Uremic Toxins, Chronic Kidney Disease, and Cognitive Dysfunction: Translational Insights

Running Title: Brain Dysfunction in Kidney Disease

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Abstract **(**JASN unstructured; 300 word limit; current count: 227**)**

Individuals with chronic kidney disease (CKD), and in particular end-stage kidney disease (ESKD), experience higher rates of cognitive impairment compared to the general population. Cognitive impairment (CI) involves alterations to one's cognitive status that affects their everyday life. CKD is associated with CI in 20-70% of patients, with the highest prevalence among individuals with ESKD such that dialysis-dependent patients have twice the prevalence of aged-matched controls. In the past 5 years, the number of studies examining the "kidney-brain axis", mechanisms of CKD-related cognitive impairment, and potential therapeutics have markedly increased. This review article comprehensively summarizes recent literature on CKD-associated cognitive impairment with emphasis on uremic toxins, major advancements in understanding of brain injury mechanisms, and promising therapeutics. The topics address the prevalence and risk factors for CKD-associated cognitive impairment, and overlap between CKD-associated cognitive impairment, Alzheimer's disease, and other neurodegenerative diseases. Furthermore, we review translational studies examining uremic toxin-associated pathogenic processes including neuro-oxidative stress, neuroinflammation, and blood brain barrier dysfunction both from *in vitro* and *in vivo* models of CKD-associated brain injury. Finally, we summarize therapeutic interventions including indoxyl sulfate absorbtion, aryl hydrocarbon receptor antagonism, Kca3.1-specific inhibition, IL-1R inhibition, exercise, supplements, and kidney transplantation which in humans and animals have been examined as potential methods to alleviate CKD-associated cognitive impairment. Further, we highlight additional future targets, including cellular senescence. These scientific advancements will inform further studies that fill knowledge gaps and contribute to therapeutic targeting to improve or preserve cognitive function in individuals with CKD.

Introduction

Chronic kidney disease (CKD) affects more than one in 7 adults in the United States and more than 700 million people worldwide[1,2]. With progressive kidney function loss, metabolic waste products in the form of uremic toxins accumulate in the heart, vasculature, bone, bone marrow, and brain[3]. Brain function is among the many CKD sequela affecting patients' physical function and quality of life.

Cognitive Impairment (CI), mild CI, and dementia represent different degrees of cognitive dysfunction. Cognitive impairment can be measured via many modalities, including the clinical dementia rating (CDR), a widely used tool that assesses decline in cognition and function[4,5]. In mild CI, individuals may show some cognitive impairments but their daily life is unaffected[6]. Typically, the definition of dementia is when social and/or occupational functioning is impacted by the decline in cognition[7]. [8]. Symptomatic Alzheimer's Disease (AD) is the leading cause of dementia. AD is defined by the presence of amyloid-beta plaques and tau-tangles[8]. Mild CI can be an early sign of incipient AD[6], and may also show similar neuropathological substrates. have Contirbutors to mild CI are typically considerd to be neurodegenerative, but more systemic factors, such as CKD[6], may play a less well-recognized role.

Between 20-70% of patients with CKD show CI , with the highest prevalence among individuals with end stage kidney disease (ESKD)[9]. In fact, the prevalence of CI in dialysis-dependent patients is twice that of age-matched controls[10]. Since 2019, there has been an increase in the number of studies which have examined the kidney-brain axis relationship, mechanisms of CKD-related cognitive impairment, and potential treatments. However, knowledge gaps remain in the understanding of CKD and cognitive impairment, including the relationship between CKD and other common causes of cognitive impairment, specifically Alzheimer's disease (AD) and AD-related diseases (ADRD).

This article reviews recent literature on CKD-associated cognitive impairment with emphasis on their prevalence and shared risk factors, direct effects of CKD on CI, and promising therapeutics. . Furthermore, we summarize translational studies examining uremic toxin-associated pathogenic processes including neuro-oxidative stress, neuroinflammation, and blood brain barrier dysfunction both using *in vitro* and *in vivo* models. Finally, we summarize therapeutic interventions tested in humans and animals to alleviate CKD-associated cognitive impairment, and highlight future promising molecular targets.

