REVIEW ARTICLE

Cognitive disorders in patients with chronic kidney disease: Approaches to prevention and treatment

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Abstract

Background: Cognitive impairment is common in patients with chronic kidney disease (CKD), and early intervention may prevent the progression of this condition.

Methods: Here, we review interventions for the complications of CKD (anemia, secondary hyperparathyroidism, metabolic acidosis, harmful effects of dialysis, the accumulation of uremic toxins) and for prevention of vascular events, interventions that may potentially be protective against cognitive impairment. Furthermore, we discuss nonpharmacological and pharmacological methods to prevent cognitive impairment and/or minimize the latter's impact on CKD patients' daily lives.

Results: A particular attention on kidney function assessment is suggested during work-up for cognitive impairment. Different approaches are promising to reduce cognitive burden in patients with CKD but the availabe dedicated data are scarce.

Conclusions: There is a need for studies assessing the effect of interventions on the cognitive function of patients with CKD.

KEYWORDS
chronic kidney disease, cognition, dialysis, glomerular filtration rate, vascular risk factors

INTRODUCTION

Chronic kidney disease (CKD) is a major public health issue that affects >10% of the world's population. Previous studies have shown that relative to the general population, individuals with CKD have a substantially greater risk of developing cognitive impairment (CI) [1–3]. The prevalence of CI among people with CKD ranges from 10% to 40%, depending on the definition and assessment of CI and the CKD stage [4]. In older CKD patients (aged ≥66 years) on hemodialysis (HD), the lifetime risks of incident dementia and Alzheimer disease (AD) were estimated to be ~20% and ~4%, respectively [5]. Although a low estimated glomerular filtration rate (eGFR) and albuminuria are both risk factors for the development of CI, changes affecting cognitive function can occur early in the course of CKD [2]. When HD patients undergo systematic cognitive testing, the prevalence of normal cognitive function is typically very low. Physicians (and especially nephrologists, neurologists, and geriatricians) may have to confront this problem in their daily clinical practice. CI is common among individuals with CKD and is characterized by a range of symptoms and features, including memory, attention, and executive function deficits. Symptoms such as slowed processing speed, memory impairment, challenges with attention and concentration, and language and communication diffculties are frequently observed in this population [2, 6]. Diagnosis approaches for CI differ between patients with CKD and the normal population, as CKD patients may require specialized assessment tools to evaluate cognitive function, and contributing factors such as vascular issues, electrolyte imbalances, and uremic toxins need to be assessed. Likewise, treatment approaches for CI differ between patients with CKD and the normal population, considering that the primary focus is on effectively managing and slowing down the progression of kidney disease, while adjusting medication dosages based on kidney function, addressing contributing factors specific to CKD, and considering dialysis-related considerations are important. In the present narrative review, a multidisciplinary working group addressed the assessment of kidney function in patients with CI, therapeutic strategies for reducing the CI burden (whether related to CKD per se and its complications or to vascular factors) in patients with CKD, nonpharmacological options, and pharmacological strategies for treating neurocognitive disorders in patients with CKD.

### Assessment of kidney function in patients with CI

The prevalence of CI is 3 or 4 times greater in patients with CKD, especially those with end-stage kidney disease (ESKD) than in the general population [2, 7, 8]. Screening and identifying CKD in cognitively impaired subjects might have beneficial effects on either kidney function or cognitive function through multidisciplinary care.

For a diagnosis of CKD, several functional or structural criteria must have been present for >3 months. Patients with an eGFR <60 mL/min/1.73 m^2 or with albuminuria (urine albumin/creatinine ratio ≥ 30 mg/g or urine albumin ≥ 30 mg/day), hematuria (>10 erythrocytes in microscopic examination), or other structural abnormalities (e.g., polycystic kidney disease) and kidney transplant patients are classified as having CKD [9] (Figure 1).

The Kidney Disease–Improving Global Outcomes (KDIGO) expert group recommends using serum creatinine (SCr) or cystatin C-based equations for the initial estimation of the GFR. In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation replaced the Modification of Diet in Renal Disease equation because it was more accurate in adults [10]. The recent 2021 CKD-EPI equation no longer requires information on race to estimate GFR [11]. The European Kidney Function Consortium developed a SCr-full-age spectrum equation that also shows interesting performance in the European population [11, 12]. However, SCr-eGFR equations may be inaccurate, especially in patients with low lean mass, which is common in older adults. Equations that combine SCr and serum cystatin C values may be more accurate in such a context. To circumvent these limitations and when greater accuracy is required, the GFR can also be measured directly (e.g., using iohexol-based methods) [13]. Albuminuria is associated with a greater risk of kidney function decline. The literature data suggest that greater albuminuria (which is often missed, as it is not regularly assayed) is associated with a higher risk of mild cognitive impairment (MCI) or dementia; this observation strengthens the link between the kidney and the brain [14]. The spot urine albumin/creatinine ratio is acknowledged to be the best screening test; albuminuria is confirmed if the value is ≥30 mg/g (≥3 mg/mmol). Twenty-four-hour urine collection is a cumbersome procedure but constitutes the gold standard for measuring albuminuria and quantifying total protein excretion.

The GFR appears to decline by approximately 1 mL/min/1.73 m^2 per year after the 4th decade of life [15]. Whether this decline is a harmless consequence of aging or has implications for health is still subject to debate. Various researchers have suggested that not considering the age-related fall in GFR might lead to the erroneous diagnosis of CKD in some older patients. This is an important issue, given that most of the patients with CI are aged 65 years or older. A recent population-based cohort study of 208,341 adults showed that age adjustment minimized the inclusion of healthy older adults in CKD cohorts [16]. In contrast, KDIGO does not recommend using different thresholds for the diagnosis of CKD in older patients [17]. The KDIGO guidelines are based on the results of a meta-analysis covering 2,051,244 people over the period 1972–2011, where the risks of death and ESKD risks were higher at a lower eGFR and a higher albuminuria value in every age category. Therefore, the utility of changing the eGFR threshold for the diagnosis of CKD in older patients warrants further investigation.

