HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Am J Kidney Dis. 2019 December ; 74(6): 782–790. doi:10.1053/j.ajkd.2019.05.017.

Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention

David A. Drew, **Daniel E. Weiner**, **Mark J. Sarnak**

Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA

Abstract

Patients with chronic kidney disease (CKD) are at substantially higher risk for developing cognitive impairment compared with the general population, and both lower glomerular filtration rate and the presence of albuminuria are associated with the development of cognitive impairment and poorer cognitive function. Given the excess of vascular disease seen in individuals with CKD, cerebrovascular disease is likely the predominant pathology underlying these associations, though impaired clearance of uremic metabolites, depression, sleep disturbance, anemia, and polypharmacy may also contribute. Modification of vascular disease risk factors may be helpful in limiting decline, though definite data are lacking. Specific to CKD, targeting a low blood pressure and reduction in albuminuria with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may slow cognitive decline, albeit modestly. Initiation of dialysis can improve severe impairment associated with uremia but does not appear to affect more subtle chronic cognitive impairment. In contrast, kidney transplantation appears to lead to improved cognitive function in many transplant recipients, suggesting that dialysis methods do not provide the same cognitive benefits as having a functioning kidney. Management of patients with both CKD and cognitive impairment should include a comprehensive plan including more frequent follow-up visits; involvement of family in shared decision making; measures to improve compliance, such as written instruction and pill counts; and a focus on advance directives in conjunction with an emphasis on understanding an individual patient's life goals. Further research is needed on novel therapies, including innovative dialysis methods, that aim to limit the development of cognitive impairment, slow decline in those with prevalent impairment, and improve cognitive function.

Epidemiology of Cognitive Impairment in Chronic Kidney Disease

Cognitive impairment is a deficit in one or more key brain functions, such as memory, learning, concentration, and decision making. Cognitive impairment can range from mild to severe, with severe impairment that impairs daily living and independence typically referred to as dementia.[1] Individuals with chronic kidney disease (CKD), defined as glomerular filtration rate (GFR) < 60 mL/min/ 1.73 m^2 or the presence of a marker of kidney damage, often albuminuria, are at substantially higher risk for cognitive impairment when compared with the general population. The prevalence of cognitive impairment in those with CKD is

Address for Correspondence: Mark J. Sarnak, MD, MS, Box 391, Division of Nephrology, Tufts Medical Center, 800 Washington St, Boston MA 02111. msarnak@tuftsmedicalcenter.org.

Financial Disclosure: The authors declare that they have no relevant financial interests.

an astonishing 10% to 40%, depending on the method of cognitive impairment assessment and the CKD stage.[2,3]

Low estimated GFR (eGFR) and albuminuria are both independent risk factors for cognitive impairment, with albuminuria the stronger risk factor at higher eGFRs and eGFR the stronger risk factor in advanced CKD.[4–7] The prevalence of cognitive impairment is highest among those with kidney failure requiring dialysis. In one of the first comprehensive studies, Murray et al[8] evaluated 374 hemodialysis patients with a cognitive battery, finding that only 13% had normal cognitive function, while 50% had mild to moderate impairment and 37% had severe impairment. Similarly, a study by Sarnak et al[3] demonstrated a very high prevalence of cognitive impairment in hemodialysis patients in comparison to normative data from the general population, showing that hemodialysis patients performed below "normal" on many neurocognitive tests (Fig 1).

There are fewer data for patients receiving peritoneal dialysis,[7] with 1 study showing a similar high prevalence of cognitive impairment, suggesting that dialysis modality is not the only contributing factor in the pathogenesis of CKD-related cognitive impairment. Though there are only a few studies examining the impact of cognitive impairment on patient-related outcomes, existing data suggest that patients with cognitive impairment who receive maintenance hemodialysis require greater time from dialysis staff,[9] spend more time hospitalized, are at higher risk for death,[10,11] and are likely to have poorer adherence to treatment plans.