CI: prevalence in CKD, dialysis, and kidney transplantation

CKD is one of the strongest risk factors for CI and dementia[11]. The prevalence of CI has been estimated at around 62% in pre-dialysis CKD patients, compared to 26% in matched controls suggesting that those with CKD are ~3 times more likely to experience CI than the general population[11].

CI and CKD: A summary of clinical studies evaluating the relationship between CI and CKD is provided in **Table 1**. Several studies have found that individuals with reduced kidney function exhibit CI as measured by validated cognitive measures and screening tools[12-19]. Lower eGFR, in particular eGFR<45 mL/min/1.73m^2, and lower kidney clearance of metabolic waste products is associated with poorer performances on cognitive measures[13,15,16,18,19]. Kurella et al.[19] found that advanced CKD had 5-fold higher risk for global CI and that for each 10 mL/min/1.73m^2 decrease in eGFR, the risk for CI increased up to 25%. Some studies did not find a relationship between eGFR and cognitive impairment or probable dementia[20-23]. However, modest associations were identified for albuminuria and urine biomarkers of kidney tubule injury/dysfunction and cognitive performance[20,21].

Dementia and CKD: Both lower eGFR and advanced CKD have been associated with an increased incidence of dementia[24-28]. Using ICD-10 based diagnoses or the initiation of anti-dementia therapy in over 300,000 patients (mean age 74±8; eGFR>15 mL/min/1.73m^2), Xu et al.[26] found that declines in eGFR were associated with X fold higher risk of all-cause dementia and vascular dementia. Some studies observed that this relationship remains after controlling for sociodemographic covariates and factors such as ApoE genotype[24,28]. ApoE, or apolipoprotein E, is a protein involved in cholesterol and fat transport and the ApoE ε4 genotype is a known genetic risk factor for AD[29].

CI and Dementia in Dialysis: Studies have also examined the association between CI and dementia in dialysis-dependent patients. Many individuals that are dialysis-dependent - requiring hemodialysis or peritoneal dialysis - have mild to severe CI[30,31]. In a prospective cohort study of 150 hemodialysis patients, Drew et al[30] found that nearly 80% of the cohort had CI (mild 17%, moderate 33%, severe 29%) based on the Montreal Cognitive Assessment (MoCA).
In addition, dialysis has been suggested to improve cognitive status for end stage renal disease patients[32,33]. To establish a time course for this association, Findlay et al.[32] conducted transcranial Doppler ultrasound and MRI studies in nearly 100 hemodialysis patients and found that hemodialysis induces transient redcutions in cerebral blood flow within X hours after the procedure. Interestingly, these correlated with longer-term CI. However, Drew et al.[34] were unable to detect lower cognitive performance during the first hour of hemodialysis when compared to the hour prior to dialysis[34], suggesting a limited effect of acute dialysis on CI. Recently, a study by Long et al.[25] found that among 216,000 dialysis-dependent patients, the presence of a sleep disorder (26%) increased risk of dementia (all cause, symptomatic AD, vascular dementia, or mixed dementia) and that the use of positive airway pressure associated with a lower risk dementia. Hence, other CKD comorbidities which independently associate with neurodegenerative diseases, appear to have effects in mediating CI in CKD.

CI and Kidney transplantation:

Given that kidney transplantation restores kidney function, several studies have examined the the potential reversibility of CI after transplantation. Gupta et al.[35] identified low scores on cognitive measures prior to kidney transplant which subsequently improved to a level similar to age-matched healthy controls within 1 year of transplantation. Findlay et al.[32] found that after kidney transplant, dialysis patients showed improved memory, and that increased fractional anisotropy of the white matter which correlated with executive function. Notably, Chu et al.[36] found that kidney transplant associated with a 1.3 point improvement on the Modified Mini-

Mental State Examination. These findings suggest a limited degree of CI reversibility after kidney transplantation.