The early referral of CKD patients to a nephrologist >16 weeks before the initiation of renal replacement therapy is known to be beneficial for reducing the mortality rate [18]. According to the KDIGO guidelines, patients meeting one of the following criteria should be referred to a specialist kidney care service: acute kidney injury, eGFR <30/mL/min, rapid progression of CKD (eGFR decline >5 mL/min/1.73 m^2/year), severe albuminuria (urine albumin creatinine ratio >300 mg/g), urinary sediment abnormalities (urine red cell casts >20), treatment-refractory hypertension, recurrent or extensive nephrolithiasis, and hereditary kidney disease [19]. Screening for CKD is suggested to be cost-effective in patients with diabetes or hypertension and in populations with higher incidence of CKD, such as older adults [20].
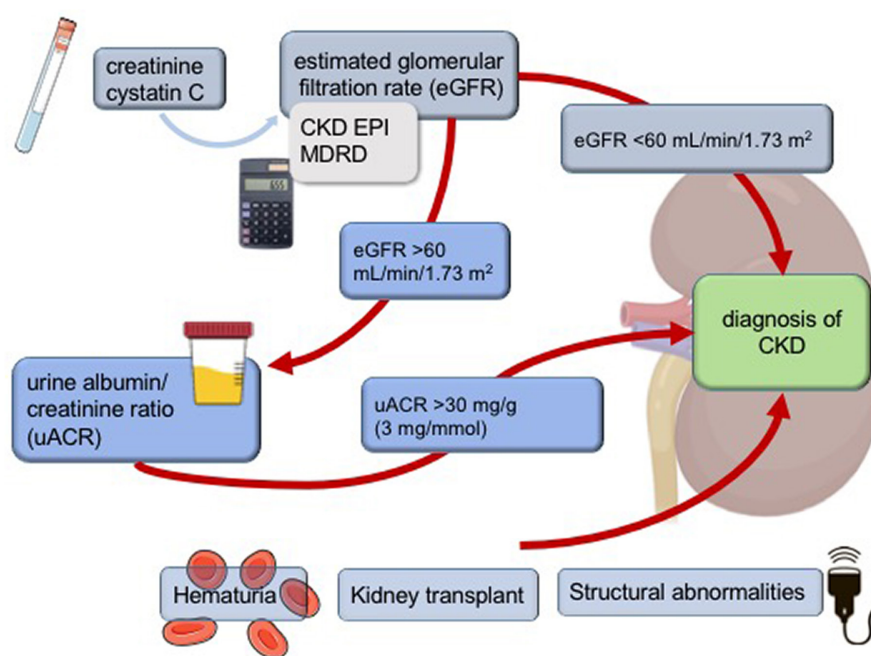
FIGURE 1 Diagnosis of chronic kidney disease. CKD, chronic kidney disease; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

Treating CKD and its complications, with a view to preventing CI

Anemia and iron deficiency

Anemia is common in CKD and is associated with a greater incidence of stroke and CI [21]. Cause-and-effect relationships are difficult to assess, because it is not clear whether anemia affects cognition directly (perhaps through decreased perfusion/oxygenation) and/or indirectly (by increasing the risk of cerebrovascular events, including stroke) or whether it is simply a sign of a higher risk phenotype for comorbid conditions, including CI. In patients with CKD, the correction of anemia from low values (<9 g/dL) improves several aspects of quality of life (including breathlessness and physical performance), which in turn may be beneficial for cognitive function.

Unfortunately, treatment with erythropoiesis-stimulating agents (ESAs) appears to be complex and may potentially be harmful (with a greater risk of stroke) if the hemoglobin target threshold is too high (13.5 g/dL) [22]. The neuroprotective effect of ESAs is associated with biological activities (e.g., preservation of the blood–brain barrier's activity, neurotrophic effects) other than the hematocrit or blood hemoglobin level per se. This property was shown to persist in a rodent model treated with a nonerythropoietic cytokine (asialoerythropoietin, a recombinant human erythropoietin that did not increase the hematocrit) [23]. There are currently no data to recommend a target level of hemoglobin for reducing the risk of incident CI in patients with CKD. KDIGO estimates that it is reasonable to use ESA therapy to maintain hemoglobin values of between 10 and 12 g/dL; the exact target value in this range is chosen as a function of the patient's comorbidities [24].

Hypoxia-inducible factor prolyl hydroxylase enzyme inhibitors are a new class of drugs for treating anemia in both nondialysis and dialysis patients and have already been approved in some countries (e.g., Japan and China). These inhibitors mimic the human response to hypoxia and thus induce the expression of a wide range of genes. In the central nervous system, neuroprotective hypoxia-inducible factors are involved in neurogenesis, nerve cell differentiation, neuronal apoptosis, and oxidative stress reduction. The potential benefits of these drugs on stroke or MCI require further investigation [25].

Iron deficiency anemia is frequent in patients with CKD. Symptoms like fatigability, cold intolerance, inability to concentrate, and effort intolerance are often attributed to anemia or uremia. However, it is rarely recognized that iron deficiency per se can also cause these symptoms. Iron has an important role in neurotransmitter synthesis, uptake, and degradation. The results of some studies have suggested that iron supplementation has an effect on the improvement of cognitive performance, independently of anemia correction [26]. Dedicated studies on the link between iron deficiency and cognitive dysfunction in patients with CKD are lacking. Nevertheless, investigators recently observed that serum levels of iron storage biomarkers (such as transferrin saturation index and ferritin) are associated with cardiovascular events, all-cause mortality, and worse health-related quality of life in nondialyzed patients with CKD (either with or without anemia) [27].

Hyperparathyroidism and vitamin D deficiency

An inverse correlation between higher serum parathyroid hormone levels and poorer cognitive function has been observed in the general population, although the level of evidence was variable [28]. Secondary hyperparathyroidism can potentially interfere with neurotransmission by increasing calcium levels in the brain; hence, controlling secondary hyperparathyroidism with calcimimetics might help to improve cognitive function [29]. According to a recent study that assessed the risk of dementia in older patients (age ≥66 years) with secondary hyperparathyroidism (SHPT), it was found that treatment for SHPT was linked to a 42% lower risk of dementia compared to untreated SHPT patients (adjusted hazard ratio=of 0.58, 95% confidence interval=0.56–0.59) [30].

Although patients with CKD often have vitamin D deficiency, supplementation should be initiated with caution and with regard to parathyroid hormone levels. Vitamin D has neuroprotective and regulatory activities in the central nervous system. A meta-analysis by Balion et al. [31] showed that a serum 25-hydroxyvitamin D level of <20 ng/mL is associated with poorer cognitive performance. However, studies of the putative long-term effects of native vitamin D supplementation on cognitive function in CKD are lacking.

Dialysis modalities

The dialysis modality has been implicated in the development of CI. HD (particularly with a higher blood flow rate) results in rapid hemodynamic shifts, which in turn are associated with brain injury. Moreover, HD sessions may be responsible for wide swings in blood pressure (BP), and intradialytic hypotension might contribute to ischemia and cerebral atrophy [32]. Initiation of HD in patients older than 65 years was associated with an average 10% fall in cerebral blood flow and a decline at every measured site in the brain [33]. Moreover, greater decreases in cerebral blood flow were associated with worse cognitive function, together with the progression of white matter disease on magnetic resonance imaging (MRI) [34]. Peritoneal dialysis (PD) supposedly generates gentler fluid shifts than HD and does not usually require the administration of anticoagulants. In principle, PD does not expose the patient to recurrent hypotension and so should be associated with less frequent and less severe brain damage. However, there are no published data on cerebral blood flow in patients during PD. The hypothesis whereby PD preserves cognitive function (relative to HD) is supported by observational studies [35].

Because higher dialysate temperatures, ultrafiltration rates, and volumes are associated with lower cerebral blood flow [32,

34], the maintenance of stable cerebral blood flow during dialysis might help to protect cognitive function. Dialysate cooling is one of the inexpensive, simple, and beneficial interventions for slowing CI by partially preventing the decrease in brain blood flow and repetitive brain injury that occur during HD sessions [32, 34]. Using diffusion tensor MRI, significant brain white matter changes were observed in a "warmer dialysate" (37°C) group but not in a "cooler dialysate" group (0.5°C below the core body temperature) 1 year after the initiation of dialysis treatment [36]. A randomized controlled trial (RCT) found that cool dialysate was associated with less baroreflex variability and less intradialytic hypotension, and a systematic review and meta-analysis showed that cooling the dialysate leads to a 70% reduction in intradialytic hypotension, a reduction that could be improved further by lengthening the HD session [37]. There is no direct evidence of an improvement in cognitive function with longer or more frequent HD sessions, although some studies have observed an improvement in quality of life and physical performance (especially with nocturnal HD) [38]. Hence, nocturnal HD or the use of cooled dialysate might be promising methods for reducing the impact of HD on the patient's neurocognitive functions and quality of life.

