included in assessments of cognition. While our sample size limits our ability to assess the impact of these on cognitive performance, a larger scale study including patients with these conditions could better elucidate the role they each play in cognitive decline.

Additionally, participants were matched based on age and sex to a control group; matching did not take into consideration other comorbidities or match based on underlying disease without the need for dialysis. When stratified by comorbidities and dialysis parameters, however, we did not find any signal of correlation. The study was not powered for this analysis and the effects of these factors on CI may be trivial. This suggests that there might be factors intrinsic to HD that are more relevant to the development of CI. Intradialytic hypotension is a likely mechanism associated with CI in HD patients (13, 44). indeed, cumulative exposure to intradialytic hypotension has been linked to new-onset dementia in HD patients (45). From a pathophysiological standpoint, ultrafiltration rates and intradialytic hypotension are associated with cerebral hypoperfusion and white matter injury (46–48). Intradialytic cerebral blood flow decline has correlated with ultrafiltration volumes and a measurable decline in executive function. This persists in those who remained on dialysis but not those who undergo renal transplant (49, 50). Compared to patients on PD, HD patients have worse cognitive function and higher rates of dementia (15). HD patients have been shown to have higher prevalence of brain atrophy than the general population and that loss of gray matter is seen more rapidly in dialysis patients than CKD and is associated with loss of executive function (51). One study found lower cerebral venous oxygen saturation in patients on HD compared to healthy controls and cognitive function was also statistically significantly lower in the HD group (12). Timing of neuropsychological testing (intradialytic vs. non-dialysis day) has been shown to affect cognitive performance in HD patients. Cognitive performance has been suggested to be optimal 24 h after HD, whereas it is likely negatively affected by intradialytic osmolar shifts and cerebral hypoperfusion (13, 52). In homogeneous conditions for CBS testing in this study may have led to overestimations of CI in our study sample, especially in the verbal skills domain. A future, large-scale study, using patients as their own controls and measuring CI using the CBS longitudinally in the CKD phases, and over time during chronic HD and even after transplantation would be helpful in determining the direct effects of uremia, HD and duration of HD on CI.

In conclusion, this study demonstrates that CBS testing provides an effective way to readily screen for CI in the maintenance HD population. We showed evidence of CI early after initiating HD with a more pronounced effect on reasoning and verbal processing skills. The CBS battery would be an effective tool in larger scale studies to examine changes in cognition over time, to explore the correlation between CBS with recognized risk factors for CI associated with HD, and to test interventions aimed at preventing or slowing the progression of CI in the HD population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article, if requested, will be made available by the authors without undue reservation

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Western University Research Ethics Board, study identification number 111721. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM conceived, designed, and supervised the study. MZ and CH recruited and enrolled participants and collected data. MS, JG, CW, and FS synthesized and analyzed data. MS wrote and revised the manuscript with input and edits from FS and CM. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Intersection of SGLT2 Inhibitors, Cognitive Impairment, and CKD

J. Ariana Noel[1,2], *Ingrid Hougen*[1,2] *and Manish M. Sood*[1*]

[1] *Department of Nephrology, The Ottawa Hospital, Ottawa, ON, Canada,* [2] *Postgraduate Medicine, University of Ottawa, Ottawa, ON, Canada*

Impairment in cognition and decline in kidney function often converge in the aging individual with chronic kidney disease (CKD). Cognitive impairment (CI) may be preventable through modification of health behaviors and risk factors that contribute to the vascular disease burden. CKD patients often have multiple coexisting comorbid conditions contributing to vascular risk. These comorbidities include hypertension, diabetes, cerebrovascular disease, and cardiovascular disease. Emerging evidence suggests that the management and prevention of vascular risk factors and cardiovascular diseases may indirectly contribute to the prevention of CI in CKD. Sodium glucose transport protein 2 inhibitors (SGLT2i) are emerging as the standard of care for selected individuals with CKD, type 2 diabetes (T2DM), and heart failure with rapidly expanding indications being actively investigated. In this narrative review, we examine the intriguing hypothesis that SGLT2i demonstrate potential disease modifying properties in CI among individuals with CKD.

Keywords: chronic kidney disease, cognitive impairment, dementia, albuminuria, SGLT2 inhibitor

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***Correspondence:**
Manish M. Sood
manishsood999@gmail.com

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INTRODUCTION

Cognitive impairment (CI) is the loss of brain functions including concentration, attention, executive function, verbal fluency, and memory beyond what is expected for age (1–3). Chronic kidney disease (CKD) is defined by two sequential measures of estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or albuminuria >30 mg/g more than 90 days apart (4, 5). CKD is a worldwide emerging epidemic with an estimated incidence between 8 and 16% of the population with a mortality rate of 42% (2, 5). CKD is not only related to increased mortality, but to other comorbidities associated with CI such as T2DM, hypertension, stroke, and heart failure (6–8). End stage kidney disease (ESKD) patients have significantly worse memory performance in comparison to moderate CKD (9, 10). However, by CKD III, it is estimated that up to 20% of patients have mild CI and up to 30% of patients with CKD IV have CI when screened with the Mini-Mental Status Exam (MMSE) or Montreal Cognitive Assessment (MoCA) (11, 12). CI is less prevalent in patients with early-stage CKD suggesting that there is a critical window for intervention to prevent progression of both CKD and CI.

CKD patients experience a disproportionately greater number of vascular risk factors than the general population, including T2DM, hypertension, congestive heart failure, and cerebrovascular disease (7, 10, 13, 14). Vascular risk factors are a major contributor to the development of CI (14, 15). Not surprisingly, CI steadily worsens with decline in eGFR (9, 13, 16). This triangulation of CKD, comorbid illnesses that lead to vascular disease, and aging are key contributors to the development and progression of CI. For example, CKD patients are at a 27% risk of atrial fibrillation compared to the general population's 10% risk (14). Atrial fibrillation places CKD patients at higher

likelihood of developing cerebrovascular disease, which is a significant factor in CI development. CKD patients also have both an independently increased risk of stroke when eGFR is <60 ml/min/1.73 m^2 and when macro-albuminuria is present (10, 17, 18). This can be correlated with increased microangiopathy and silent infarcts identified in white matter lesions on MRI in patients with lower eGFR (14).

