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Review Article

Insights into Cognitive Brain Health in Chronic Kidney Disease

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Abstract

Cognitive impairment and Chronic Kidney Disease (CKD) are common in older adults. With advances in medicine, the average lifespan is expected to increase, further increasing the prevalence of both conditions. The mechanisms underlying cognitive impairment in CKD are unclear. While mild-moderately low estimated glomerular filtration rate (eGFR) may not be associated with cognitive impairment, severely decreased eGFR and albuminuria do. Patients on dialysis have a high prevalence of cognitive impairment. Cognitive function improves after kidney transplantation. However, some residual cognitive deficits persist after transplantation, indicating that restoring the kidney function alone may not be enough to restore cognitive function, and other etiological factors may play a role. Albuminuria, another marker of CKD is also associated with cognitive impairment. However, albuminuria is often undiagnosed. Improving early identification and management of patients with albuminuria may be a good population-based dementia prevention strategy. Other factors associated with cognitive impairment in CKD include anemia and other metabolic derangements commonly observed in CKD. In this article, we reviewed the prevalence of cognitive impairment in CKD, the potential mechanisms underlying cognitive impairment in CKD, and the current evidence on the association between cognitive impairment and eGFR and albuminuria.

Keywords: Albuminuria; Cognitive impairment; Chronic kidney disease; Dementia; eGFR; End stage kidney disease

Abbreviations

CKD: Chronic Kidney Disease; Egfr: Estimated Glomerular Filtration Rate; ESKD: End Stage Kidney Disease; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State Examination; Moca: Montreal Cognitive Assessment; DSST: Digit Symbol Substitution Test; PTH: Parathyroid Hormone

Introduction

Cognitive impairment is common in patients with Chronic Kidney Disease (CKD) [1,2] and negatively impacts daily activities, quality of life, morbidity, mortality, and access to kidney transplantation [3-7]. Despite these adverse consequences, cognitive problems in patients with CKD are often unrecognized and untreated [6]. CKD itself remains under diagnosed limiting interventions to prevent dementia in this high-risk population. Even when diagnosed with CKD, patients remain unaware of their higher risk for cognitive impairment and dementia. The understanding of mechanisms underlying cognitive impairment in CKD is also limited, contributing to the lack of early preventive and management strategies. While there is growing interest in cognitive impairment in CKD, clear guidelines on diagnosis and management of CKD at risk for future dementia are lacking. In this review, we discuss the prevalence, pathophysiology, and future directions in cognitive impairment in CKD.

Epidemiology of Cognitive Impairment in CKD

CKD defined by an estimated glomerular filtration rate of <60mL/min/1.73m^2, affects ~37 million adults in the United States [8] and has a prevalence of 38% in people 65 years or older. Similarly, dementia is also highly prevalent in the old, affecting ~6.2 million individuals, with a prevalence of 11% in people 65 years or older. With advances in medicine and increase in average life expectancy, the prevalence of both CKD and dementia is expected to increase further [9-11]. There is a wide variation in prevalence of cognitive impairment in CKD, partly due to different methodologies and thresholds used for defining cognitive impairment and dementia. A uniform approach to diagnosis and detect cognitive impairment in CKD is lacking. Cognitive function is affected in 27-62% of patients with CKD compared to 11-26% in age matched general population [12,14]. Furthermore, cognitive function worsens as the estimated glomerular filtration rate (eGFR) decreases [15-17] and patients with End Stage Kidney Disease (ESKD) have the highest prevalence of cognitive impairment of up to 87% [2,6,18-20]. Compared to the prevalence of dementia of 5% in the general population [21], patients with ESKD are 3-5 times more likely to have dementia with a prevalence of 10-40% [6,22,23].