Uremic toxin removal

Uremic toxins are harmful compounds that accumulate in the body as kidney function declines. Some toxins (such as indoxyl sulfate) appear to be linked to the higher prevalence of cerebrovascular manifestations in patients with CKD. The putative effect of drugs that modulate uremic toxin concentrations (e.g., the administration of intestinal chelators) on neurological outcomes has yet to be assessed in robust, well-designed clinical trials [39]. Hence, it remains to be seen whether new dialysis techniques or better methods for removing protein-bound uremic toxins might reduce the neurologic signs and symptoms that frequently affect patients on HD [39].

Electrolyte abnormalities and acid–base metabolism

Electrolyte disturbances (especially hyponatremia) are more frequent in patients with CKD than in the general population. Hyponatremia is independently associated with cognitive performance in CKD patients on PD [40]. The plasma sodium level was also found to be associated with depressive symptoms and CI in HD patients [41]. Moreover, it is possible that the metabolic acidosis that characterizes patients with CKD has an effect on cognitive ability, although there are currently few studies on this subject [42]. What is surprising, however, is the lack of correlation between the prevalence of MCI and that of metabolic acidosis, especially in the later stages of CKD [43]. The central nervous system might therefore operate an effective buffering system that prevents large changes in pH and mitigates the latter's cellular effects.

Sleep disturbances and depression

Sleep disturbances and/or depression are frequent in patients with CKD. Both of these conditions have negative effects on cognitive performance [44]. Sleep-disordered breathing, commonly known as sleep apnea, is widely prevalent among individuals with CKD and has been observed to impact cognitive testing in CKD patients, leading to detrimental effects on cognitive functioning [45, 46]. The glymphatic (paravascular) pathway clears waste from the central nervous system. The glymphatic clearance of waste products occurs primarily during sleep and is altered by depression and neuroinflammation [47]. Given the endothelial dysfunction and the relatively high incidence of sleep alterations and depression observed in CKD, it is likely that glymphatic fluid transport is suppressed and that potentially neurotoxic waste products accumulate in the brain [47]. The evidence base for improving sleep quality and related outcomes using medications such as benzodiazepines, melatonin, and dopaminergic agonists for adults with CKD is sparse. Most of the trials included in a recent Cochrane review reported no difference in sleep quality among the comparison groups. Similarly, pharmacological interventions for depression in CKD or ESKD patients did not show convincing efficacy in reducing depressive symptoms [48]. However, psychological interventions such as cognitive–behavioral therapy are more promising [49].

Therapeutic strategies for preventing CI associated with vascular factors

Patients with CKD have an increased risk of poor cerebrovascular outcomes (including ischemic and hemorrhagic stroke, vascular CI, and dementia) and are also more susceptible to common cardiovascular and cerebrovascular risk factors (such as hypertension, diabetes mellitus, atrial fibrillation, uremia, oxidative stress, and mineral and bone disorders). However, it is important to note that antiplatelet treatment or oral anticoagulation is not recommended with the sole objective of preventing cognitive decline in patients with CKD. There is a lack of RCTs specifically focused on preventing cerebrovascular complications in CKD populations, and most of the available data on drug treatments are derived from post hoc or subgroup analyses conducted within studies that primarily examined other endpoints.

Antiplatelet agents

An RCT on patients with stage 3b–5 CKD did not find a significant benefit (with regard to stroke) of taking 75 mg acetylsalicylic acid daily. However, subgroup analyses showed that cardiovascular events (including stroke) were significantly less frequent in patients with an eGFR < 45 mL/min/1.73 m^2 treated with acetylsalicylic acid [50]. A meta-analysis of trials evaluating the efficacy of antiplatelet therapy on the cardiovascular risk in high-risk patients (including

those with ESKD) showed that acetylsalicylic acid reduced the incidence of major cardiovascular events (including nonfatal stroke) in HD patients by 41% (risk ratio = 0.59, 95% confidence interval = 0.40–0.89), although this benefit was outweighed by the risk of additional major bleeding [51]. The bleeding risk associated with antithrombotic agents increases as kidney function decreases, especially when the antiplatelet agents are combined with oral anticoagulants [52]. The recently published results of the ASPREE trial (comparing 100 mg of enteric-coated acetylsalicylic acid daily with placebo for the prevention of dementia, persistent physical disability, or death in community-dwelling older adults in Australia and the United States) were disappointing and showed no benefit in the composite endpoint in CKD and non-CKD groups [53]. Treatment with clopidogrel (as an add-on to acetylsalicylic acid) has no clear benefit in CKD; this is probably due to the high prevalence of clopidogrel resistance (up to 50%–80% in patients with ESKD). RCTs and large cohort studies of CKD populations have failed to show a beneficial effect of clopidogrel on stroke risk [54]. In Europe and the United States, the guidelines issued by KDIGO, the UK National Institute for Health and Care Excellence, and the American Heart Association/American Stroke Association recommend the use of acetylsalicylic acid only for the secondary prevention of stroke in CKD [55]. Recent published data suggested a beneficial effect of acetylsalicylic acid in primary prevention of cardiovascular disease in people with moderate to advanced stage CKD [56].

Oral anticoagulants

Use of oral anticoagulation is beneficial for stroke prevention in individuals with atrial fibrillation, in either the general population or patients with moderate CKD. However, high-quality randomized data in patients with advanced CKD or ESKD are lacking. Observational studies of patients on dialysis have shown that the risk of stroke or systemic embolism is lower in individuals receiving warfarin than in individuals not receiving antithrombotic drugs. In ESKD, the incidence of major bleeding was lower for patients on apixaban than for patients on warfarin. However, these observational studies had some major limitations, such as selection bias and confounding by indication. A meta-analysis that included observational studies showed that the incidence of major bleeding was higher in dialysis patients on oral anticoagulants than in patients not taking anticoagulants [57]. Warfarin is also associated with calciphylaxis, a vascular calcification syndrome probably due to a warfarin-induced deficiency in vitamin K-dependent calcification inhibitors. Use of warfarin in this setting may thus be hard to justify for most patients with KD. Direct oral anticoagulants (DOACs) appear to have more favorable safety and efficacy profiles in CKD, relative to vitamin K antagonists. A meta-analysis of 11 trials demonstrated the superiority of high-dose DOACs over vitamin K antagonists with regard to stroke and all-cause mortality in patients with CKD and a creatinine clearance rate > 25 mL/min [58]. However, a recent report on the international CKDopps cohort found a low prescription rate for DOACs (relative to warfarin) in CKD stage 3–5 patients [59]. The use of DOACs also appears to be effective and safe (with fewer bleeding complications) in patients with ESKD [60, 61]. It should nevertheless be noted that (i) the various DOACs differ with regard to their renal elimination, (ii) dose adjustment is probably necessary, and (iii) DOACs are often compared with warfarin only. In a recently published observational study, apixaban was not associated with a lower incidence of stroke in dialysis patients (relative to no anticoagulation) but was associated with a higher incidence of fatal or intracranial bleeding [62]. KDIGO does not recommend the routine initiation of anticoagulation for protection against embolism in patients with ESKD [63]. A new version of these guidelines is currently open to public discussion.