Risk factors for CI and neurodegenerative diseases in CKD:

As shown in **Figure 1**, multiple risk factors have been identified that make those living with CKD more susceptible to CI, dementia, and neurodegenerative diseases, including AD. These traditional and nontraditional factors include age, sex, race, education level, hypertension, stroke, small vessel disease, diabetes mellitus, exercise and activity, sleep disorders, and obesity. Contributing processes in kidney disease include uremia, dialysis exposure, neuroinflammation, neurooxidative stress, and blood brain barrier dysfunction which have been previously summarized in a review by Kelly et al.[11]. This review will focus on mechanisms contributing to kidney-brain axis dysfunction.

Overlap between CKD and AD/ADRD

Patients with CKD have an estimated 1.14-fold increased risk of developing AD dementia as defined by International Classification of Diseases[37]. Several factors may underpin this increase in risk such as aging and cerebral small vessel disease (cSVD). cSVD, which has been implicated with cognitive impairment includes pathological, clinical, and radiological cerebrovascular changes[38]. Inflammatory and immunologically mediated cSVD is presented by a surplus immune cell permeation into vessel walls from systemic inflammation[38]. Systemic low-grade inflammation has been well established in CKD. In fact, the role of inflammation has been implicated in the progression of CKD. This has been well reviewed previously[39]. The most common risk factors for CKD, and CKD CI, such as age, hypertension, and diabetes, are also common risk factors for cSVD[11,38].

Interestingly, both CKD and AD disproportionately affect certain populations including the elderly, women, and Black Americans[1,40]. More than three in 10 (33.2%) adults over the age of 65 will have CKD[1]. Approximately one in 9 (10.7%) adults over 65 years old will develop AD[40]. Among U.S. adults, CKD is more common in women (15.4%) than in men (12.6%)[1] and for AD nearly two in three are women[40]. Black Americans, in comparison to white Americans, are more than four times likely to develop kidney failure[1]. Similarly, in AD, older Black Americans are nearly two times as likely to have AD in comparison in older white Americans[40]. Given the stark similarities in risk and other pathogenic factors between CKD and AD, further investigations are needed to understand the role of CI and other brain injuries in CKD.

CKD and AD are both aging-related conditions with pro-inflammatory states. Scheppach et al.,[41] found that estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR) were associated with structural brain damage. However, this damage was not in regions typically associated with AD. They also determined that patients with lower eGFR have higher volume of white matter hyperintensities, a sign of cerebral small vessel disease, thus in alignment with prior reports[41,42]. Vascular CI is an umbrella term relating to any vascular brain pathology resulting in CI. One of the main cerebrovascular pathologies in vascular CI are white matter hyperintensities. Indeed, CKD patients have increased white matter hyperintensity volumes as detected by fluid-attenuated inversion recovery magnetic resonance imaging [42]. Cerebrovascular disease often co-exists with AD, particularly in older patients[43].

Uremia effects on brain pathology: uremic toxins, inflammation, and oxidative stress

As kidney function diminishes, metabolic waste products or uremic toxins accumulate. Uremic toxins are generally divided into three groups: small water-soluble compounds, medium peptide compounds with a molecular weight more than 500 Dalton compounds, and protein bound compounds[44]. Over 100 uremic toxins have been identified[45]. The two most commonly studied bacterial-derived protein-bound uremic toxins include indoxyl sulfate (IS) and p-cresol sulfate (PCS)[45]. IS is derived from dietary tryptophan that is later metabolized by intestinal microbiota into indole which is then converted into IS by the liver and eliminated by the kidney. In non-CKD patients, serum IS concentration ranges between 0.1–2.39 µM whereas this number can exceed 500 µM in CKD patients[46]. PCS originates from dietary tyrosine (and phenylalanine) that is later metabolized by intestinal microbiota into p-cresol which is then converted into PCS by the liver. PCS is eliminated by the kidney. The conjugated form of PCS ($C_7H_8O_4S$) is found in the blood of CKD patients. Using ultra-performance liquid chromatography, serum PCS levels average 2.8 ± 1.7 mg/L in patients without kidney impairment and 21.8 ± 12.4 mg/L in CKD patients[46]. Both have been implicated in CI.