Albuminuria is another aspect of CKD which has been repeatedly linked to risk of CI (19–22). A prospective cohort study found higher levels of albuminuria to be associated with increased risk of incident dementia in a cohort of 9,967 patients age 54–75 followed for a mean of 18 years independently of dementia risk factors such as hypertension and diabetes (23). Data from the ONTARGET and TRANSCEND study populations were used to assess the relationship between albuminuria and CI, and the effect of ACEi or ARB therapy on albuminuria and CI (19). They included 28,384 participants with vascular disease or diabetes, all of whom underwent MMSE and urine testing for albuminuria at baseline and 5 year follow up. They found that those with micro-albuminuria and macro-albuminuria were at higher risk of having a reduced MMSE score <24 (OR 1.26 95% CI 1.11–1.44 micro-albuminuria, OR 1.49 95% CI 1.20–1.85 macro-albuminuria). Patients with baseline macro-albuminuria who received ACEi or ARB therapy were at a lower risk of MMSE decline compared with patients treated with placebo (19). These findings support the notion that both albuminuria and CI may share common pathogenic factors and CI may respond to therapies that reduce albuminuria such as ACEi, ARB, and potentially SGLT2i (19).

Sodium glucose transport protein 2 inhibitors (SGLT2i) improve cardiovascular outcomes and reduce the effects of vascular risk factors (24–26). RCT evidence demonstrates that SGLT2i prevent diabetes, albuminuria, stroke, and cardiovascular mortality in CKD patients. SGLT2i are a class of medications which increase urinary glucose excretion by inhibiting the sodium-glucose cotransporter 2 (26). They lower blood pressure through by an osmotic effect, decreasing plasma volume and natriuresis. Randomized controlled trials of several SGLT2i showed protective effects including all-cause mortality, decrease in death from cardiovascular disease, hospitalization for heart failure and all-cause mortality (26–28). Studies including DAPA-CKD which showed decreased composite risk of sustained decline in eGFR of at least 50%, ESKD, or death from renal or cardiovascular causes, and DAPA-HF showing decrease in cardiovascular death and worsening heart failure in those with reduced ejection fraction have led to changes in practice and guidelines (24, 29–31). As such, they have become standard of care in patients with type 2 diabetes (T2DM) and cardiovascular disease (32, 33). With the effects these medications have on cardiovascular outcomes, blood pressure, glycemic control, CKD and albuminuria (26, 27, 34), one can speculate that these protective effects could extend to prevention of CI. In this review, we outline the factors associated with CI in CKD and the potential benefits of SGLT2i in the prevention and management of CI in CKD.

Abbreviations: AD, Alzheimer's dementia; ACEi, Angiotensin converting enzyme inhibitor; ACR, Albumin to creatinine ratio; ARB, Angiotensin II receptor blocker; CI, Cognitive impairment; CKD, Chronic kidney disease; DPP4, Dipeptidyl peptidase-4; eGFR, Estimated glomerular filtration rate; ESKD, End stage kidney disease; HFpEF, Heart failure with preserved ejection fraction; MMSE, Mini-mental status exam; MoCA, Montreal Cognitive Assessment; RCT, Randomized controlled trial; SGLT2i, Sodium glucose transporter 2 inhibitor; T2DM, Type 2 diabetes mellitus.

SGLT2I: A NOVEL THERAPY FOR VASCULAR RISK FACTORS AND RENOPROTECTION

The SGLT2i include dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, and tofogliflozin. SGLT2i inhibit the SGLT2 enzyme on the apical surface of segments 1 and 2 of the proximal convoluted tubule of the nephron that reabsorbs glucose back into the blood, inducing glucosuria and natriuresis (35). Potential adverse events related to SGLT2i use include urinary tract infections, genital yeast infections, and euglycemic diabetic ketoacidosis (36–38). Reduction of intravascular volume through diuresis and natriuresis have made them an adjunct to diuretics in hypertension and heart failure (30, 39). The EMPA-REG RCT enrolled over seven thousand patients with T2DM. Patients in the trial were given 10 mg or 25 mg of empagliflozin, or placebo (26). Patients in the empagliflozin group had significantly improved outcomes including improved cardiovascular and all-cause mortality outcomes. Both superiority and non-inferiority analyses were significantly in favor of empagliflozin with respect to death from non-fatal myocardial infarction and non-fatal stroke (26). CANVAS included over nine thousand patients enrolled in the trial with 29% prescribed canagliflozin (40). The participant mean eGFR was 75 ml/min/1.73 m^2 and mean urine albumin to creatinine ration (ACR) was 12.3 mg/g. Patients in the canagliflozin treatment group had significantly improved outcomes in fatal and cardiovascular outcomes, fatal and non-fatal stroke, progression of albuminuria and use of renal replacement therapy (34). The CREDENCE RCT studied the effect of SGLT2i canagliflozin on over four thousand patients with T2DM and albuminuria with eGFR < 30 ml/min/1.73 m^2 and also treated with renin and angiotensin blockade with primary outcomes of ESKD, doubling of serum creatinine or death from renal or cardiovascular causes after being followed for almost 3 years decreasing mortality by 30% (41).

SGLT2I INHIBIT PRO-INFLAMMATORY PATHWAYS IN NEURONS OF ANIMAL MODELS OF VASCULAR DISEASE

Recently, the SGLT2 protein has been shown to be implicated in CI-related neuronal pathways in animal models. Several studies demonstrated that SGLT2 inhibition results in amelioration of signaling involved in oxidative stress pathways. It's been hypothesized that the SGLT2 protein has a binding site for acetylcholinesterase in computational biology studies and it's through this mechanism that SGLT2i serve a role in both blood glucose regulation and cognition (42, 43). Lin et al. published one

of the first animal studies examining the effects of SGLT2i on cardiovascular, renal, and cognitive outcomes in an obese mouse model (44). Mice treated with empagliflozin for 10 weeks were found to have decreased cardiac and coronary interstitial fibrosis thought to be associated with a reduction in oxidative stress. Lin et al. also examined the cognitive effects of empagliflozin on their mice. Cognition was assessed by the Morris water maze test and was found to be impaired in diabetic mice. Mice given empagliflozin had improved performance after treatment with SGLT2i, suggesting a role for empagliflozin in preservation and/or improvement in cognitive function (44).