BP-lowering treatments

Several studies of the general population have shown that antihypertensive therapies and BP control are effective in reducing the incidence and/or delaying the progression of cognitive decline [64]. However, data on the effect of BP-lowering drugs on cognition in patients with CKD are scarce. The KDIGO 2021 Clinical Practice Guideline on the Management of Blood Pressure in CKD has recommended a systolic BP target of <120 mmHg in CKD for primary and secondary prevention (when tolerated), using standardized office BP measurements. This recommendation was influenced by a subgroup analysis of the results of SPRINT (Systolic Blood Pressure Intervention Trial), in which targeting a systolic BP of <120 mmHg (compared with <140 mmHg) was associated with lower rates of major cardiovascular events and all-cause death in patients with CKD [65]. The optimum BP target in ESKD has not been determined, and it remains to be seen whether some classes of antihypertensive drugs are more beneficial than others for cognitive outcomes. In a recently published retrospective cohort study of 21,208 patients in the Taiwan nationwide database with 11 years of follow-up, angiotensin receptor blockers exerted a significant protective effect (hazard ratio = 0.578, 95% confidence interval = 0.520–0.643) on the incidence of dementia in hypertensive patients with CKD [66]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers might help to limit cognitive decline through BP control, albuminuria reduction, or other beneficial effects on vascular health [4, 14]. The controversial issue here is that brain ACE also catabolizes cognition-enhancing brain peptides and amyloid peptides; for example, it converts toxic Aβ42 into less toxic Aβ40. Therefore, an association between ACE inhibitors and a greater long-term Aβ42 brain burden cannot be ruled out [67].

Lipid-lowering drugs

The efficacy of statin therapy for the primary prevention of stroke in patients with CKD was demonstrated in the SHARP (Study of Heart and Renal Protection) trial; the risk of ischemic stroke was 25% lower in CKD patients treated with a combination of

simvastatin and ezetimibe [68]. However, statins have little or no beneficial effect on stroke or other cardiovascular events in dialysis patients, despite the observation of a clinically relevant reduction in serum cholesterol levels [69]. KDIGO recommends statin/ezetimibe treatments in adults ≥50 years old with an eGFR <60 mL/min per 1.73 m^2 without renal replacement therapy; it is also suggested in dialysis patients if initiated before dialysis start and in kidney transplant recipients if well tolerated [70]. The statins' impact on cognitive functions has not been clearly determined, and the results of RCTs and well-conducted observational studies do not support a causal effect of late-life statin use on the prevention of cognitive decline [71]. Studies with a focus on CKD are scarce, and the few such studies had small sample sizes. A monoclonal anti-PCSK9 antibody (evolocumab) was found to have no effect on cognition in the EBBINGHAUS study, an ancillary study to the FOURIER trial that included approximately 16% of the total number of patients with an eGFR <60 mL/min/1.73 m^2 [72].

Antidiabetic agents

In people with diabetes, the pathophysiology of cognitive decline can involve several interrelated factors. Both hyperglycemia and hypoglycemia have detrimental effects on cognition [73]. There are few data on a putative beneficial effect on cognition of glycemia control, even though some interventions are known to improve kidney-related outcomes (e.g., albuminuria). The results of preclinical studies of antidiabetic agents have suggested that these drugs have neuroprotective effects, although the clinical results on cognition are conflicting. SGLT-2 inhibitors were associated with a lower risk of major adverse cardiac events (particularly heart failure) in diabetic or nondiabetic patients with CKD but not with a lower risk of stroke [74]. There are other examples for antidiabetic drugs with pleiotropic effects that may confer benefits in cognition. Among them, pioglitazone, a synthetic ligand of peroxisome proliferator-activated receptors, and liraglutide, a GLP-1 receptor agonist, have shown neuroprotective effects by diminishing the cognitive decline in experimental and observational studies in humans [75, 76]. Future clinical studies of antidiabetic agents and cognitive function might benefit from measuring albuminuria and kidney function [73].

Nonpharmacological interventions

Lifestyle modifications may help to prevent CI in both the general population and patients with CKD. These modifications might be easier to achieve and safer in late-stage CKD, when compared with the already high drug burden and elevated risk of adverse drug reactions in these patients. To date, several nonpharmacological approaches have demonstrated their potential to reduce CI or minimize its effects on daily functioning and well-being in patients with chronic diseases.

Physical activity

In healthy subjects, neuronal plasticity is accentuated by physical activity (PA) via various phenomena: (i) neurotrophic signaling through an increase in the production of brain-derived neurotrophic factors; (ii) neurogenesis, as animal studies have demonstrated that PA increases neurogenesis in the dentate gyrus of the hippocampus; and (iii) a reduction in levels of proinflammatory/pro-oxidant factors.

The literature data emphasize that PA is one of the most appropriate nonpharmacological tools for preventing cognitive decline. The key role of PA has been demonstrated by several meta-analyses in which exercise improved attention, processing speed, memory, working memory, and executive function and protected against cognitive decline [77, 78]. Approaches such as aerobic exercise training and resistance training were associated with better cognitive performance and related outcomes in adults with MCI, stroke, traumatic brain injury, or other neurological disorders [79, 80]. However, some of these research studies were limited by poor methodological quality and a high risk of various types of bias, and so well-designed, larger studies are now needed to accurately determine the effectiveness of the aforementioned interventions [80].

The impact of exercise on cognitive function in patients with CKD remains uncertain, and there is a scarcity of published data in this area. In a small-scale, nonrandomized study of a population of dialysis patients, exercise training was associated with better cognitive function (as judged by the Modified Mini-Mental State Examination score) [81]. Similarly, a small pilot RCT in HD patients showed that intradialytic aerobic training three times per week for 4 months led to significant improvements in cognitive function and basilar blood flow velocity [82]. Preliminary findings from another pilot RCT indicated that cognitive decline in psychomotor speed and executive function (as assessed with the Modified Mini-Mental State Examination and the Trail Making Test) might be prevented by intradialytic cognitive and exercise training [83]. Another 6-month, randomized, multicenter trial looked at whether a simple, home-based, personalized walking exercise program could improve functional status in adult patients on dialysis; the self-reported cognitive function and quality of social interaction scores were dramatically higher in the exercise arm than in the control arm [84]. In contrast, a recent RCT designed to probe the possible effects of a home-based exercise program on physical functioning and health-related quality of life in PD patients did not find any significant differences in cognitive function between the exercise group and the standard of care group [85]. In a study of a small number of nondialyzed patients with CKD stage 3–4, a 24-week exercise program was associated with better memory function in older adults [86].

Cognitive stimulation

Cognitive training is another promising nonpharmacological intervention for slowing the decline in executive function. Attention process training and computerized cognitive training are efficacious

TABLE 1 Available drugs for AD and dose adjustments with regard to kidney function [105].