Uremic toxins can enter the brain via the blood–brain barrier (BBB) which is composed of endothelial cells, astrocytes, pericytes, and the extracellular matrix[47]. Typically, organic anion channel 3 (OAT3) shuttles protein-bound uremic toxins from he brain into the blood. It is widely believed that OAT3 malfunction leads to the accumulation of uremic toxins in the brain[44]. Therefore, metabolic wastes interact with brain cells, such as neurons and astrocytes, affecting the veins and trafficking them to other areas of the brain in individuals with reduced kidney function[47]. Others have hypothesized other issues with the BBB in patients with CKD. In a human study, brain derived neurotrophic factor, tight-junction protein claudin-5, occludin, and JAM-1 – all markers of an intact BBB - were decreased in CKD patients in comparison to healthy controls in peripheral fat tissue[48]. Zimmermann et al.[49] found evidence of IBA-1 positive microglia activation in the human prefrontal cortex. Collectively, these findings support several mechanisms by which brain injury may occur in CKD.

These multiple effects attributed to CKD are likely compounded in patients with brain dysfunction from other problems—particularly AD/AD related dementias, in which neuroinflammation, BBB dysfunction, vascular change are already presumed to contribute. The ultimate effects of this “double hit” may be additive or multiplicative, compounding neurodegeneration, accelerating cognitive declines, and compromising cognitive outcomes.

Below are several terms which the non-specialist may be unfamiliar with – I'd like to see you define them briefly e.g. a calcium permeable potassium channel or an endothelial cell line….

In vitro studies examining CKD-related brain injury

Several *in vitro* studies have investigated the effects of uremic toxins and states on brain cells, (**Table 2**), emphasizing the contributions of neuroinflammation, blood brain barrier dysfunction, and neuro-oxidative stress to CKD-related brain injury.

Neuroinflammation: Using a microglial SIM-A9 mouse cell line treated with CKD patient plasma, Zimmermann et al.[49] found increased IL-1β protein expression in comparison to control plasmas. Treatment with TRAM34, a $K_{Ca}3.1$-specific inhibitor, reduced protein IL-1β expression. In a C6 rat tumor astrocyte cell line, exposure to IS led to an increase in NF-kB activation. In primary mouse astrocytes and mixed glia?or neurons (astrocytes are glia) cells treated with IS, TNF-α levels increased in culture supernatants[50]. In C6 rat tumor brain cell line, after induction with lipopolysaccharide plus interferon, treatment with CKD patient plasma led to an increase in TNF-α protein levels [51]. A similar trend was seen in primary mouse astrocytes and mixed glia cells treated with IS where increases IL-6 was observed[51].

Blood brain barrier dis-integrity: Zimmermann et al.[49] treated bEnd.3 cells with CKD patient plasma. They identified increases in barrier permeability, as visualized by dextran entering the lower chamber, and by immunofluorescence staining, suggesting depletion?or dysfunction of endothelial cell monolayer. Fang et al.[52] found that in both human induced pluripotent brain microvascular endothelial cells and bEnd.3 cells treated with patient plasma and gut-derived uremic toxins (IS, PCS, and trimethylamine N-oxide), there were reductions to the trans-endothelial electrical resistance. This suggested impaired endothelial barrier function. Matsuki et al.[53] treated bEnd.3 cells with urea and found significant decreases in claudin-5 and CD31. Additionally, when bEnd.3 cells were treated with urea and a matrix metalloproteinase (MMP2?)

inhibitor, marimastat, there was an increase in claudin-5 . Matsuki et al.[50] concluded that urea altered BBB integrity through MMP2 activation.