Both empagliflozin and dapagliflozin improve cognition in animal models of dementia and CI with a high fat diet. SGLT2 inhibition in rodent studies of neuroprotection in diabetes is significantly more effective than other classes of medications such as dipeptidyl peptidase-4 (DPP4) inhibitors (45). Sa-Nguanmoo et al. used a rat model of high-fat diet induced diabetes to investigate the effects of DPP4 inhibitors vs. SGLT2i on insulin resistance and cognitive function (45). Dapagliflozin administered to rats at a dose of 1 mg/kg showed improved hippocampal synaptic plasticity in comparison to the DPP4 treated group. Furthermore, in rats fed a high fat diet, a marker of inflammation (NFkB) activity, decreased with SGLT2i treatment. Their results demonstrated that SGLT2i were more effective in comparison to the DPP4 inhibitors at improving hippocampal synaptic plasticity in rats fed a high fat diet. The researchers hypothesize the improvement in neuronal plasticity occurred through prevention of insulin resistance and decreased neuronal apoptosis in the SGLT2i group (45).

Aside from reducing inflammation, SGLT2i may reduce CI through their role in energy metabolism pathways such as the mTOR pathway. The mTOR pathway is linked to changes in the regulation of anabolism and catabolism, especially nocturnal regulation of homeostasis of glycemic pathways (46). The SGLT2i role in regulation of the mTOR pathway is in its glucosuria, which is hypothesized to confer more favorable outcomes for mTOR signaling that could relate to a decrease in CI. The theory from Esterline et al. regarding SGLT2i improvements in multi-organ function relate to its glucosuria that is hypothesized to restore diurnal switching between anabolic and catabolic states by mTOR signaling (46). The increase in glycogenolysis and gluconeogenesis with SGLT2i decreases mTOR signaling (46).

Lastly, SGLT2 may reduce the physical disruption of neurons. In a murine model of AD and T2DM, researchers demonstrated treatment with empagliflozin at a dose of 10 mg/kg for 22 weeks reduced neuronal loss on necropsy (47). Specifically, SGLT2 treated mice showed reductions in amyloid plaques and tau protein (47). The investigators hypothesized that a decrease in cortical thinning is due to improved glycemic control with empagliflozin. In addition to histopathological differences, empagliflozin-treated mice also demonstrated significant improvement in their memory and learning performance.

SGLT2I MAY REDUCE CI THROUGH REDUCTION IN CEREBROVASCULAR DISEASE

Macrovascular complications of diabetes such as stroke play a significant role in the development of CI (27, 40). From the major RCTs for SGLT2i and cardiovascular outcomes, it was previously thought that SGLT2i had a neutral effect on stroke outcomes (48). In a meta-analysis of the RCTs of SGLT2i, Tsai et al. performed a subgroup analysis of stroke outcomes (48). Their search included 5 studies including EMPA-REG OUTCOME, CANVAS, DECLARE TIMI 58, and VERTIS where number of participants ranged from 4,000 to 17,000 from 2 to 4 years study length (48). SGLT2i were not associated with a reduction in ischemic stroke, transient ischemic attack, or fatal stroke, but that use of SGLT2i may be associated with a significant 50% reduction in hemorrhagic stroke (RR = 0.49, 95% CI 0.30–0.82, $P = 0.007$); however, this was among a small absolute number of events (48).

CKD and micro-albuminuria increase patients' risk of hemorrhagic and ischemic stroke. In a meta-analysis of the CREDENCE trial, subgroups with diabetes and atrial fibrillation were assessed for stroke events using a *post-hoc* analysis (49). There was a total of 142 patients diagnosed with stroke during the trial (49). It was determined that patients with decreased eGFR influenced SGLT2i effects on stroke. For patients included in the analysis with the lowest renal function (eGFR <45 ml/min/1.73 m^2), there was evidence for protective effect in the SGLT2i treatment group (49). They concluded from their subgroup analysis that there may be benefit for protection against hemorrhagic stroke prevention for patients with CKD.

A study reporting a significant association between cognitive impairment and short term SGLT2i use was recently published. A single center RCT from Mone et al. examined the effects of SGLT2i on frail elderly with diabetes and heart failure with preserved ejection fraction (HFpEF) (50). In their study, seniors were randomized to empagliflozin (N = 52), metformin, or insulin and administered the MoCA at baseline and 1 month after treatment (50). The study included adults >65 with MoCA scores < 26 and approximately one third of their participants had previous diagnoses of CKD (50). There was a significant improvement in MoCA sores in the empagliflozin treatment group: The mean MoCA scores in the three groups at baseline and 1-month follow-up were 19.80 ± 3.77 vs. 22.25 ± 3.27 ($P < 0.001$) in the empagliflozin group (50). The metformin and insulin groups did not have significant improvement in MoCA scores. This study provides promising evidence that empagliflozin may have CI benefits over other diabetes treatments (50).

DISCUSSION

CI is common in patients with CKD and CI may be preventable by targeting vascular risk factors associated

with CKD progression. A relatively new treatment for CKD and cardiovascular disease has become available, allowing Nephrologists to potentially target multiple vascular risk factors for CI in CKD with one medication. SGLT2i demonstrate significant benefit in reducing all-cause mortality and cardiovascular adverse outcomes in virtually all published SGLT2i RCTs.

However, the understanding of SGLT2i's putative role in cognitive impairment is in its very early stages. In animal model studies published to date, SGLT2i-treated rodents have improved memory performance. There are few studies of animal model cognitive function after treatment with SGLT2i, however, these studies suggest that use of SGLT2i are protective from CI mainly through regulation of blood glucose and decreased activity of inflammatory pathways. Why do the human participant RCTs and the animal model evidence differ with respect to their results regarding SGLT2i putative involvement in preventing cognitive impairment? Animal models showed potential for SGLT2i involvement in cognition whereas the RCTs showed some significant composite all-cause mortality results when non-fatal stroke was included. There were no CI outcomes included in the major human SGLT2i RCTs. There may be several reasons to account for this discrepancy: The animal model studies had shorter study durations and larger doses of the SGLT2i (i.e., 1 mg/kg) than the human RCTs. The N number of animal models is much smaller than RCTs with possibility that the neurological improvements in the animal studies may bias the results due to large variability and low reliability.