Just as cognitive impairment increases with age in the general population, cognitive impairment in CKD also increases with age. However, unlike the general population, cognitive impairment in CKD affects younger adults also [6,7]. The domains of cognition affected also seem to be different in CKD; common cognitive domains affected include executive function, attention, and memory [24,27]. These are different from other common etiologies of dementia such as Alzheimer's disease that tends to affect memory more than some

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other domains. Furthermore, while cognitive impairment is often progressive and irreversible in the general population, cognitive function in CKD improves with kidney transplantation [28,29]. Despite this improvement, however, the prevalence of cognitive impairment in kidney transplant recipients is about 58%, much higher than the general population [30]. This indicates that factors other than impaired kidney function and low eGFR are at play. While the kidney function is restored after a kidney transplant, other factors such as vascular disease from longstanding hypertension or diabetes causing cognitive impairment may not be reversed with kidney transplantation. Conversely, it is possible that transplant associated factors such as surgery associated delirium or post-transplant immune suppression also affect post-transplant cognitive function.

Cognitive Impairment, eGFR and Albuminuria

Cognitive impairment in CKD increases with declining eGFR [15-17]. With over 20,000 participants, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is the largest cross-sectional study evaluating the association between eGFR and cognitive function. Participants were 64.9 ± 9.6 years old, with a mean eGFR of 85.9 ± 23.7 mL/min/1.73m^2 (mean eGFR 47.7 ± 10.4 mL/min/1.73m^2 for the 11% with CKD). Each 10 ml/min/1.73 m^2 decrease in eGFR below 60 ml/min/1.73 m^2 was associated with an 11% increase in prevalence of cognitive impairment [31]. Table 1 summarizes some other cross-sectional studies showing similar associations. Some prospective studies also indicated a similar association between eGFR and cognitive impairment. The Cardiovascular Health Cognition Study included 3,349 participants without dementia and followed them for 6 years. A serum creatinine of >1.3mg/dl in women and >1.5mg/dl in men was associated with 37% increased risk of dementia [17]. The Rush Memory and Aging Project showed a higher rate of cognitive decline with a baseline eGFR of 15 mL/min/1.73 m^2 or lower; an effect similar to being additional 3 years older [32]. The INVADE study [33], the Northern Manhattan Study [34], and the Singapore Longitudinal Aging Study [35] also associated baseline kidney function with increased risk of cognitive decline.

While these older studies indicated an association between eGFR and cognitive impairment, emerging evidence suggests that this association may not be true for older adults with mild to moderate CKD [12,16,36-41]. This may be related to the limited ability of eGFR to accurately identify kidney disease in older adults and differentiate age related decrease in eGFR from an actual kidney 'disease' [42-46]. Moreover, serum creatinine varies with muscle mass, and serum creatine-based equations widely used to calculate eGFR can be misleading in older adults with lower muscle mass. Age associated decline in eGFR [47] is prognostically different from disease related decline in eGFR, the risk of progression to ESKD and adverse cardiovascular outcomes with age associated decline in GFR is low [48-50]. Brain health may follow a similar course where the age associated decrease in eGFR may not adversely affect cognitive function. We recently analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to understand the association between cognitive function and eGFR. The unadjusted analysis showed increased risk of cognitive impairment with lower eGFR, however, we found no such association when adjusted for confounding variables such as age [39,40]. Similarly, eGFR >30 mL/min/1.73m^2 was not associated with cognitive impairment in older adults in the BRain IN Kidney disease (BRINK) study [51].The 3C study [37], the HUNT [52], and Hisayama [53] studies also did not show an increased risk of cognitive decline or dementia with low baseline eGFR. The Adult Changes in

Table 1: Key cross-sectional studies assessing the association between CKD and Cognitive Impairment.