Drug class	Indications	Maintenance dose	Dose adjustment in CKD	Comments	Common adverse drug reactions
Cholinesterase inhibitors					
Donepezil	Mild-to-moderate AD	Mild-to-moderate AD: 5 or 10 mg daily	Mild-to-severe renal impairment: no dose level adjustment necessary	Most likely to be titrated to the maximum dose	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
		Moderate to severe AD: 10 or 23 mg daily	HD or PD: no supplemental dose or dose level adjustment necessary	Easy to use because of the once-daily dosing	
Galantamine	Mild-to-moderate AD	16–24 mg daily	Mild renal impairment: no dose adjustment		Nausea, vomiting, bradycardia, syncope, dizziness, headache, depression, fatigue, drowsiness, lethargy, weight loss, loss of appetite, dyspepsia, tremor, muscle spasm
			Moderate renal impairment (CrCl = 9–59 mL/min): max dose 16 mg daily		
			Severe impairment (CrCl < 9 mL/min): use is not recommended		
Rivastigmine [103]	Mild-to-moderate AD and Parkinson disease dementia	Oral: effective dose 3 to 6 mg, twice daily; maximum dose: 6 mg, twice daily	No dose adjustment necessary	Transdermal patch is preferred (better tolerated with similar efficacy)	Dizziness, headache, somnolence, tremor, anorexia, loss of appetite, weight loss, nausea, vomiting, diarrhea, abdominal pain, dyspepsia, hyperhidrosis, nightmares, agitation, confusion, anxiety, asthenia, bradycardia
		Transdermal patch: dosage 4.6 mg or 9.5 mg once daily; maximum dosage (in some countries) 13.3 mg per 24-h patch, applied once daily			
N-methyl-D-aspartate receptor antagonist					
Memantine [104]	Moderate-to-severe AD	Maximum dose: 20 mg/day	Mild renal impairment: no dose adjustment	Add-on to cholinesterase inhibitors	Hypertension, drug hypersensitivity, constipation, dizziness, balance disorders, somnolence, headache, dyspnea, elevated transaminases
			Moderate impairment (CrCl = 30 to 49 mL/min): 10 mg per day, increased to 20 mg/day after 7 days if well tolerated		
			Severe impairment (CrCl = 5 to 29 mL/min): 10 mg per day		

Abbreviations: AD, Alzheimer disease; CrCl, creatinine clearance (Cockcroft–Gault formula); HD, hemodialysis; PD, peritoneal dialysis.

in improving performance in neurocognitive tests in the laboratory; however, the interventions' effects on real-world functioning are less clear [87]. Cognitive rehabilitation interventions (including problem-solving training and memory notebook training) have given positive results in diverse clinical populations, such as people with AD, MCI, acquired brain injury, and other chronic medical conditions affecting cognitive function [87, 88]. In the FINGER RCT, a multidomain intervention that included cognitive training showed a beneficial effect on cognitive functioning at 2 years [89].

Interventions that combine cognitive and physical stimulation are promising for preserving cognition in patients with ESKD. An RCT is currently looking at whether intradialytic combined cognitive and exercise training can efficaciously preserve cognitive health [90]. One can assume that stimulation of this type improves cognitive performance by reducing depressive symptoms and improving quality of life [44].

Although several nonpharmacological approaches are available, it is unfortunate that very few studies have focused on or reported on cognitive outcomes in patients with CKD. Further research is needed to evaluate the potential benefits of nonpharmacological interventions, such as healthy diet (i.e., Mediterranean diet) [91] and dietary interventions like low-protein diets, on gut-derived uremic toxins in CKD patients [92].

Pharmacological interventions

The use of certain drugs may have an (indirect) adverse effect on cognitive function in patients with CKD. The latter have a substantial comorbidity burden, which often results in polypharmacy [93]. Some drugs frequently taken by patients with CKD (such as antidepressants, benzodiazepines, opiates, and drugs with anticholinergic properties) are known to aggravate cognitive disorders or to induce dizziness, sedation, confusion, and delirium. Specific risk scales have been developed for assessment of the anticholinergic medication burden in older adults [94]. A post hoc analysis of the ASPREE study (which included 25% of patients with CKD) observed that anticholinergic burden was associated with cognitive decline during 5 years of follow-up [95].

Drugs indicated in cases of AD dementia (or for some drugs in cases of Parkinson disease dementia or Lewy body dementia) include cholinesterase inhibitors (ChEis; donepezil, galantamine, and rivastigmine) and an N-methyl-D-aspartate receptor antagonist (memantine; Table 1). All of the ChEis were efficacious (vs. placebo) for cognitive performance and activities of daily living in patients with AD [96]. In vascular CI, these drugs are not recommended, because the effects were modest and severe adverse events were observed [97]. Data from the Swedish Dementia registry on long-term effects of ChEi treatment showed that the associated cognitive benefits were modest but persisted over time and were associated with a lower mortality rate. Another study in Sweden found that ChEi use was associated with a lower risk of myocardial infarction and death in a nationwide cohort of people diagnosed with AD [98]. Unfortunately, these studies did not provide specific information on kidney function. A causal effect

of ChEis remains to be demonstrated, especially because cardiac adverse events are associated with the use of ChEis and memantine [99, 100]. The choice of a drug is more difficult in patients with impaired renal function, because few studies have addressed the issue of dose adjustment (Table 1). In the absence of studies in a CKD setting, the drug treatment should be selected on a patient-by-patient basis, and according to the most likely underlying etiology (in that sense, fluid or imaging biomarkers of amyloidosis and neurodegeneration might help for a more accurate diagnosis and treatment). CKD is another reason for improving the safety of drug dispensation (by a close relative or a nurse), because patients with CKD are presumably more likely to experience severe adverse events. Inflammation and autonomic dysfunction are prevalent in CKD and ESKD and contribute to a markedly greater risk of death. The cholinergic anti-inflammatory pathway is a vagal neuroimmune circuit that maintains the homoeostatic balance of inflammatory activity [101]. Ex vivo experiments have shown that the cholinergic anti-inflammatory pathway is still functional in dialysis patients with inflammation and autonomic dysfunction. Controlling inflammation by neuroimmune modulation (including ChEi use and vagus nerve stimulation) might lead to new treatment options and might decrease underlying chronic inflammation and thus neuronal stress in both CKD and dementia [101, 102].

CONCLUSIONS

Patients with CKD have an elevated risk of cognitive decline. We suggest that kidney function tests should be included in a comprehensive assessment of patients presenting CI, especially in older individuals. The modification of cardiovascular risk factors and the correction of complications of CKD (such as anemia, hyperparathyroidism, and the accumulation of uremic toxins) are reasonable measures that might limit cognitive deterioration. Promoting PA and cognitive stimulation is a low-risk strategy for slowing cognitive decline, although evidence of efficacy in patients with CKD is lacking. Future studies should be conducted to examine the relationship between exercise and cognitive function in individuals with CKD, while also providing detailed information on the specific cognitive domains that may be improved. Likewise, robust data on the efficacy and safety of pharmacological interventions for dementia among patients with CKD are scarce. The use of drugs with anticholinergic activity must be carefully evaluated, because these compounds are associated with an elevated risk of cognitive decline. New dialysis methods and stimulation of the cholinergic anti-inflammatory pathway by pharmacological or nonpharmacological means might help to reduce the cognitive burden in patients with ESKD, although further research is needed to confirm the potential benefits.