It is difficult to compare or conclude that CI can be improved from the limited RCT data we have at this time. We could hypothesize that SGLT2i function to improve CI risk through their reduction in vascular risk factors based on the outcomes of the trials. For example, CREDENCE primary endpoints were cardiovascular and renal disease and included stroke as a secondary outcome without inclusion of CI, dementia as secondary outcomes (25). Similarly, both EMPA-REG-OUTCOME and CANVAS did not examine outcomes in cognitive impairment but did have a significant primary outcome of non-fatal stroke (26, 27). In DAPA-CKD, patients with stroke or TIA were excluded from the study and CI, CVA or related adverse event was not included in their study analysis; however, significant reduction in renal and cardiovascular mortality demonstrated suggests dapagliflozin improves vascular risk factors (24). We do not know if SGLT2i directly impact CI development in patients with CKD, but the RCT data show compelling data to choose SGLT2i in patients with CI/vascular risk factors.

We now have the first preliminary evidence to suggest that SGLT2i improve CI in patients with T2DM (50). SGLT2i may be associated with neuroprotection including possible reduction in inflammation, and inhibition of acetylcholinesterase (50). To this end, there is increasing interest in further examination of SGLT2i role in CI. The EMPA REG ELDERLY is underway in Japan using the MMSE-J to measure CI and may provide further support for the use of SGLT2i in the elderly for CI protection (51). Results of these studies will provide further insight into the promising involvement of SGLT2i in prevention of CI.

CI is a progressive, and irreversible disease that is prevalent in older patients with CKD. Vascular risk factors for CI including hypertension, diabetes, cardiovascular disease, albuminuria, and cerebrovascular disease can be preventable if early intervention occurs. SGLT2i are an emerging therapy to manage and prevent all of these risk factors. Like ACEi and ARBs, SGLT2i decrease albuminuria, which may have benefit in prevention of CI. SGLT2i demonstrate compelling evidence for reduction in mortality and adverse cardiovascular outcomes in RCTs and a modest, but significant reduction in hemorrhagic stroke in RCT sub-analysis. Clinicians could consider earlier use of SGLT2i in older patients to provide cardiovascular and renoprotective benefits with potential downstream cognition benefits. Further longitudinal data are needed to determine if SGLT2i have a similarly protective effect against CI in CKD.

AUTHOR CONTRIBUTIONS

JN was responsible for drafting of the initial manuscript. IH contributed to the initial draft. MS was the supervisor. All authors contributed to the critical revision of the manuscript.

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EDITED BY
Dearbhla Kelly,
Trinity College Dublin, Ireland

REVIEWED BY
David J. Werring,
University College London,
United Kingdom
Pinar Yilmaz,
Erasmus Medical Center, Netherlands

*CORRESPONDENCE
Kaori Miwa
miwak@ncvc.go.jp;
miwa@osaka-njm.net

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Covert vascular brain injury in chronic kidney disease

Kaori Miwa* and Kazunori Toyoda

Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

Chronic kidney disease (CKD) contributes to the increased risk of stroke and dementia. Accumulating evidence indicates that structural brain abnormalities, such as cerebral small vessel disease, including white matter hyperintensities, lacunes, perivascular spaces, and cerebral microbleeds, as well as brain atrophy, are common in patients with CKD. All of these imaging findings have been implicated in the development of stroke and dementia. The brain and kidney exhibit similar impairments and promote structural brain abnormalities due to shared vascular risk factors and similar anatomical and physiological susceptibility to vascular injury in patients with CKD. This indicates that kidney function has a significant effect on brain aging. However, as most results are derived from cross-sectional observational studies, the exact pathophysiology of structural brain abnormalities in CKD remains unclear. The early detection of structural brain abnormalities in CKD in the asymptomatic or subclinical phase (covert) should enable stroke risk prediction and guide clinicians on more targeted interventions to prevent stroke in patients with CKD. This article summarizes the currently available clinical evidence linking covert vascular brain injuries with CKD.

KEYWORDS

chronic kidney disease, albuminuria, cerebral small vessel diseases, brain, stroke

Introduction

Chronic kidney disease (CKD) affects 9.1% of the global population (1). Patients with CKD have an increased burden of cardiovascular disease, and the risk of dying from a cardiovascular event is greater than the risk of end-stage renal disease (ESRD). CKD has continued to rise in rank among the leading causes of death in relation to aging and increased burden of vascular risk factors (1). Stroke is the leading cause of death in patients with CKD worldwide, and is associated with a 5-fold increase in stroke, and even mild reductions in glomerular filtration rate (GFR) are associated with substantial increase in the risk of stroke (2, 3). Moreover, CKD is an independent high-risk factor for neurological deterioration, disability, and mortality after stroke (4–6). Given the overwhelming clinical impact of CKD, it is important to evaluate kidney dysfunction to predict CKD progression. GFR and albuminuria are used to classify CKD; GFR is a marker of renal excretory function, while albuminuria is an indicator of renal barrier dysfunction.

The increased incidence of stroke in CKD is not only due to the aging process (7), but also due to the high prevalence of vascular risk factors, including hypertension

and diabetes, and CKD-induced factors, such as hyperuricemia and anemia. Particularly, CKD increases vascular dysfunction and accelerates endothelial dysfunction, arterial media stiffness, and media calcification, which in turn increases the risk of stroke (8). Even mild CKD accelerates endothelial dysfunction and promotes vascular stiffness due to changes in the proin?ammatory and pro-thrombotic microenvironment (9). Specifically, abnormalities in the kidney measurements can be associated with a chronic proinflammatory state, which may accelerate microvascular damage by endothelial dysfunction, resulting in blood-brain barrier (BBB) dysfunction and causing microglial activation with subsequent neuronal injuries (10).

Thus, apart from clinically overt stroke, there is an increasing interest in understanding the coexistence of decreased GFR or increased albuminuria and brain structural abnormalities. Adaptive changes in brain structural abnormalities include cerebral small-vessel disease (SVD) and large-vessel disease, all of which lead to an increased risk of overt stroke and dementia with aging (11–14). Early detection of structural brain abnormalities in CKD and ESRD in the asymptomatic or subclinical phase (covert) should provide crucial insights into the pathobiology of CKD, improve stroke risk prediction, and guide clinicians regarding better-targeted interventions to prevent stroke in patients with CKD. We aimed to provide a narrative overview of the main clinical manifestations of covert vascular brain injury and its pathologies in patients with CKD. This review discusses magnetic resonance imaging (MRI) markers of SVD, including white matter hyperintensities (WMHs) of presumed vascular origin, lacunes, perivascular spaces (PVSs), cerebral microbleeds (CMBs), intracranial atherosclerotic stenosis, microstructural changes in the white matter, brain atrophy, and impaired cerebral blood flow (CBF) in patients with CKD.