Study, Year, and Sample size	Age (years)	Assessment of cognitive function	Results summary
Kurella et al., 2004, n=80 [134]	62.5 ± 14.3	3MS, Trails B, CVLT	Cognitive impairment was associated with the severity of CKD
NHANES III, 2007 n=4849 [15]	20-59	Simple Reaction Time Test, DSST, Serial Digit Learning Test	Moderate CKD (eGFR 30-59ml/min/1.73m^2) associated with poorer performance in visual attention and learning/concentration
REGARDS, 2008 n=23,405 [31]	64.9 ± 9.6	6-Item NP Test	Higher prevalence of cognitive impairment in CKD
Elias et al., 2009 n=923 [135]	control: 62.3 ± 11.7 CKD: 68.5 ± 11.6	Battery of 17 NP tests	CKD affects global cognitive function
CRIC-COG, 2010, n=825 [136]	64.9 ± 5.6	Battery of NP tests	Higher prevalence of global cognitive impairment with lower eGFR
CRIC, 2011, n=3591 [14]	58.2 ± 11.0	3MS	Higher prevalence of cognitive impairment with eGFR <30 ml/min/1.73m^2 compared eGFR 45-59 ml/min/1.73m^2
Szerlip et al., 2015, n=437 [137]	61.2 ± 8.3	A battery of NP tests	Lower cognitive function in Mexican Americans with lower eGFR. eGFR <45 ml/min/1.73m^2 associated with impaired processing speed, executive function, visuospatial skills, delayed memory, and global cognitive function.
Torres et al; 2017, n=898 [138]	controls: 61.6 ± 11.3 CKD: 70.8 ± 11.1	A battery ofNP tests	Lower cognitive function with lower eGFR
The Maastricht Study, 2017, n=2987 [64]	59.6 ± 8.2 years	A battery of NP tests	Lower processing speed with albuminuria. No association between $eGFR_{cr\text{-}cys}$ and cognitive function
Gupta et al., 2020, n=1181 [39]	73.7 ± 7.1	ADNI-Memory and ADNI-Executive Function	No association between eGFR and cognitive function in mild-moderate CKD
SCOPE Study, 2020, n=2256 [139]	79.5	MMSE	No difference in eGFR across the MMSE categories
Gela et al., 2021, n=232 [140]	54.1 ± 17	MMSE	Cognitive impairment more prevalent with eGFR <60 ml/min/1.73m^2 and proteinuria.

ADNI: Alzheimer's Disease Neuroimaging Initiative; CVLT: California Verbal Learning Test; eGFR: estimated Glomerular Filtration Rate; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State Examination; SPPB: DSST: Symbol Digit Substitution Test; NP: Neuropsychological

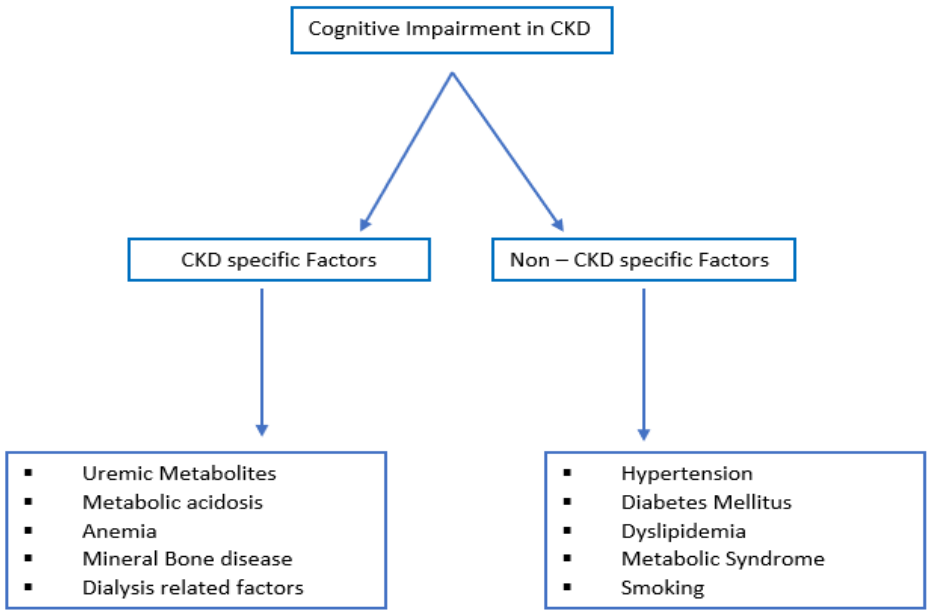

Figure 1: Proposed risk factors for development of cognitive impairment in chronic kidney disease.