***Neuro-oxidative stress**:* Watanabe et al.[54] investigated neuro-oxidative stress in a in HT-22 cells. In this system, several uremic toxins including IS, methylglyoxal, IAA, and indole significantly decreased levels of glutathione, an antioxidant. Also, IS significantly increased the protein expression of Nrf2 and mRNA expression of NADPH oxidase isoform 2– state the importance of this e.g., implicating ….. Adesso et al. [50] [51] found that CKD patient plasma and, more specifically, IS exposure resulted in increased ROS in C6 cells, astrocytes, and glial cells. Hence, using models designed to mimic a CKD-like environment, neuroinflammation, blood brain barrier dysfunction, and oxidative stress are induced, and may all contribute to brain injury *in vivo*.

In vivo (animal) studies examining CKD-related brain injury

Increasingly, knowledge of brain pathogenesis is being gained through studies involving experimental models of CKD (**Figure 2**). A variety of animal methods have been used to assess the effects of both uremic toxins (IS and PCS) and directly reduced kidney function. These include dietary measures with adenine rich diet (with or without IS injections) or surgical models inducing either 5/6 nephrectomy or unilateral nephrectomy with uremic toxin intraperitoneal injections. Importantly, recent studies have focused on AhR and employed conditional knockouts to eliminate the neuroinflammation, blood brain barrier disturbances, and cognitive impairment induced by CKD. Collectively, these murine CKD models primarily examined neurooxidative stress and neuroinflammation-related outcomes while a minority pursued cognitive assessments for neurobehavioral deficits or BBB dysfunction (**Table 3**).

***Neuroinflammation**:* Zimmerman et al.[49] employed a 5/6 nephrectomy mouse model and found cortices had increased activated caspase-1 and IL-1β levels in comparison to sham mice. Fang et al.[52] used an adenine-rich diet CKD model, which induced fibrosis in the kidneys in aged mice and found an increase microglia activation, without changes reactive astrocytes. Sun et al.[55], used a mouse model of unilateral nephrectomy with and without IS intraperitoneal injections, and found that IL-1β was increased in the prefrontal cortical tissue in mice treated with IS. Sun et al.[56] also used unilateral nephrectomy in a mouse model with and without PCS injections and found that BNDF was decreased, and that serum and prefrontal cortical tissue levels of IL-1β were increased. BDNF is important for neuronal cell survival, neurogenesis, and synaptic plasticity and BDNF reductions are associated with several neurodegenerative diseases[57]. Adesso et al.[50] found that IS injections significantly increased the serum levels of IL-6. Degaspari et al.[58] found that in a 5/6 nephrectomy in rats, only the cognitively impaired 5/6 nephrectomy rats had increased TNF-α and NF-κB binding activity in the hippocampus and frontal cortex of brain. Hencem, several lines of evidence implicate cytokine and cellular neuroinflammation may be induced in models of CKD.

***Neuro-oxidative stress**:* Utilizing an adenine-rich diet (why? What is its relevance to CKD), Sun et al.[59] found significant increases of ROS in the cerebral cortex of mice, including prefrontal regions, in both nephrectomy and PCS injections models.[55] Fujisaki et al.[60] found increased 8-OHdG what is this componund?immunoreactivity in the nuclei of hippocampal CA3 neurons, in a 5/6 nephrectomy model. A similar finding was reported by Haruyama et al.[61] using the same mouse model, hippocampal CA3? Also showed stronger immunoreactivity of 8-OHdG in CKD mice.