CONFLICT OF INTEREST STATEMENT

FUNDING INFORMATION

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Etgen T, Chonchol M, Förstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol.* 2012;35(5):474-482. doi:10.1159/000338135
2. Berger I, Wu S, Masson P, et al. Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med.* 2016;14(1):206. doi:10.1186/s12916-016-0745-9
3. O'Lone E, Connors M, Masson P, et al. Cognition in people with end-stage kidney disease treated with hemodialysis: a systematic review and meta-analysis. *Am J Kidney Dis.* 2016;67(6):925-935. doi:10.1053/j.ajkd.2015.12.028
4. Drew DA, Weiner DE, Sarnak MJ. Cognitive impairment in CKD: pathophysiology, management, and prevention. *Am J Kidney Dis.* 2019;74:782-790. doi:10.1053/j.ajkd.2019.05.017
5. McAdams-DeMarco MA, Daubresse M, Bae S, Gross AL, Carlson MC, Segev DL. Dementia, Alzheimer's disease, and mortality after hemodialysis initiation. *Clin J Am Soc Nephrol.* 2018;13(9):1339-1347. doi:10.2215/CJN.10150917
6. Torres RV, Elias MF, Seliger S, Davey A, Robbins MA. Risk for cognitive impairment across 22 measures of cognitive ability in early-stage chronic kidney disease. *Nephrol Dial Transplant.* 2017;32(2):299-306. doi:10.1093/ndt/gfw005
7. Sarnak MJ, Tighiouart H, Scott TM, et al. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. *Neurology.* 2013;80(5):471-480. doi:10.1212/WNL.0b013e31827f0f7f
8. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis.* 2008;15(2):123-132. doi:10.1053/j.ackd.2008.01.010
9. Lameire NH, Levin A, Kellum JA, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a kidney disease: improving global outcomes (KDIGO) consensus conference. *Kidney Int.* 2021;100(3):516-526. doi:10.1016/j.kint.2021.06.028
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006
11. Gansevoort RT, Anders HJ, Cozzolino M, et al. What should European nephrology do with the new CKD-EPI equation? *Nephrol Dial Transplant.* 2022;38(1):1-6. doi:10.1093/ndt/gfac254
12. Pottel H, Björk J, Courbebaisse M, et al. Development and validation of a modified full age Spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. *Ann Intern Med.* 2021;174(2):183-191. doi:10.7326/M20-4366
13. Delanaye P, Ebert N, Melsom T, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? *Clin Kidney J.* 2016;9(5):682-699. doi:10.1093/ckj/sfw070
14. Bikbov B, Soler MJ, Pešić V, et al. Albuminuria as a risk factor for mild cognitive impairment and dementia-what is the evidence? *Nephrol Dial Transplant.* 2021;37:gfab261. doi:10.1093/ndt/gfab261
15. Waas T, Schulz A, Lotz J, et al. Distribution of estimated glomerular filtration rate and determinants of its age dependent loss in a German population-based study. *Sci Rep.* 2021;11(1):10165. doi:10.1038/s41598-021-89442-7
16. Liu P, Quinn RR, Lam NN, et al. Accounting for age in the definition of chronic kidney disease. *JAMA Intern Med.* 2021;181(10):1359-1366. doi:10.1001/jamainternmed.2021.4813
17. Coresh J, Gansevoort RT, CKD Prognosis Consortium, Levin A, Jadoul M. KDIGO. Current CKD definition takes into account both relative and absolute risk. *J Am Soc Nephrol.* 2020;31(2):447-448. doi:10.1681/ASN.2019101049
18. Hommel K, Madsen M, Kamper AL. The importance of early referral for the treatment of chronic kidney disease: a Danish nationwide cohort study. *BMC Nephrol.* 2012;13:108. doi:10.1186/1471-2369-13-108
19. Shlipak MG, Tummalapalli SL, Boulware LE, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int.* 2021;99(1):34-47. doi:10.1016/j.kint.2020.10.012
20. Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. *Am J Kidney Dis.* 2014;63(5):789-797. doi:10.1053/j.ajkd.2013.12.012
21. Kurella Tamura M, Xie D, Yaffe K, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the chronic

renal insufficiency cohort (CRIC) study. *Clin J Am Soc Nephrol.* 2011;6(2):248-256. doi:10.2215/CJN.02660310

22. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006;355(20):2085-2098. doi:10.1056/NEJMoa065485

23. Jarero-Basulto JJ, Rivera-Cervantes MC, Gasca-Martínez D, García-Sierra F, Gasca-Martínez Y, Beas-Zárate C. Current evidence on the protective effects of recombinant human erythropoietin and its molecular variants against pathological hallmarks of Alzheimer's disease. *Pharmaceuticals (Basel).* 2020;13(12):E424. doi:10.3390/ph13120424

24. Locatelli F, Bárány P, Covic A, et al. Kidney disease: improving global outcomes guidelines on anaemia management in chronic kidney disease: a European renal best practice position statement. *Nephrol Dial Transplant.* 2013;28(6):1346-1359. doi:10.1093/ndt/gft033

25. Iyalomhe O, Swierczek S, Enwerem N, et al. The role of hypoxia-inducible factor 1 in mild cognitive impairment. *Cell Mol Neurobiol.* 2017;37(6):969-977. doi:10.1007/s10571-016-0440-6

26. Agarwal R. Nonhematological benefits of iron. *Am J Nephrol.* 2007;27(6):565-571. doi:10.1159/000107927

27. Guedes M, Muenz D, Zee J, et al. Serum biomarkers of iron stores are associated with worse physical health-related quality of life in nondialysis-dependent chronic kidney disease patients with or without anemia. *Nephrol Dial Transplant.* 2021;36(9):1694-1703. doi:10.1093/ndt/gfab050

28. Jiang W, Hu CY, Li FL, Hua XG, Huang K, Zhang XJ. Elevated parathyroid hormone levels and cognitive function: a systematic review. *Arch Gerontol Geriatr.* 2020;87:103985. doi:10.1016/j.archger.2019.103985

29. Miglinas M, Cesniene U, Janusaite MM, Vinikovas A. Cerebrovascular disease and cognition in chronic kidney disease patients. *Front Cardiovasc Med.* 2020;7:96. doi:10.3389/fcvm.2020.00096

30. Mathur A, Ahn JB, Sutton W, et al. Secondary hyperparathyroidism (CKD-MBD) treatment and the risk of dementia. *Nephrol Dial Transplant.* 2022;37(11):2111-2118. doi:10.1093/ndt/gfac167

31. Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. *Neurology.* 2012;79(13):1397-1405. doi:10.1212/WNL.0b013e31826c197f

32. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between hypotension and cerebral ischemia during hemodialysis. *J Am Soc Nephrol.* 2017;28(8):2511-2520. doi:10.1681/ASN.2016060704

33. Polinder-Bos HA, García DV, Kuipers J, et al. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. *J Am Soc Nephrol.* 2018;29(4):1317-1325. doi:10.1681/ASN.2017101088

34. Findlay MD, Dawson J, Dickie DA, et al. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. *J Am Soc Nephrol.* 2019;30(1):147-158. doi:10.1681/ASN.2018050462

35. Neumann D, Mau W, Wienke A, Girndt M. Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course. *Kidney Int.* 2018;93(2):430-438. doi:10.1016/j.kint.2017.07.022

36. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol.* 2015;26(4):957-965. doi:10.1681/ASN.2013101086