Thought study did not find the average eGFR or the trajectory of eGFR to be associated with dementia in older adults [54]. The Sydney Memory and Ageing Study [55] found kidney disease to be protective against decline in memory; this may however be due to the falsely high eGFR from low muscle mass associated with cognitive impairment. The association between cognitive function and eGFR may differ in the young vs the old. For example, the sub-group analysis of the health ABC study [16] showed that in participants >73 years of age, eGFR 45-60 ml/min/1.73m^2 was not associated with an increase in cognitive decline when compared to participants with eGFR >60 ml/min/1.73m^2. However, in participants <73 years, eGFR 45-60 ml/min/1.73m^2, and <45 ml/min/1.73m^2 were associated with cognitive decline. In addition, mild-moderately low eGFR is not associated with brain structural changes such as brain atrophy [56].

Due to problems with accurately measuring eGFR with serum creatinine, some studies have used Cystatin C based eGFR (eGFRcys) with cognitive decline [57-59]. However, cystatin C is also a marker of inflammation, and it remains unclear if it was the lower kidney function or inflammation that was responsible for the increased Cystatin C in these studies.

While a low eGFR may not predict cognitive decline, the association between albuminuria and cognitive function seems more robust [60-64]. The Maastricht Study [64] included ~3000 participants aged 59.6 ± 8.2 years, with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine -cystatin C equation (eGFRcr-cys) based eGFR of 88.4 ± 14.6 mL/min/1.73m^2. While eGFR was not associated with cognitive impairment, albuminuria (urine albumin excretion ≥30 mg/24 hours) present in 8% of the cohort was associated with lower processing speed [64]. In the prospective analysis of 19,399 adults in the REGARDS study who were followed for 3.8+1.5 years, UACR of 30-299mg/g and >300 mg/g with preserved eGFR was independently associated with 31% and 57% higher risk of cognitive impairment respectively [65]. The HUNT [52], ARIC [66], Honolulu–Asia Aging [67] and Hisayama [53] studies also found an independent association of albuminuria with cognitive decline. The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study, the longest prospective study assessing the association between CKD and cognitive function followed 4,128 participants for 12 years. Albuminuria at baseline was associated with a faster decline in memory [68]. (Table 2) presents a summary of these key prospective studies.

Cognitive Function after Kidney Tranplantation

Kidney transplantation is the treatment of choice in ESKD. In addition to improving survival and quality of life [69,70], kidney transplantation also improves cognitive function [29,71]. Despite improvement, the prevalence of cognitive impairment in transplant recipients remains as high as 58% [30,72]. In addition, the middle cerebral artery kinetics response profile during moderate-intensity exercise is altered in kidney transplant recipients [73]. These data along with the high prevalence of vascular risk factors, and brain alterations in CKD indicate that vascular factors, independent of eGFR may also play an important role in cognitive impairment in ESKD. In addition, the transplant surgery, post-surgery delirium, and immunosuppression can also affect cognitive function in transplant recipients [74].

Diagnosis of Cognitive Impairment

Several tests are available to screen for cognitive impairment. Most were developed for screening of Alzheimer disease. The common tests clinically used include the Mini Mental State Examination (MMSE), the Modified Mini Mental State Examination (3MS), the Montreal Cognitive Assessment (MoCA), the Trail making B, the Mini-Cog test, and the Digit Symbol Substitution Test (DSST). Drew et al. compared the predictive ability of these screening tests in patients on maintenance hemodialysis and found the MoCA to be the best

Table 2: Key longitudinal studies assessing the relationship between CKD and Cognitive Impairment.