Pathophysiology of CKD-Related Cognitive Impairment

Vascular Disease and Traditional Cardiovascular Risk Factors

Because individuals with kidney disease often have multiple comorbid conditions, it is unsurprising that the cause of cognitive impairment in patients with CKD is multifactorial (Fig 2). Importantly, many patients with CKD are elderly and are therefore at risk for developing Alzheimer disease (AD), which affects predominantly memory in its early stages. However, rates of AD dementia in patients with CKD appear similar to rates in patients without kidney disease of similar age and similar burden of comorbid conditions, suggesting that AD is not the predominant or primary reason for excess risk.[12] Notably, it is important to recognize that AD likely does have a vascular component,[13] and most cognitive impairment is multifactorial.

In contrast, patients with CKD are significantly more likely to have disproportionate levels of cerebrovascular disease, particularly small-vessel cerebrovascular disease, suggesting that this may be an important factor in the development of CKD-related cognitive impairment.

There are several lines of evidence supporting this hypothesis. First, individuals with CKD have a high prevalence of cardiovascular disease (CVD) and CVD risk factors, including diabetes, hypertension, and dyslipidemia, often of sufficient severity to result in kidney failure.[14,15] Second, those with CKD are more likely to experience clinical cerebrovascular disease, including stroke and transient ischemic attack, as well as have subclinical cerebrovascular disease on imaging such as small-vessel infarcts, lacunes, and white matter

disease (Fig 3).[16,17] Third, the cognitive deficits associated with cerebrovascular disease predominantly affect processing and executive function, cognitive domains that affect planning and carrying out tasks, and most studies demonstrate that processing speed and executive function are the domains most affected in individuals with CKD.[3,8,18] Fourth, CVD and its risk factors are associated with worse executive function.[18] Moreover, in earlier stages of CKD, the presence of albuminuria, likely representative of systemic vascular injury, is associated with worse executive function and incident dementia.[12,19–21]

Cerebrovascular disease is unlikely to be the only contributing factor to cognitive impairment in individuals with CKD because cognitive performance steadily worsens as kidney function declines[5] and then often improves with kidney transplantation.[22,23] Longitudinal studies evaluating cognitive function pre- and posttransplantation show improvement in cognitive function within the first 6 to 12 months posttransplantation, with improved function still apparent several years later, though such improvement may be modified by frailty.[22–24] The potential explanations of this finding are 2-fold: first, successful transplantation restores crucial functions of the kidney, such as filtration, secretion, tubular function, hormonal balance (that are not replicated by dialysis), and clearance of medications, both of which may be essential for optimal cognitive function; and second, transplantation eliminates the need for dialysis and the associated complications that may promote cognitive impairment, particularly with hemodialysis, such as sudden hemodynamic shifts, routine use of anticoagulation that may predispose to microbleeds, and intermittent rather than continual solute clearance.

Nontraditional Kidney Disease–Related Factors

Uremic Metabolites—Progression of CKD is accompanied by the steady accumulation of various metabolites that are removed by filtration and/or tubular secretion by the healthy kidney.[25] Though overt uremia is typically recognized only when GFR has declined to less than 10 to 15 mL/min/1.73 m^2, it is clear that metabolite accumulation occurs at earlier stages.[26] Encephalopathy associated with uremia is a late complication[27] and is now rare due to better detection of kidney disease and the routine use of kidney replacement therapies.[28] Treatment of kidney failure with maintenance dialysis using high-flux high-efficiency membranes and monthly assessment of dialysis adequacy has eliminated much of the severe cognitive impairment (encephalopathy) associated with uremia.[28] Despite these advances in hemodialysis, it is becoming increasingly clear that current dialysis membranes are much less efficient at clearing medium-sized and highly protein-bound metabolites.[29,30] Though there are potentially hundreds if not thousands of such compounds, one metabolite, 4-hydroxyphenylacetate, was recently identified as potentially contributing to CKD-related cognitive impairment.[31]

Future research should be aimed at further evaluating whether uremic metabolites affect cognitive function. If this proves to be the case, developing new membranes and novel dialysis techniques to improve clearance of such compounds presents a promising avenue to improve cognitive impairment in patients on dialysis therapy.