***Neurobehavioral deficits**:* Zimmermann et al.[49] in a 5/6 nephrectomy CKD mouse model identified cognitive deficits in comparison to age and sex matched sham controls. Notably, use of TRAM34 (triarylmethane-34) to suppress microglia potassium efflux in the 5/6 nephrectomy CKD mouse model resulted in improvements to cognition. In 5/6 nephrectomy CKD mice without IL-1R1 expression specifically in neurons through a CRE-LOXP mechanism, learning and memory was significantly improved in this mouse group. Anakinra, an IL-1R inhibitor, was given to 5/6 nephrectomy CKD mice and subsequent rescued cognition. Spatial working memory deficits were observed by Matsuki et al.[53] after administering 0.2% adenine diet for 6 weeks. Using a 5/6 nephrectomy CKD mouse model, Li et al.[62] found that IS increased in several brain regions as measured by high-performance liquid chromatography and found working memory deficits. Sun et al.[55] using a mouse model with a unilateral nephrectomy with and without IS injections observed behavioral abnormalities. Bobot et al. [63] used multiple models including adenine rich diet induced, 5/6 nephrectomy, and adenine rich diet plus IS overload to assess cognitive status changes. The rats on the adenine-based diet had significant cognitive deficits. Sun et al.[56] used mice with a unilateral nephrectomy with or without administration of PCS and it resulted in several neurobehavioral abnormalities. Both Fujisaki et al.[60] and Haruyama et al.[61] identified spatial working memory impairment in CKD.

***Blood brain barrier dis-integrity**:* Zimmermann et al.[49] in 5/6 nephrectomy mice found increased amount of Evans Blue dye in the brain tissue vs. controls, suggesting increased BBB permeability. Matsuki et al.[53] in mice fed an adenine-rich diet (0.2%) for 6 weeks found diffuse IgG in the subendothelial area of the hippocampus parenchyma, suggestive of a weakened BBB. Bobot et al.[63] in both rats fed an adenine-rich diet and in those undergoing 5/6 nephrectomy had higher levels of ^{99m}Tc-DTPA in the brain. ^{99m}Tc-DTPA is used as a marker of BBB permeability because in normal physiological conditions it cannot cross the BBB.

Interventions to improve CKD-associated CI in animal and cell models

A multitude of *in vitro* and *in vivo* studies have tested the efficacy of AST-120 (a charcoal adsorbent), CH-223191, TRAM34, anakinra, marimastat for their abilities to ameliorate the CKD-induced central nervous system damage (**Table 4**). These studies provided additional mechanistic insights and were the foundation for subsequent drug development for testing in human clinical trials.

Interventions to improve CKD-associated CI in humans

Several clinical trials have been performed to assess the impact of various interventions on cognition in kidney dysfunction (**Table 5**). Collectively, these interventions include exercise, B-vitamins, AST-120, valerian (agonist of adenosine A1 receptors), thiamin plus folic acid, and lanthanum (a phosphorus binder).

***Exercise interventions**:* Bradshaw et al.[64] previously reviewed the effects of exercise as an intervention for cognitive impairment in CKD. Otobe et al.[65] measured several different measures of cognition: MMSE, Wechsler Memory Scale-Revised Logical Memory, the Trail Making Test parts A and B, and the verbal fluency test. They found that a 26-week exercise intervention improved memory function in older adults with eGFR 15-59 mL/min/1.73m^2 in comparison to controls. Similarly, Sheshadri et al.[66] implemented a 3-month pedometer-based exercise intervention and assessed cognitive status via the Telephone Interview for Cognitive Status (TICS). They observed that participants with worse cognitive scores had less adherence to the program, fared worse in steps during the intervention, and post intervention did not perform as well in comparison to non-cognitively impaired patients.

***AST-120**:* AST-120 lowers IS levels through intestinal binding of indole, a precursor of IS, and is the most well-studied intervention for uremic toxin removal. Cha et al.[67] in a randomized controlled, parallel group, open-label, multicenter trial administered AST-120, an IS absorbent, to pre-dialysis CKD patients. Cha et al.[67] state that those who received the AST-120 intervention had increased kidney function and cognitive function (the exact cognitive measures used were not explicitly described in the paper). Although AST-120 received approval for delaying CKD progression in several Asian countries, it is currently not approved for use in the U.S.