Pathogenesis of vascular abnormalities in renal impairment

The kidney and brain share similar microvasculature and vasoregulation, leading to shared susceptibility to microvascular dysfunction. They are both low-resistance end organs that are continuously exposed to high-volume blood flow (15 and 20% of resting cardiac output, respectively) and fluctuations in pressure, and they have local autoregulation. Although the kidneys are relatively small and account for only 1% of the total body weight, they have twice the oxygen consumption of the brain and receive a 7-fold higher blood flow than that of the brain under resting conditions (10).

Brain arterioles arising from perforating arteries are morphologically similar to kidney juxtamedullary arterioles, and both are responsible for maintaining a strong vascular tone, leading to a sufficient pressure gradient from parent vessels to capillaries (15). The perforating vessels in the brain and the afferent arterioles of the glomerulus are short in length and are exposed to blood pressure (BP) changes and consequently sustain high-pressure loads over this length, and, consequently, often branch out from large arteries at sharp angles (16). The kidneys and brain are continuously and passively perfused at a high-flow volume throughout systole and diastole, leading to low microvascular resistance. These similar hemodynamic characteristics make the brain and kidney vascular beds vulnerable to fluctuations in BP; thus, both organs are susceptible to microvascular damage (8). Moreover, shared vascular risk factors, such as hypertension, lead to endothelial dysfunction and vascular remodeling, creating a vicious cycle that perpetuates end-organ damage and, in turn, affects local autoregulation. Specifically, CKD narrows the zone of renal autoregulation, which is regulated through the myogenic reflex of the afferent glomerular arteriole and tubule-glomerular feedback (17). Elevated BP variability may further increase the susceptibility of the brain and kidney vasculature to endothelial dysfunction. Current evidence suggests that elevated BP variability is associated with cardiovascular events and death in the CKD population (18–20).

Cerebral small-vessel disease

Cerebral SVD is the umbrella term used to describe pathologies of vascular structures (small arteries, arterioles, capillaries, small veins, and venules) that supply the brain (21). The consistently identified risk factors for all forms of SVD are advanced age and hypertension, adding to evidence from genetic studies which have shown associations between SVD and hypertension (22, 23). SVD is characterized by a heterogeneous spectrum of histopathological features possibly initiated by endothelial dysfunction, BBB disruption, inflammation, oxidative stress, cerebrovascular reactivity decline, and genetic predisposition (24). The Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) definitions were developed to standardize terms that describe the appearance of sequelae of cerebral SVD, including recent small subcortical infarcts, lacunes, WMHs of presumed vascular origin, PVSs, CMBs, cortical superficial siderosis, and brain atrophy on imaging (25). All forms of SVD have a clinical impact on various conditions such as stroke, cognitive impairment, dementia, and

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BBB, blood-brain barrier; CBF, cerebral blood flow; CKD, chronic kidney disease; CMBs, cerebral microbleeds; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PVSs, perivascular space; GFR, glomerular filtration rate; IL, interleukin; MRI, magnetic resonance imaging; STRIVE, Standards for Reporting Vascular Changes on Neuroimaging; SVD, small-vessel disease; WMHs, white matter hyperintensities.

disabilities (motor and gait impairment, urination disorder, and depression) (24).

Shared vascular risk factors, predominantly hypertension and diabetes, either independently or in combination, predispose patients with CKD to simultaneous systemic endothelial impairment (26). Even in early renal impairment, oxidative stress, low-grade inflammation, and reduced nitric oxide availability make the endothelium more vulnerable to slight vascular shifts, which, in turn, compromise the BBB integrity and facilitate infiltration by white blood cells (9, 27). There is an overlap between circulating inflammatory markers, such as C-reactive protein, interleukin-1 (IL)-1, IL-6, and tumor necrosis factor-α in patients with CKD, suggesting a similar course of inflammation in both organs (9, 28).

Although overt uremia is typically recognized when GFR declines to <15 mL/min/1.73 m^2, it is clear that metabolite accumulation occurs at an earlier stage of CKD (26). Uremic toxins have been reported to directly alter the integrity of vascular endothelial cells and induce BBB disruption and arterial stiffness through increased oxidative stress (9, 27). Indoxyl sulfate decreases cerebral endothelial cell viability *in vitro*, which is associated with a decrease in nitric oxide production and an increase in the production of reactive oxygen species, inducing arterial stiffness (29). The aryl hydrocarbon receptor is the receptor of indoxyl sulfate in endothelial cells and is widely expressed in the central nervous system, such as the hippocampus. Activation of aryl hydrocarbon receptor by indoxyl sulfate also causes BBB disruption, which induces cognitive impairment in rodent models with CKD (30). These findings suggest a pathogenic role for uremic toxins in affecting BBB permeability and promoting SVD development.

Accumulating evidence has indicated that cerebral SVD is commonly observed in patients with renal impairment. A meta-analysis of pooled results from 27 studies (largely cross-sectional) confirmed the independent association between microalbuminuria and SVD, including WMHs, lacunes, CMBs, and PVSs in both the centrum semiovale and basal ganglia (31). These articles provide compelling evidence that albuminuria is a surrogate marker of microvascular disease and may be reflective of systemic vascular endothelial damage (31).

CKD contributes to medial calcification, remodeling, and stiffening of the large arteries. In a population-based study (Atherosclerosis Risk In Communities [ARIC] study), transcranial Doppler measurements revealed an inverse association between the degree of cerebral artery stiffness and CKD (32). When the pulsatility in large-artery disease is compromised, the downstream pressure pulsatility can be readily transmitted into the small vessels of the brain and kidney and is characterized by a low hydrodynamic resistance, resulting in subsequent vascular injury, SVD, and brain atrophy (33, 34). In a retrospective hospital-based study involving post-stroke patients, those with CKD were found to have a significantly higher SVD burden and higher distal intracranial resistance in the anterior cerebral circulation (35). In all, the small and large vessels are likely to exhibit parallel impairments in patients with CKD.