Dialysis Factors—Dialysis modality also has been implicated in the development of cognitive impairment.[32] Hemodialysis, in contrast to peritoneal dialysis, results in rapid fluid shifts that can often lead to wide swings in blood pressure.[33] Intradialytic hypotension has been linked with cerebral atrophy,[34] while hemodynamic instability on hemodialysis has also been associated with brain injury.[35]

Recent studies have attempted to better characterize how hemodynamic changes associated with hemodialysis affect blood flow to the brain. MacEwen et al[36] used real-time near-infrared spectroscopy to measure cerebral ischemia during hemodialysis treatments. They found that nearly a quarter of 635 individual hemodialysis sessions showed evidence of cerebral ischemia, with a third of those events symptomatic. Confirming this phenomenon with a different form of real-time imaging, positron emission tomography–computed tomography, Polinder-Bos et al[37] demonstrated that initiation of hemodialysis in elderly individuals resulted on average in a 10% decline in cerebral blood flow, with every brain location/volume showing declines (Fig 4). Higher dialysate temperature, ultrafiltration rates, and volume were associated with lower cerebral blood flow.

Finally, Findlay et al[38] used yet another noninvasive imaging technique, transcranial Doppler, to measure cerebral blood flow of 97 participants receiving maintenance hemodialysis. Mean flow velocity (the primary measure of cerebral blood flow) declined significantly during dialysis and was correlated with ultrafiltration volumes. More importantly, in a subgroup, greater decreases in cerebral blood flow were associated with worse cognitive function in addition to progression of white matter disease, as measured by brain magnetic resonance imaging (MRI). These studies collectively suggest that strategies that mitigate decreases in cerebral blood flow during hemodialysis are potentially beneficial. Later in this review, we discuss dialysate cooling as a potential strategy to preserve cognitive function.

Cerebral microbleeds may be another hemodialysis-related risk factor for cognitive impairment. Cerebral microbleeds are common in patients treated with hemodialysis[39] and may signify increased risk for larger intra-cranial hemorrhage.[39] It is reasonable to question whether these findings are related to the routine use of anticoagulants, primarily heparin, during the hemodialysis treatment.

Peritoneal dialysis is thought to involve much more gentle hemodynamic shifts and does not routinely involve the use of anticoagulation. Therefore, peritoneal dialysis theoretically could provoke fewer and less severe instances of brain injury. However, the prevalence of cognitive impairment among peritoneal dialysis patients remains high,[7] and longitudinal data suggesting that better cognitive performance over time in peritoneal dialysis compared to hemodialysis patients are susceptible to selection and survival biases, considerations in nearly every non-randomized study comparing dialysis modalities.[40]

Anemia and Aluminum—Individuals with CKD often have concomitant anemia, which has been linked to both a greater incidence of stroke[41] and cognitive impairment.[42] However, cause-and-effect relationships are difficult to ascertain because it is unclear whether anemia directly affects cognition (perhaps through decreased perfusion/

oxygenation), indirectly affects cognition by way of higher risk for cerebrovascular events, or simply identifies a higher risk phenotype for greater comorbid condition burden, including cognitive impairment. In addition, these studies are often confounded by the use of erythropoiesis-stimulating agents, which at high doses also confer greater stroke risk.[43] Historically, aluminum brain deposition caused dementia in dialysis patients.[44] Currently, the combination of strict water testing and limitations on the use of aluminum-based phosphorus binders has essentially eliminated this condition, but we believe it is important to highlight if there is concern regarding aluminum overload.

Other Factors—Critically, it is likely that depression, including both clinical and subclinical depression, contributes to impaired cognitive function. Depression, due to functional and psychological reasons, may also limit the ability to properly test for cognitive impairment. Supporting this association, a prior study of hemodialysis patients noted that depression was associated with poor cognitive function,[45] although the direction of the relationship and exact pathophysiology remain undetermined. Although there are limited data in patients with CKD, we believe that polypharmacy also likely contributes to cognitive impairment. The high absolute number of medications, combined with the potential for drug-drug interactions and impaired kidney clearance, creates a high risk for sedation, delirium, and cognitive impairment. Finally, there also may be a role for sleep (or lack of quality sleep) in cognitive impairment; dialysis patients in particular have sleep disturbances and this may lead to impaired daytime cognitive function.[46]