37. Mustafa RA, Bdair F, Akl EA, et al. Effect of lowering the dialysate temperature in chronic hemodialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2016;11(3):442-457. doi:10.2215/CJN.04580415

38. Dumaine CS, Ravani P, Parmar MK, Leung KCW, MacRae JM. In-center nocturnal hemodialysis improves health-related quality of life for patients with end-stage renal disease. *J Nephrol.* 2022;35(1):245-253. doi:10.1007/s40620-021-01066-2

39. Stringuetta Belik F, Silva OE, Rugolo V, et al. Chronic kidney disease and neurological disorders: are uraemic toxins the missing piece of the puzzle? *Nephrol Dial Transplant.* 2021;37:gfab223. doi:10.1093/ndt/gfab223

40. Xu R, Pi HC, Xiong ZY, et al. Hyponatremia and cognitive impairment in patients treated with peritoneal dialysis. *Clin J Am Soc Nephrol.* 2015;10(10):1806-1813. doi:10.2215/CJN.02240215

41. Fan SS, Lin LF, Chen VCH, et al. Effects of lower past-year serum sodium and hyponatremia on depression symptoms and cognitive impairments in patients with hemodialysis. *Ther Apher Dial.* 2020;24(2):169-177. doi:10.1111/1744-9987.13395

42. Viggiano D, Wagner CA, Blankestijn PJ, et al. Mild cognitive impairment and kidney disease: clinical aspects. *Nephrol Dial Transplant.* 2019;35:10-17. doi:10.1093/ndt/gfz051

43. Imenez Silva PH, Unwin R, Hoorn EJ, et al. Acidosis, cognitive dysfunction and motor impairments in patients with kidney disease. *Nephrol Dial Transplant.* 2021;37(Suppl 2):ii4-ii12. doi:10.1093/ndt/gfab216

44. Pépin M, Ferreira AC, Arici M, et al. Cognitive disorders in patients with chronic kidney disease: specificities of clinical assessment. *Nephrol Dial Transplant.* 2021;37:ii23-ii32. doi:10.1093/ndt/gfab262

45. Kang EW, Abdel-Kader K, Yabes J, Glover K, Unruh M. Association of sleep-disordered breathing with cognitive dysfunction in CKD stages 4–5. *Am J Kidney Dis.* 2012;60(6):949-958. doi:10.1053/j.ajkd.2012.08.033

46. Nicholl DDM, Ahmed SB, Loewen AHS, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. *Chest.* 2012;141(6):1422-1430. doi:10.1378/chest.11-1809

47. Viggiano D, Wagner CA, Martino G, et al. Mechanisms of cognitive dysfunction in CKD. *Nat Rev Nephrol.* 2020;16(8):452-469. doi:10.1038/s41581-020-0266-9

48. Natale P, Ruospo M, Saglimbene VM, Palmer SC, Strippoli GF. Interventions for improving sleep quality in people with chronic kidney disease. *Cochrane Database Syst Rev.* 2019;5(5):CD012625. doi:10.1002/14651858.CD012625.pub2

49. Gregg LP, Hedayati SS. Pharmacologic and psychological interventions for depression treatment in patients with kidney disease. *Curr Opin Nephrol Hypertens.* 2020;29(5):457-464. doi:10.1097/MNH.0000000000000629

50. Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol.* 2010;56(12):956-965. doi:10.1016/j.jacc.2010.02.068

51. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324(7329):71-86. doi:10.1136/bmj.324.7329.71

52. Laville SM, Lambert O, Hamroun A, et al. Consequences of oral antithrombotic use in patients with chronic kidney disease. *Clin Transl Sci.* 2021;14(6):2242-2253. doi:10.1111/cts.13084

53. Wolfe R, Wetmore JB, Woods RL, et al. Subgroup analysis of the ASPirin in reducing events in the elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease. *Kidney Int.* 2021;99(2):466-474. doi:10.1016/j.kint.2020.08.011

54. Tanios BY, Itani HS, Zimmerman DL. Clopidogrel use in end-stage kidney disease. *Semin Dial.* 2015;28(3):276-281. doi:10.1111/sdi.12338

55. Kelly DM, Rothwell PM. Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines. *Kidney Int.* 2020;97(2):266-278. doi:10.1016/j.kint.2019.09.024

56. Mann JFE, Joseph P, Gao P, et al. Effects of aspirin on cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int.* 2023;103(2):403-410. doi:10.1016/j.kint.2022.09.023

57. Wong CX, Odutayo A, Emdin CA, Kinnear NJ, Sun MT. Meta-analysis of anticoagulation use, stroke, thromboembolism, bleeding, and mortality in patients with atrial fibrillation on dialysis. *Am J Cardiol.* 2016;117(12):1934-1941. doi:10.1016/j.amjcard.2016.03.042

58. Ha JT, Neuen BL, Cheng LP, et al. Benefits and harms of Oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2019;171(3):181-189. doi:10.7326/M19-0087

59. Liabeuf S, Laville SM, Bieber B, et al. Prescription of direct Oral anticoagulants to patients with moderate-to-advanced CKD: too little or just right? *Kidney Int Rep.* 2021;6(9):2496-2500. doi:10.1016/j.ekir.2021.06.004

60. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with Apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation.* 2018;138(15):1519-1529. doi:10.1161/CIRCULATIONAHA.118.035418

61. Coleman CI, Kreutz R, Sood NA, et al. Rivaroxaban versus warfarin in patients with Nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. *Am J Med.* 2019;132(9):1078-1083. doi:10.1016/j.amjmed.2019.04.013

62. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus No anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. *Clin J Am Soc Nephrol.* 2020;15(8):1146-1154. doi:10.2215/CJN.11650919

63. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from kidney disease: improving global outcomes (KDIGO). *Kidney Int.* 2011;80(6):572-586. doi:10.1038/ki.2011.223

64. Ungvari Z, Toth P, Tarantini S, et al. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol.* 2021;17(10):639-654. doi:10.1038/s41581-021-00430-6

65. Johansen KL, Garimella PS, Hicks CW, et al. Central and peripheral arterial diseases in chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int.* 2021;100(1):35-48. doi:10.1016/j.kint.2021.04.029

66. Chen YH, Chen YY, Fang YW, Tsai MH. Protective effects of angiotensin receptor blockers on the incidence of dementia in patients with chronic kidney disease: a population-based Nationwide study. *J Clin Med.* 2021;10(21):5175. doi:10.3390/jcm10215175

67. Fournier A, Oprisiu-Fournier R, Serot JM, et al. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert Rev Neurother.* 2009;9(9):1413-1431. doi:10.1586/ern.09.89

68. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. *Lancet.* 2011;377(9784):2181-2192. doi:10.1016/S0140-6736(11)60739-3

69. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev.* 2013;9:CD004289. doi:10.1002/14651858.CD004289.pub5

70. Wanner C, Tonelli M. Kidney disease: improving global outcomes lipid guideline development work group members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int.* 2014;85(6):1303-1309. doi:10.1038/ki.2014.31

71. Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia—systematic review and methodological commentary. *Nat Rev Neurol.* 2015;11(4):220-229. doi:10.1038/nrneurol.2015.35

72. Gencer B, Marston NA, Im K, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet.* 2020;396(10263):1637-1643. doi:10.1016/S0140-6736(20)32332-1