White matter hyperintensities

The predominant radiological manifestations of SVD are WMHs in the periventricular and deep white matter, with ischemic demyelination, axonal loss, and gliosis, corresponding to the WMHs seen on T2-weighted MRI (36). The prevalence of WMHs of presumed vascular origin increases exponentially with age at any degree of severity, and occurs in 90% of individuals older than 80 years. In addition to aging, WMHs are also more common in individuals with a history of stroke or dementia. In a recent meta-analysis involving 14,000 participants from the general population and those with vascular risk factors, WMHs burden was associated with more than a 2-fold risk of ischemic stroke and a 3-fold higher risk of intracranial hemorrhage than those patients with no or mild WMHs burden (13).

Studies have reported that increased WMHs burden was observed in the CKD population with or without a history of stroke (37–45). As CKD worsens with age due to exposure to vascular risk factors and the cumulative effects of endothelial dysfunction and inflammation, WMHs are generally manifested in patients with CKD, particularly patients undergoing hemodialysis (41). In patients approximately 60 years of age undergoing hemodialysis, WMHs burden is present in >50%, while WMHs was incidentally observed in 11–21% of the age-matched general population (41). Three population-based cross-sectional studies demonstrated that renal impairment (decreased estimated GFR [eGFR] and/or albuminuria) at baseline was independently associated with WMHs burden (37, 38, 40). This association has been replicated in the population-based AGES-Reykjavik study (n = 2,671), which considered a longitudinal change in kidney function, and demonstrated participants with an eGFR decline of >3 mL/min/1.73 m^2/year or incident albuminuria was associated with the progression of WMHs volume (difference [95% confidence interval]:8% [4–12%], 21% [14–29%], respectively) (39). These results may indicate that SVD development could simultaneously progress with renal function decline. In a recent meta-analysis, pooling results from seven prospective cohort studies (n = 2,796), systolic BP variability (per 1SD increase) was associated with 1.26 higher odds of the presence or progression of WMHs (46). Any time scale of BP variability (visit-to-visit, day-to-day, hour-to-hour) has contributed to a higher risk of the presence of SVD (46). However, it remains to be elucidated whether this association suggests a target for

therapeutic intervention or is the reflection of advanced systemic vascular burden.

Lacunes

Lacunes are thought to result from the occlusion of penetrating arteries predominantly due to lipohyalinosis or *in situ* microatheroma, which results in focal necrosis in the neural tissue (47). According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, lacunar strokes are small subcortical brain infarcts visible on MRI, <1.5 cm in the axial diameter, and associated with one of the traditional clinical lacunar syndromes (14). STRIVE proposed the term recent lacunar infarcts to define the neuroimaging evidence of recent infarction with an axial diameter of 2 cm in diffusion-weighted imaging MRI sequences in the territory of one perforating arteriole (deep cerebral white matter, basal ganglia, thalamus, or pons), in addition to imaging features or clinical symptoms consistent with a lesion (25). As the lesions are interrelated due to the shared pathogenesis, acute small subcortical infarcts can disappear, remain as WMHs, or form lacunes (25).

Previous studies on the association between renal impairment and lacunar infarcts have been conflicting. Results of a systematic review showed no specific association between renal impairment (decreased eGFR and/or albuminuria) and symptomatic lacunar stroke, but silent lacunar infarction was associated with renal impairment (48). Similarly, in a population-based study of 3,178 patients with acute stroke, a lower frequency of symptomatic lacunar stroke was observed in the CKD population with acute ischemic stroke, and the association between CKD and lacunar stroke was diminished after adjusting for age, sex, and hypertension (49). In the population-based Rotterdam study, a higher albumin-to-creatine ratio or lower cystatin C-based eGFR (eGFR-cystC) was associated with a higher prevalence of asymptomatic lacunes and with WMHs volume (38). Renal impairment was associated with WMHs, CMBs, and PVSs in patients with lacunar infarcts (50, 51). In a longitudinal study, involving 89 patients with lacunar stroke, decreased eGFR was associated with new CMBs progression (52).

Cerebral microbleeds

CMBs are small (2–10 mm in diameter) round or ovoid hypointense foci with associated blooming with enhanced visibility on MRI sequences sensitive to susceptibility effects (25). Histopathologically, CMBs represent hemosiderin-laden macrophages. The risk factors for CMBs in elderly populations largely differ according to the location of CMBs, suggesting different underlying microangiopathies. Cerebral amyloid angiopathy (CAA) primarily affects the superficial perforating arteries, whereas hypertensive angiopathy mainly affects the deep perforating arteries (25). Consistently identified risk factors for CMBs are advanced age and hypertension. CKD has been associated with an increased prevalence of CMBs. In a single-center study for health screening, moderate to severely decreased eGFR (<60 mL/min/1.73 m^2) was associated with the presence of CMBs, particularly deep/infratentorial CMBs (53). As mentioned above, in the population-based Rotterdam study with a cross-sectional design, the participants with the highest quartile of albumin to creatine ratio at baseline, but not decreased eGFR, had a higher frequency of CMBs compared to those with the lowest quartile (38). These associations have been replicated in the longitudinal population-based AGES-Reykjavik study, indicating that participants with incident albuminuria had 1.86 higher odds of developing deep CMBs (39). Several small studies found CMBs in up to 35–50% of patients undergoing hemodialysis (54–56). Apart from aging and hypertension, experimental studies suggest that elevated levels of urea may alter the cytoskeleton of endothelial cells and tight junction proteins and may be partly responsible for CMBs (57). Uremic serum potentially disrupts the cultured brain endothelial monolayer due to disarranged actin cytoskeleton and decreased tight junction proteins in the cells (57).

Perivascular spaces

PVSs are interstitial fluid-filled cavities surrounding the small penetrating vessels and function as the brain drainage system, such as the glymphatic system (58). Cerebral waste clearance via the glymphatic system relies on the convective movement of perivascular cerebrospinal fluid into the parenchymal interstitial fluid space and adequate drainage into the perivenular space (58). Increasing evidence suggests that the topography of PVSs is characteristic of a specific underlying SVD type: (1) when located in the basal ganglia, PVSs are associated with hypertensive arteriolosclerosis, such as arterial stiffening; and (2) PVSs in the centrum semiovale are related to CAA. This highlights the possible mechanisms behind the impaired clearance of vascular β-amyloid, consistent with the role of PVSs as the brain glymphatic system (58). In a single-center study involving 413 patients with a first-ever acute lacunar stroke, proteinuria and eGFR<60 mL/min/1.73 m^2 were correlated with PVSs severity in both the centrum semiovale and basal ganglia (50). In a single hospital-based study for acute stroke, white patients with CKD had higher odds of severe centrum-semiovale PVSs when comparing patients with and without CKD within racial groups (59). Among patients with CKD, black patients had 2-fold higher odds of severe PVSs in the basal ganglia and centrum semiovale compared to whites and other racial groups (59). In a single hospital-based study for 304 patients with autosomal-dominant polycystic kidney disease (ADPKD), ADPKD was associated with a higher degree of PVSs, but not with the WMHs severity, lacunes, or CMBs,

compared to age-, sex-, and eGFR-matched controls, suggesting that ADPKD-associated cilia dysfunction may induce chronic cerebral glymphatic system dysfunction (60).