Prevention and Treatment of CKD-Related Cognitive Impairment

The centerpiece of any strategy aimed at combating CKD-related cognitive impairment rests in prevention (Table 1). As such, the focus should be on the likely pathophysiologic mechanisms underlying the development and progression of cognitive impairment. Control of traditional CVD risk factors, including management of dyslipidemia, hypertension, and hyperglycemia, appear to have beneficial effects on cognitive function in the general population,[47,48] but there are limited data in those with CKD, including those requiring dialysis. Importantly, what is true for those with mild to moderate CKD may not extend to those receiving dialysis. For example, among dialysis patients, lower blood pressure is associated with worse outcomes,[49,50] appropriate targets levels for glycemic control are unclear,[51,52] and no trials have shown a benefit with statins.[53,54] In contrast, targeting these CVD risk factors in earlier stages of CKD may prevent or limit cerebrovascular disease, leading to cognitive benefits.

Strategies for CKD Patients Not Requiring Dialysis

For patients with mild to moderate CKD, there are at least 2 specific interventions that may reduce the risk for developing cognitive impairment or the rate of progression of cognitive impairment. First, targeting reduction of albuminuria with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be associated with slower cognitive decline. A multivariable-adjusted post hoc analysis of the ONTARGET/TRANSCEND trial data, in which 25% of participants had CKD, showed that participants who were able to either reduce or completely eliminate albuminuria had 20% to 40% lower

odds of having a decrease in Mini-Mental State Examination score of 3 or greater compared with those who had an increase or no change in albuminuria.[55]

Given the observational study design of these post hoc analyses, these results do not prove that reduction in albuminuria is beneficial to cognitive health but rather suggest that ACE-inhibitor/ARB therapy may play a role in limiting cognitive decline either through blood pressure control, albuminuria reduction, or other benefits to vascular health.

Second, intensive blood pressure control has recently been evaluated in SPRINT, which included nearly 3,000 individuals with eGFRs < 60 mL/min/1.73 m^2.[56] The trial included a detailed set of neurocognitive tests and specifically evaluated cognitive decline as one of its many outcomes. The recently published SPRINT MIND results showed that randomization to the intensive blood pressure arm was associated with a lower incidence of mild cognitive impairment compared to standard blood pressure control, with no significant interaction by CKD status.[56] This finding in SPRINT is consistent with existing observational data and with results from several other trials in hypertension and high-risk CVD populations.[57] Although these results are limited by the difficulty conducting longer term trials of cognitive function and the focus of most trials on cardiovascular rather than cognitive outcomes, overall results suggest a likely benefit of blood pressure control on subsequent cognitive function.

Strategies for CKD Patients Requiring Maintenance Dialysis

Patients with kidney failure requiring maintenance dialysis are more likely to have severe cognitive impairment. At least 2 dialysis-specific interventions have been tested to protect or improve brain health. First, it was hypothesized that greater clearance of small-molecule uremic toxins may lead to improved cognitive performance. Specifically, the Frequent Hemodialysis Network Study evaluated whether more intensive 6-days-a-week hemodialysis (and the greater solute clearance provided by this schedule) would result in better cognitive performance than standard thrice-weekly in-center hemodialysis.[58] Unfortunately, this intervention produced no difference in cognitive performance after 1 year despite successfully achieving a significantly higher weekly Kt/V in the intervention arm. However, this null finding should not serve as the last trial of improved dialytic clearance because the prior trial focused primarily on greater clearance of small molecules using standard high-flux dialysis membranes.

As stated, there appears to be a consistent global improvement in cognitive function in patients the year after kidney transplantation.[22,23,59] Improvement is seen in both child and adult recipients, in preemptive and post-dialysis recipients, and with living and deceased donor kidney recipients.[22,23,59] However, a recent publication found that frailty may modify both the magnitude and likelihood of sustained improvement in cognitive function after transplantation.[24] This finding suggests that overall health may be a crucial factor in determining how much cognitive benefit a transplant recipient can expect to receive. As such, there should be renewed focus on developing novel interventions, including dietary changes and enhancing gastrointestinal clearance (or reducing production) of gut-derived metabolites, as well as improved dialysis methods and membranes that better approximate natural kidney function by providing better clearance of larger and protein-bound molecules.