73. Ariton DM, Jiménez-Balado J, Maisterra O, Pujadas F, Soler MJ, Delgado P. Diabetes, albuminuria and the kidney-brain Axis. *J Clin Med.* 2021;10(11):2364. doi:10.3390/jcm10112364

74. Tsai WH, Chuang SM, Liu SC, et al. Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. *Sci Rep.* 2021;11(1):15364. doi:10.1038/s41598-021-94945-4

75. Lu CH, Yang CY, Li CY, Hsieh CY, Ou HT. Lower risk of dementia with pioglitazone, compared with other second-line treatments, in metformin-based dual therapy: a population-based longitudinal study. *Diabetologia.* 2018;61(3):562-573. doi:10.1007/s00125-017-4499-5

76. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(9):839-848. doi:10.1056/NEJMoa1616011

77. Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S. The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res Rev.* 2014;16:12-31. doi:10.1016/j.arr.2014.05.002

78. Pentikäinen H, Savonen K, Ngandu T, et al. Cardiorespiratory fitness and cognition: longitudinal associations in the FINGER study. *J Alzheimers Dis.* 2019;68(3):961-968. doi:10.3233/JAD-180897

79. Cai H, Li G, Hua S, Liu Y, Chen L. Effect of exercise on cognitive function in chronic disease patients: a meta-analysis and systematic review of randomized controlled trials. *Clin Interv Aging.* 2017;12:773-783. doi:10.2147/CIA.S135700

80. Vanderbeken I, Kerckhofs E. A systematic review of the effect of physical exercise on cognition in stroke and traumatic brain injury patients. *NeuroRehabilitation.* 2017;40(1):33-48. doi:10.3233/NRE-161388

81. Martins CTB, Ramos GSM, Guaraldo SA, Uezima CBB, Martins JPLB, Ribeiro JE. Comparison of cognitive function between patients on chronic hemodialysis who carry out assisted physical activity and inactive ones. *J Bras Nefrol.* 2011;33(1):27-30.

82. Stringuetta Belik F, Silva OE, Rugolo V, et al. Influence of intradialytic aerobic training in cerebral blood flow and cognitive function in patients with chronic kidney disease: a pilot randomized controlled trial. *Nephron.* 2018;140(1):9-17. doi:10.1159/000490005

83. McAdams-DeMarco MA, Konel J, Warsame F, et al. Intradialytic cognitive and exercise training may preserve cognitive function. *Kidney Int Rep.* 2018;3(1):81-88. doi:10.1016/j.ekir.2017.08.006

84. Manfredini F, Mallamaci F, D'Arrigo G, et al. Exercise in patients on dialysis: a multicenter, randomized clinical trial. *J Am Soc Nephrol.* 2017;28(4):1259-1268. doi:10.1681/ASN.2016030378

85. Uchiyama K, Washida N, Morimoto K, et al. Home-based aerobic exercise and resistance training in peritoneal dialysis patients: a randomized controlled trial. *Sci Rep.* 2019;9(1):2632. doi:10.1038/s41598-019-39074-9

86. Otobe Y, Yamada M, Hiraki K, et al. Physical exercise improves cognitive function in older adults with stage 3–4 chronic kidney disease: a randomized controlled trial. *Am J Nephrol.* 2021;52(12):929-939. doi:10.1159/000520230

87. Cicerone KD, Goldin Y, Ganci K, et al. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. *Arch Phys Med Rehabil.* 2019;100(8):1515-1533. doi:10.1016/j.apmr.2019.02.011

88. Chandler MJ, Parks AC, Marsiske M, Rotblatt LJ, Smith GE. Everyday impact of cognitive interventions in mild cognitive impairment: a systematic review and meta-analysis. *Neuropsychol Rev.* 2016;26(3):225-251. doi:10.1007/s11065-016-9330-4

89. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385(9984):2255-2263. doi:10.1016/S0140-6736(15)60461-5

90. McAdams-DeMarco MA, Chu NM, Steckel M, et al. Interventions made to preserve cognitive function trial (IMPCT) study protocol: a multi-dialysis center 2x2 factorial randomized controlled trial of intradialytic cognitive and exercise training to preserve cognitive function. *BMC Nephrol.* 2020;21(1):383. doi:10.1186/s12882-020-02041-y

91. Chauveau P, Aparicio M, Bellizzi V, et al. Mediterranean diet as the diet of choice for patients with chronic kidney disease. *Nephrol Dial Transplant.* 2018;33(5):725-735. doi:10.1093/ndt/gfx085

92. Lauriola M, Farré R, Evenepoel P, Overbeek SA, Meijers B. Food-derived uremic toxins in chronic kidney disease. *Toxins (Basel).* 2023;15(2):116. doi:10.3390/toxins15020116

93. Liabeuf S, Laville M. Drug prescription in patients with chronic kidney disease: a true challenge. *Nephrol Dial Transplant.* 2021;36(3):385-386. doi:10.1093/ndt/gfaa164

94. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol.* 2013;69(7):1485-1496. doi:10.1007/s00228-013-1499-3

95. Broder JC, Ryan J, Shah RC, et al. Anticholinergic medication burden and cognitive function in participants of the ASPREE study. *Pharmacotherapy.* 2022;42(2):134-144. doi:10.1002/phar.2652

96. Dou KX, Tan MS, Tan CC, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. *Alzheimers Res Ther.* 2018;10(1):126. doi:10.1186/s13195-018-0457-9

97. Battle CE, Abdul-Rahim AH, Shenkin SD, Hewitt J, Quinn TJ. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. *Cochrane Database Syst Rev.* 2021;2:CD013306. doi:10.1002/14651858.CD013306.pub2

98. Nordström P, Religa D, Wimo A, Winblad B, Eriksdotter M. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. *Eur Heart J.* 2013;34(33):2585-2591. doi:10.1093/eurheartj/eht182

99. Morris R, Luboff H, Jose RP, et al. Bradycardia due to donepezil in adults: systematic analysis of FDA adverse event reporting system. *J Alzheimers Dis.* 2021;81(1):297-307. doi:10.3233/JAD-201551

100. Kambayashi R, Goto A, Hagiwara-Nagasawa M, et al. Analysis of clinically-reported, memantine-induced cardiovascular adverse responses using the halothane-anesthetized dogs: reverse translational study. *J Pharmacol Sci.* 2022;148(4):343-350. doi:10.1016/j.jphs.2022.01.011

101. Hilderman M, Bruchfeld A. The cholinergic anti-inflammatory pathway in chronic kidney disease-review and vagus nerve stimulation clinical pilot study. *Nephrol Dial Transplant.* 2020;35(11):1840-1852. doi:10.1093/ndt/gfaa200

102. Decourt B, D'Souza GX, Shi J, Ritter A, Suazo J, Sabbagh MN. The cause of Alzheimer's disease: the theory of multipathology convergence to chronic neuronal stress. *Aging Dis.* 2022;13(1):37-60. doi:10.14336/AD.2021.0529

103. EMA. Exelon. European Medicines Agency. 2018 Accessed July 13, 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/exelon

104. EMA. Ebixa. European Medicines Agency. 2018 Accessed July 13, 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/ebixa

105. Noetzli M, Eap CB. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clin Pharmacokinet.* 2013;52(4):225-241. doi:10.1007/s40262-013-0038-9

APPENDIX A

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