Intracranial atherosclerotic stenosis

The systemic arteriosclerotic process in CKD is characterized by structural alterations in the intrinsic stiffness of the media in the aortic wall (8, 61, 62). These alterations occur during the early stages of renal impairment and simultaneously progress to renal function decline, leading to arterial enlargement and wall thickening. Although the mechanism underlying arterial stiffening in CKD has not been fully elucidated, metabolic abnormalities due to renal impairment, such as uremic milieu-induced oxidative and carbonyl stress, and the decreased clearance of pro-inflammatory cytokines may contribute to the pathogenesis of atherosclerosis (9).

Intracranial atherosclerotic stenosis of major cerebral arteries is a common cause of ischemic stroke. Although CKD affects stroke prognosis in large-artery atherosclerotic stroke (63), studies evaluating the prevalence of intracranial atherosclerotic stenosis remain scarce in both population- and hospital-based cohorts. Previous hospital-based studies of Caucasian patients with stroke/transient ischemic attack (TIA) have reported a wide range of prevalence of symptomatic intracranial stenosis, probably reflecting differences in the definition of intracranial stenosis, imaging techniques, inclusion criteria, and completeness of ascertainment. A population-based study of stroke/TIA (Oxford Vascular Study [OXVASC]) showed symptomatic or asymptomatic 50–99% intracranial stenosis in 17.6% of patients, with the highest rates at older ages (64). The prevalence of any intracranial stenosis (50–99%) increased with age from 7.0% at <50 years to 45.1% at ≥90 years (64). A population-based study (ARIC study), involving 1,762 participants (mean age, 76.3 years), found that eGFR-cysC (<60 mL/min/1.73 m^2) was associated with the presence of intracranial atherosclerotic stenosis on high-resolution vessel-wall MRI (65). Albuminuria (urine albumin-to-creatinine ratio ≥30) was associated with 50–70% intracranial stenosis. In two Chinese population-based studies, decreased eGFR (<45 mL/min/1.73 m^2) was independently associated with intracranial atherosclerotic stenosis assessed by transcranial Doppler (66, 67). A causal relationship between intracranial atherosclerotic stenosis and CKD was not established because these previous studies were limited by their cross-sectional design.

Microstructural changes

Diffusion tensor imaging is a molecular MRI technique that allows the measurement of the diffusion of water molecules along the nerve tracts. It can also be used to evaluate the structural integrity of the white matter and is a sensitive marker of microstructural changes in the brain. A population-based study (Rotterdam study), involving 2,726 participants (mean age, 56.6 years), found that a lower eGFR-cysC and higher albumin-to-creatinine ratio were associated with worse global white matter microstructural integrity (68). Microstructural damage, such as decreased white matter integrity, was consistently observed in patients with ESRD, particularly those undergoing long-term hemodialysis. Previous studies reported decreased fractional anisotropy and increased mean diffusivity in patients undergoing hemodialysis compared to age-matched controls, indicating insidious white matter damage (69–73). Hemodialysis-specific circulatory stress, intradialytic BP variation, and direct uremic toxins may contribute to worsened white matter integrity. No longitudinal study has allowed for the determination of causality between hemodialysis and white matter microstructural integrity. Nevertheless, in a study in which progressive WMHs burden was demonstrated in patients undergoing hemodialysis, improvements in cerebral anisotropic diffusion and CBF were noted in the post-transplantation period, suggesting possible reversibility (74). This result supports the hypothesis that CKD may accelerate covert white matter damage independent of vascular risk factors.

Brain atrophy

Imaging studies show a consistent positive association between brain atrophy and renal impairment, particularly in patients with ESRD undergoing hemodialysis (75–78) although inconsistent results were observed in the early stages of CKD (79–82). In a cross-sectional study of medical check-up centers comprising 1,215 participants, albuminuria contributed to cortical thinning, predominantly in the frontal and occipital regions (83). The study also suggested that albuminuria was associated with frontal lobe atrophy partially mediated by WMHs burden [83. It is hypothesized that systemic endothelial dysfunction accompanied with albuminuria occurs in the brain, resulting in the extravasation of serum proteins into the brain extracellular spaces and causing brain injury (84). Moreover, brain atrophy could partly occur based on the severity of SVD, which is prominently observed in patients with CKD (85). In patients undergoing hemodialysis, intradialytic hypotension may be involved in brain atrophy. Progression in frontal atrophy, as assessed by MRI, was found to be inversely correlated with the number of intradialytic hypotensive episodes in a longitudinal study (86). In addition, a cross-sectional study revealed that patients with CKD had a lower hippocampal volume and smaller cortical thickness than those in matched controls, providing evidence of a potential link between Alzheimer's disease-related

pathology and kidney function, while the mechanisms of hippocampal atrophy in the CKD population are largely unknown (87, 88).