Besides the frequency and adequacy of hemodialysis, dialysate temperature has also been evaluated as an inexpensive and simple intervention to preserve cognitive function. Eldehni et al[60] randomly assigned 73 patients on maintenance hemodialysis to dialysate temperatures of 37°C or 0.5°C below core body temperature. The primary outcome was 1-year change in fractional anisotropy, a measure of brain white matter integrity, as determined by diffusion tensor MRI. Alterations in white matter fractional anisotropy have been linked to both cerebrovascular disease and cognitive decline in the general population. The trial noted that the intervention group (cooler dialysate) had no change in brain white matter, while the control group (warmer dialysate) displayed significant white matter changes. In addition, the intervention group was found to have less hemodynamic instability, leading the authors to suggest that cooler dialysate may deliver its benefit through the systemic vasculature, including through fewer hypotensive events. A major limitation was that the trial had significant drop out, though no dropouts were reported to be the result of intolerance to the cooling intervention. A second limitation was that the direction of the white matter change for the control group was not consistent with that seen in observational studies of brain injury.[61] Despite these limitations, there are additional data that indirectly support a possible cognitive benefit for dialysate cooling.

A recent meta-analysis by Mustafa et al[62] pooled the existing trials of dialysate cooling, noting that cooling dialysate resulted in a 70% reduction in intradialytic hypotension. In theory, cooling may thereby prevent some of the decrease in brain blood flow and repetitive brain injury that occurs during hemodialysis sessions.[36–38] Conversely, it would stand to reason that peritoneal dialysis, which physiologically involves more gentle shifts between fluid compartments, may be less prone to brain injury and thus cognitive decline. At present, this remains a hypothesis because there are no published studies examining cerebral blood flow while receiving peritoneal dialysis.

Screening for Cognitive Impairment in CKD

Who should be screened for cognitive impairment? Older age is the most significant risk factor for cognitive decline in patients with kidney disease and as such, elderly patients, especially those initiating dialysis, should be most closely evaluated.[63] We would also recommend that individuals with existing cerebrovascular disease be considered for screening. At present, there are no guidelines stating the optimal screening test to identify cognitive impairment or dementia in patients with CKD.

In our opinion, if cerebrovascular disease is the predominant contributing factor, tests that incorporate assessment of executive function are preferred. The Montreal Cognitive Assessment could be considered as it is a simple 1-page cognitive test that has been extensively used in other patient populations.[64] Although the Montreal Cognitive Assessment has not been formally validated as a screening test in patients with CKD, a small study of prevalent hemodialysis patients found that Montreal Cognitive Assessment scores correlated well with performance on a broader array of neurocognitive tests.[65] For patients with CKD receiving maintenance hemodialysis, administering cognitive tests during the first hour of hemodialysis appears to be a practical option.[66]

If a patient is found to have mild or moderate cognitive impairment on a screening test, more detailed neurocognitive testing should be considered. Further evaluation, which is based on a framework suggested for addressing cognitive impairment in the general population, may include referral to either a geriatric medicine specialist or a neurologist. Neuroimaging, using either computed tomography or MRI, should be done in any case with focal deficits, rapid decline, or recent trauma and should also be considered in patients with cognitive impairment of unclear cause. Finally, we suggest screening for reversible causes of cognitive impairment, such as vitamin B_{12} deficiency or thyroid dysfunction, given that the tests for these conditions are simple and low cost.

Caring for Individuals With Kidney Disease and Cognitive Impairment

Care management should broadly focus on both reducing further progression of cognitive impairment (using strategies in Table 1 as appropriate) and implementing strategies to best provide care to individuals with cognitive impairment (Box 1). As discussed, general strategies include optimizing traditional CVD risk factors, avoiding sedating medications and polypharmacy, improving sleep hygiene,[46] strengthening family and social support, treating depression,[67] and encouraging mental stimulation[68] and exercise.[69] In addition, we also advise measures to improve treatment adherence, such as medication management plans, frequent check-ins, use of clear written instructions, and close involvement of social workers, dieticians, technicians, nurses, and physicians. Though many of these interventions have not been tested in patients with CKD, these are all relatively straightforward to implement and potentially beneficial.