Vitamins and herbal supplement interventions: Vitamins and supplements have also been explored for capacity to improve cognitive function in CKD patients. Lu et al.[68] implemented a thiamine and folic acid intervention in patients with ESRD and CI in a randomized, controlled, single-center study and measured their cognitive status via MoCA. Thiamin and folic acid treated patients had improved MoCA scores, with 72.7% of treated patients vs 6.2% patients in the placebo group had a MoCA score of at least 26 at week 96 (consistent with normal range cognitive function). In a 5-year multicenter randomized double-blind placebo controlled, Brady et al.[69] administered high dose B vitamins but did not witness differences in cognitive outcomes as measured by the modified TICS. In a randomized, crossover, double-blind clinical trial, Samaei et al.[70] used valerian, an herbal product, in hemodialysis patients. They found that 1-month administration of valerian significantly improved cognitive function as assessed by the MMSE.

Dialysis-related medication intervention: Altmann et al.[71] investigated lanthanum carbonate, a phosphate binder, in stage 5 CKD patients. They found that both lanthanum carbonate treated patients and those on standard therapy were shown to have worse cognitive outcomes at a 2-year follow-up.

Considerations for future kidney-brain axis investigations

Thus far, clinical trials in humans have produced limited improvement in cognition in patients with CKD. Additional investigations are needed to enhance understanding of the kidney-brain axis, perhaps through expansion of animal models used, and/or extension of focus to other untreated pathogenic processes.

Cellular senescence: Cellular senescence is a process in which cells are no longer able to proliferate due to being arrested in the G1 phase of the cell cycle and has a pivotal role in CKD pathogenesis[72]. Although cellular senescence has beneficial effects throughout the body, the CKD uremic milieu contributes to increased cellular senescence abundance and subsequent tissue damage. Senescent cells develop a senescence-associated secretory phenotype which propagates local and systemic inflammation[72]. A recent study examined the pro-senescence effects of protein-bound uremic toxins in CKD-animal models[73]. The interaction between neuro-senescence in patients with cognitive impairment due to AD/ADRD and CKD is unknown.

Alternative CKD animal models: Animal models to investigate neurological issues in CKD have been primarily limited to adult aged mice that have been induced with CKD via diet, surgery, and/or uremic toxin injections. In the future, studies could diversify the mouse models by incorporating models typically used in AD/ADRD research. For example, aged CKD mouse models may improve the translatability given that the majority of CKD patients are older individuals. Fang et al.[52] was the only study that used aged mice to induce CKD with a focus on neuroinflammation. However, no behavioral testing was completed. Further studies could allow for age-based difference assessments in CKD-associated CI with insights into neuro-oxidative stress changes and BBB disintegrity.

Conclusions

Cognitive impairment is common in patients with CKD generally and ESKD specifically. Multiple factors associated with CKD are also associated with AD/ADRD. The accumulation of uremic toxins and even the dialysis treatment may induce brain cell injury, diminish brain perfusion, and contribute to cognitive decline. Although kidney transplantation may restore impairments found in dialysis-dependent patients, frailty may nullify this potential benefit. Cell and animal models provide unique insights into the contributions of uremic toxins, organic anion transporters, and inflammatory pathways leading to neuroinflammation (activated microglia), neurooxidative stress, BBB integrity, and neurobehavioral abnormalities. Promising interventions in murine CKD models have not been replicated in human studies. However, exercise appears to have modest effects in dialysis-dependent patients. It is likely that additional pathogenic processes such as cellular senescence burden in the brain may be an untreated and underrecognized contributor in CKD. Future studies should examine this and other contributors which may also relate to aging processes. Nonetheless, the abundance of investigations in recent years have provided immense knowledge and forge the path to improve the lives of patients affected by CKD and CI.

FIGURES

TABLES

Beginning of landscape orientation mode
TABLES (see other document for tables until finalized)

End of landscape orientation mode

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