Study, Year, and Sample Size	Age (years)	Measures of cognitive function	Follow up (years)	Results summary
Seliger et al., 2004 n= 3349 [17]	75	Battery of NP tests	6	Creatinine ≥ 1.3 mg/dl for women and ≥ 1.5 mg/dl for men) associated with an increased risk of incident dementia
The Health ABC study, 2005 n= 3034 [16]	74 ± 3	3MS	4	eGFR <45 ml/min/1.73m^2 associated with an increased risk for cognitive impairment
Slinin et al., 2008 n=5529 [36]	73.6 ± 5.9	3MS and Trail Making test B	5	Reduction in eGFR (<45 ml/min/1.73m^2) associated with poor executive function at baseline, but not a risk factor for cognitive decline
The INVADE Study, 2009 n=3154 [33]	75	6-Item Cognitive Impairment Test	2	Creatinine clearance eGFR <45-59 mL/min/1.73m^2 and <45 mL/min/1.73m^2 associated with incident cognitive impairment after the 2-years
The Northern Manhattan Study, 2009 n=2172 [34]	66	TICS-m	2.9	Creatinine clearance <90ml/min/1.73m^{2}associated with worse global cognitive function
The Rancho Bernardo Study, 2010 n= 759 [141]	75	MMSE, Trails B, and Category fluency test	6-7	Albuminuria ≥30mg/g (but not low eGFR) associated with cognitive decline.
REGARDS study, 2011 n=19,399 [65]	≥65	6-Item NP Test	3.8 ± 1.5	With preserved eGFR, albuminuria >30mg/g associated with cognitive impairment. Low eGFR (<60 mL/min/1.73m^2) without albuminuria (<10 mg/g) also associated with cognitive impairment
The 3C Study, 2011 n= 7839 [37]	>65	MMSE	7	Low baseline eGFR(<60 mL/min/1.73m^2) not associated with cognitive impairment. Rapid decline in eGFR associated with cognitive impairment
O'Hare et al., 2012 n=2968 [54]	>65	CASI	6.0 (3.1-10.1)	No association between eGFR and dementia
The Singapore longitudinal aging study, 2012 n= 1315 [35]	65±7.2	MMSE IADL	4	CKD (eGFR <60mL/min/1.73m^2) in older individuals predicted cognitive and functional decline
The Cardiovascular Health Study, 2014 n=3907 [142]	>65	3MS DSST	7	eGFR$_{cys}$ (<60 mL/min/1.73 m^2) is associated with higher risk of worsening cognition
Honolulu-Asia Aging Study, 2016 n=3734 [67]	77-78	CASI	8	Midlife dipstick proteinuria predicted cognitive decline over 8 years
BRINK Study, 2016 n=554 [51]	69.3	Battery of NP tests	3	eGR<30 mL/min/1.73 m^2 associated with decline in cognitive function
Ekblad et al., 2018 n=3687 [143]	49.3	Battery of NP tests	11	Albuminuria >3 mg/mmol associated with cognitive impairment
Hisayama study, 2018 n= 1562 [53]	>60	Dementia based on DSM-III definition, clinical and imaging data	10	Albuminuria >30mg/g associated with dementia. eGFR (after adjustment for albuminuria) not associated with dementia
Aus Diab Study, 2019 n=4128 [68]	>25	CVLT SDMT	12	Albuminuria ≥3.5 mg/mmol in women and ≥2.5 mg/mmol in men associated with memory impairment. eGFR <60 ml/min/1.73 m^2 not associated with worsening of cognitive function
The HUNT Study, 2019 n=48508 [52]	49.5 ± 16.7	Dementia diagnoses based on history, clinical exam and brain imaging	7	Albuminuria > 1.78 mg/mmol associated with increased vascular dementia. No association between eGFR and dementia.
The Rancho Bernado Study, 2021 n= 1634 [144]	71.7 years	MMSE, Trails B, Buschke total recall	8.1	Albuminuria ≥30mg/g was associated with rapid cognitive decline. No such association found with eGFR and cognitive function.
Grasing et al., 2021 n=1127 [40]	74 ± 7	ADNI-Memory and ADNI-Executive Function	6 ± 2.6	Mild-moderately low eGFR was not associated with cognitive decline.