Cerebral blood flow

CKD is associated with a dysfunctional BBB due to endothelial inflammation and vascular remodeling, which can impair the regulation of local CBF. Impaired autoregulation can lead to increased pressure across the capillary bed, which could result in capillary damage and increased BBB permeability (89). Hemodialysis can induce a transient decline in CBF. Cerebral arterial mean flow velocity has been shown to significantly decline during hemodialysis, and this intradialytic hemodynamic instability could cause transient cerebral stunning (90). Two prospective studies demonstrated that hemodialysis induces decreased intradialytic cerebral perfusion, partly due to intradialytic hypotension (91, 92). In a study of the acute effect of conventional hemodialysis on CBF, measured by positron emission tomography-computed tomography, global CBF declined significantly by 10 ± 15% (92). In contrast, previous hospital-based cohort studies assessed CBF with SPECT or MRI (arterial-spin labeling or phase contrast imaging) in patients undergoing hemodialysis and reported higher CBF compared to patients with normal kidney function (93–97). Regarding patients without hemodialysis, in a large cohort of nondiabetic hypertensive adults in early CKD stages, decreased eGFR (<45 vs. ≥90 mL/min/1.73 m^2) was associated with a higher total CBF as assessed by arterial spin labeling, and albuminuria was associated with a large WMHs volume (98). However, in the Rotterdam study which excluded patients with ESRD, a cross-sectional analysis of 2,645 participants demonstrated that decreased eGFR was independently associated with lower CBF measured by MRI (99). These contradictory findings are possibly due to the differences in the method of assessing CBF or in patents characteristics such as the stages of CKD. Moreover, it remains unclear whether these CBF changes subsequently lead to cerebral structural changes.

Discussion

We briefly described the association between covert vascular brain injury and CKD. This review includes an up-to-date discussion of imaging findings in patients with CKD, which may provide important insights into the early stages of stroke and dementia. Our narrative review has limitations, as it did not involve quality assessment of the included study reports. Overall, results from the literature collectively indicate that CKD is largely associated with structural brain abnormalities. There is a multifactorial mechanism underlying

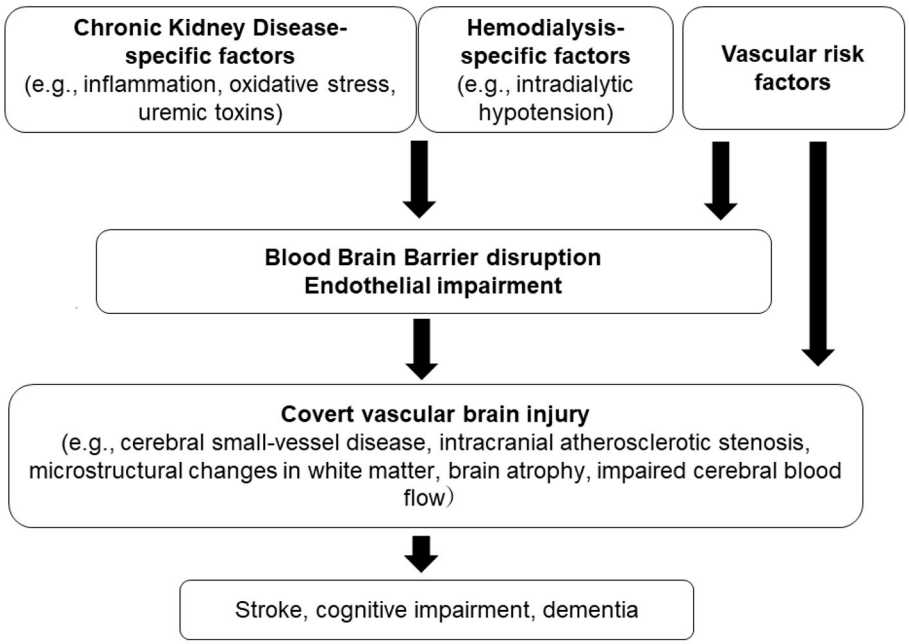

FIGURE 1
Proposed pathophysiology of chronic kidney disease–related covert brain injury.

these brain injuries in the setting of CKD (Figure 1). The kidney-brain association appears to represent greater impairment in kidney function, which could lead to more severe SVD and brain atrophy.

Recent experiments have highlighted that the direct toxicity of uremic toxins, such as the indoxyl sulfate-aryl hydrocarbon receptor pathway, may play an important role in BBB disruption and subsequent cognitive impairment in CKD (30, 57). A recent Mendelian randomization study suggested that renal impairment assessed by higher urine albumin-to-creatinine ratio and decreased eGFR are causally involved in large-artery stroke and SVD (i.e., small-vessel stroke, WMHs, and intracerebral hemorrhage), emphasizing the shared common genetic mechanisms with CKD (100). However, evidence regarding mechanistic pathways to demonstrate the development of these imaging findings is still lacking, since most results are derived from observational studies with a cross-sectional design. The amount and quality of evidence have been limited, especially in advanced CKD, including patients undergoing hemodialysis, due to the small sample sizes.

Apart from kidney transplantation, there is no direct evidence to suggest that any intervention prevents or reduces brain structural abnormalities in the CKD population. In the context of SVD, given both organs are common targets of vascular risk factors, we can speculate that people with CKD could benefit from more intensive vascular risk reduction, with a particular focus on hypertension and diabetes. There is current evidence indicating that intensive BP lowering could be associated with less WMHs progression in hypertensive patients (101, 102). In contrast, there is no evidence for glucose control in the absence of diabetes to prevent SVD progression (102). The recently published ESOC guidelines recommend patients with SVD and hypertension to have their BP well-controlled for the management of SVD with low quality of evidence (103). However, little to no data are currently available on the impact of intensive BP lowering on SVD in patients with CKD. There have been concerns that intensive BP treatment results in a greater risk of acute kidney injury inferred to reflect hemodynamic changes in kidney perfusion rather than true kidney function loss (104, 105). Considering that the pathophysiology of SVD remains incompletely understood and the evidence on the benefits in SVD progression is limited, there is still a research gap in elucidating how additional mechanisms contribute to the development and deterioration of SVD in general, as well as in the CKD population. Thus, additional prospective population-based studies with larger samples, across all CKD stages, and longer follow-up periods are needed to investigate the impact of CKD on SVD. Further experimental studies elucidating the observed association between CKD and SVD are required to identify molecular mechanisms that may enable the development of novel therapeutic approaches beyond the management of vascular risk factors.

Conclusion

Patients with CKD consistently show a high prevalence of covert vascular brain injuries, such as SVD, brain atrophy, intracranial artery stenosis, microstructural changes, and impaired CBF. These brain injuries, especially endothelial impairment, and BBB disruption are supported by rodent models pointing to CKD-specific causes such as the direct effect of uremic toxicity. Genetic variants that predispose patients to CKD have also been linked to large artery stroke and SVD. However, there is still a dearth of evidence regarding the mechanisms underlying these brain injuries in patients with CKD. Studies are needed for the CKD population to focus on how to prevent the development and progression of these brain injuries, which may be a potential strategy to protect against stroke, vascular cognitive impairment, or dementia.

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Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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