ADNI: Alzheimer's Disease Neuroimaging Initiative; CVLT: California Verbal Learning Test; CASI: Cognitive Abilities Screening Instrument ; eGFR: estimated Glomerular Filtration Rate; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State Examination; SPPB: Short Physical Performance Battery; UACR: Urine Albumin-Creatinine Ratio; DSST: Symbol Digit Substitution Test; TICS- m: Modified Telephone Interview for Cognitive Status; NP: Neuropsychological; SDMT: Symbol Digit Modalities Test; IADL: Instrumental Activities of Daily Living

performing screening test [75]. While screening tests are helpful, they have limited ability to confirm the diagnosis or grade the level of cognitive impairment. After a low score on a screening test, a follow up detailed neuropsychological assessment is still recommended to confirm diagnosis and identify the domains of cognition affected. These tools while widely used in geriatric clinics are often not readily available in a nephrology clinic. In addition, perceived cognitive status is not a reliable assessment of actual cognitive status [76]. Thus, cognitive impairment, especially in younger patients with CKD remains largely undiagnosed.

Pathophysiology of Cognitive Impairment in CKD

The mechanisms underlying cognitive impairment in CKD are complex and multifactorial. While several CKD specific factors can be implicated, it is important to recognize that patients with CKD have confounding factors such as multiple comorbidities, older age, and low physical activity that can independently increase the risk of cognitive impairment. For simplicity, we will categorize the possible etiological factors of cognitive impairment in CKD into two broad entities, i.e., CKD specific and non-CKD specific risk factors (Figure 1).

CKD Specific Factors

Uremic metabolites: Impairment of glomerular filtration and/or tubular secretion leads to accumulation of several metabolites in CKD. More than 150 such compounds have been identified and many others remain unknown. Many uremic metabolites adversely affect the central nervous system [77]. Although high serum levels of several uremic metabolites should not cross the blood brain barrier

and affect the brain, CKD causes vascular endothelial dysfunction and disruption of the blood brain-brain-barrier [78] allowing a higher-than-normal concentration of these metabolites into the brain. These uremic metabolites may also lead to alterations in brain neurochemicals, cerebral blood flow, and white matter integrity [71].

Metabolic acidosis: Metabolic acidosis is common in CKD. Hydrogen ions can cause neural excitotoxicity and modulation of N-methyl-D aspartate- activated currents leading to hyperexcitable state [79,80]. In the cross-sectional analysis of 2,853 participants from the Systolic BP Intervention Trial (SPRINT) study, low serum bicarbonate level was independently associated with cognitive impairment [81]. Longitudinal studies are needed to assess causality and explore this association further.

Anemia: Anemia is common in CKD. Both anemia and its treatment with erythropoietin stimulating agents are associated with increased risk of cerebrovascular disease and cognitive impairment [82]. It remains unclear if these associations are related hypoperfusion and hypoxia or due to increased risk of cerebrovascular events [14,83].

Mineral Bone Disease: Secondary hyperparathyroidism commonly found in advanced CKD and characterized by elevated Parathyroid (PTH), low calcium, and low vitamin D levels is also associated with cognitive impairment [84,85]. It is hypothesized that PTH crosses the blood-brain barrier and increases the release of vasopressin. Vasopressin increases vasoconstriction, causing hypoperfusion in cortical areas of the brain involved in memory and learning processes [86,87]. Furthermore, cognitive function improves after parathyroidectomy, implicating that high PTH levels may be associated with cognitive impairment independent of the severity of CKD [88]. Additional supporting data for this association and the role of vitamin D needs further exploration.

Dialysis procedure related Factors: Dialysis is a lifesaving procedure in ESKD. Initiation of dialysis clears neurotoxic uremic metabolites and improves uremic encephalopathy. However, initiation of dialysis is also associated with increase in stroke [89]; an independent risk factor for cognitive impairment and dementia. While dialysis inadequacy may affect cognitive function [20], increasing dialysis frequency or dose does not improve cognitive function [90]. Sudden fluid shifts commonly seen with in-center hemodialysis can decrease cerebral blood flow causing cerebral stunning, ischemia, and eventual atrophy [91-95]. Indeed, high ultra filtration volumes during hemodialysis reduce cerebral blood flow [96]. In addition, infarctions in watershed areas of the brain are reported in hemodialysis patients [97]. Cerebral ischemia in ESKD is independent of systemic blood pressure indicating that disruption of cerebral auto regulation and blood brain barrier may play a role in ischemic brain injury [91]. Dialysate temperature may also affect cerebral blood flow. However, the increase in fractional anisotropy at 12 months with normal dialysate temperature (37 degrees C) and a lack of improvement in fractional anisotropy with a lower dialysate temperature indicates otherwise [98]. Unlike hemodialysis, peritoneal dialysis has less hemodynamic shifts and may preserve cognitive function better [99]. Despite this theoretical advantage of peritoneal dialysis over hemodialysis in preserving cognitive function, comparative studies are lacking.

Non- CKD Specific Risk factors

Hypertension, diabetes, dyslipidemia, obesity, metabolic syndrome, and smoking; common risk factors for dementia are common in CKD. CKD is also associated with endothelial dysfunction, atherosclerosis, vascular stiffness, and vascular calcifications. These changes may explain the higher risk of cerebrovascular events, lacunar infarcts, white matter disease, and brain atrophy; (common features of vascular dementia; in CKD) [100-102]. These risk factors lead to endothelial dysfunction. Endothelial dysfunction within the renal vasculature is a key feature in progression of kidney disease. Inflammation, oxidative stress, and possibly hyperphosphatemia increase endogenous inhibitors of endothelial nitric oxide synthase [103]. Endothelial dysfunction is a well described risk factor of vascular dementia [104]. Aging itself can affect vascular endothelial function [105], and coupled with other traditional risk factors seen in CKD, this effect can be additive.

Diabetes, the leading cause of CKD in the United States [8], is an independent risk factor for vascular disease and cognitive impairment [106,107]. Hyperglycemia induces oxidative stress and over expression of cytokines increasing inflammation and lipid accumulation. This causes a pro thrombotic state largely responsible for small vessel (retinopathy, nephropathy, neuropathy) and large vessel (cardiovascular, cerebrovascular, and peripheral vascular) diseases [108,109]. An anti-inflammatory effect of metformin, an oral hypoglycemic agent is hypothesized to be neuroprotective and may delay the progression of cognitive decline [110-114]. Due to safety concerns, metformin use is however restricted in advanced CKD [115].

Hypertension, the second leading cause of CKD is also an independent risk factor for cognitive impairment in the general population [8]. Hypertension is a known risk factor for both clinical disease such as stroke and transient ischemic attacks [116] as well as subclinical disease such as lacunar infarcts and white matter disease [101,102]. Higher blood pressures are associated with higher incident dementia [117,118] and lowering blood pressure reduces cognitive decline and probable dementia [119,120].

Several other confounding risk factors are commonly present in individuals with CKD. Smoking is a risk factor for both cognitive impairment and CKD [121]. While nicotine may improve cognition in the short-term, long-term smoking is detrimental for cognitive function [122-125]. Visceral obesity is also associated with increased risk for CKD [126-130] as well as dementia [131-133].

Conclusion

Cognitive impairment in CKD is common but remains largely undiagnosed. It remains debatable whether a low eGFR is independently associated with cognitive impairment especially in older patients with mild-moderate reduction in eGFR. Albuminuria may be a better predictor of cognitive decline than eGFR. Confounding variables such as age and co-morbidities such as diabetes and hypertension make the relationship between CKD and cognitive function hard to interpret.

Normalization of brain alterations and improvement in some cognitive domains with kidney transplantation indicates reversibility in CKD associated cognitive impairment. This reversibility is

promising and can guide strategies for management of patients who are unable to receive a kidney transplant. These strategies may include lowering ultrafiltration and preserving residual kidney function and tubular secretion even on dialysis.

Careful evaluation and management of risk factors, and screening for cognitive impairment can improve patient care. Standardization of cognitive function assessment tools in CKD and frequency of screening will also be beneficial. Importantly, without any effective pharmaceutical treatment for cognitive impairment in CKD, prevention may be the best strategy to lower incident dementia. Thus, lifestyle modifications, dietary changes, better management of comorbidities such as hypertension, dyslipidemia, and diabetes, smoking cessation, and increasing physical activity may be critical. Early identification of patients at risk for future dementia can help prioritize these efforts. Future research should include the effects of early identification and aggressive management of risk factors on dementia prevention in CKD.

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