We also advocate that treatment decisions, such as dialysis modality and consideration of conservative care of kidney failure, be made as early as possible in the disease course of CKD. Early discussion with patients, before significant cognitive decline, will likely allow for better alignment of patient wishes and actual outcomes.

What should be done if an individual is found to already have severe cognitive impairment or even dementia? We acknowledge that there is a notable lack of specific treatments available. This may in part be due to exclusion of patients with CKD from trials in the general population and may also reflect the multiple different contributors to CKD-related cognitive impairment. Delivering dialysis to an individual with advanced dementia is challenging and may even be a reason to consider such treatment futile. Both hemodialysis and peritoneal dialysis involve complex tasks that involve differing degrees of patient cooperation, with peritoneal dialysis self-care virtually impossible in cases of severe dementia. In our experience, severe cognitive decline is many times the inciting reason for withdrawal from dialysis.

The patient presented in the clinical vignette is not an actual patient but represents a common clinical scenario. Interventions that would be recommended for this patient include screening for depression and cognitive impairment, checking thyroid-stimulating hormone and vitamin B_{12} levels, encouraging additional involvement of family members in the care, providing written instructions, and consideration of computed tomography of the head and neurologic evaluation.

Conclusions

Patients with CKD are at higher risk than average for developing cognitive impairment, with older patients on dialysis at the highest absolute risk. Vascular disease, in particular cerebrovascular disease, is likely a major contributor. Control of CVD risk factors, as recommended by the current standards of care, is a reasonable measure that practitioners can take to potentially limit the development of cognitive impairment, and in those with impairment, limit cognitive decline. Targeting a reduction of albuminuria through the use of ACE-inhibitor/ARB therapy and kidney transplantation, when possible, may also be beneficial. For individuals found to have cognitive impairment, we also suggest a comprehensive evaluation aimed at avoiding sedating medications, evaluating sleep hygiene, building social and family support, promoting mental stimulation and exercise, and discussing life goals and advanced directives. There is not sufficient evidence at this time to suggest any modification to dialysis prescriptions or dialysis delivery, though in patients who experience repeated episodes of intradialytic hypotension, lowering the dialysate temperature may be a reasonable intervention. Further research is needed to understand the reasons underlying the excess of vascular disease in patients with CKD, as well as to test novel strategies to prevent or limit cognitive decline.

Acknowledgments

Support: Dr Drew was supported by NIDDK grant K23DK105327.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013.
2. Yaffe K, Ackerson L, Tamura MK, et al. Chronic kidney disease and cognitive function in older adults: findings from the Chronic Renal Insufficiency Cohort Cognitive Study. J Am Geriatr Soc. 2010;58(2):338–345. [PubMed: 20374407]
3. 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. [PubMed: 23303848]
4. Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis. 2008;52(2):227–234. [PubMed: 18585836]
5. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the Health, Aging, and Body Composition Study. J Am Soc Nephrol. 2005;16(7): 2127–2133. [PubMed: 15888561]
6. Kurella M, Chertow GM, Luan J, et al. Cognitive impairment in chronic kidney disease. J Am Geriatr Soc. 2004;52(11):1863–1869. [PubMed: 15507063]
7. Kalirao P, Pederson S, Foley RN, et al. Cognitive impairment in peritoneal dialysis patients. Am J Kidney Dis. 2011;57(4):612–620. [PubMed: 21295896]
8. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. Neurology. 2006;67(2):216–223. [PubMed: 16864811]
9. Sehgal AR, Grey SF, DeOreo PB, et al. Prevalence, recognition, and implications of mental impairment among hemodialysis patients. Am J Kidney Dis. 1997;30(1):41–49. [PubMed: 9214400]
10. Drew DA, Weiner DE, Tighiouart H, et al. Cognitive function and all-cause mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2015;65(2):303–311. [PubMed: 25240262]

11. Kurella M, Mapes DL, Port FK, et al. Correlates and outcomes of dementia among dialysis patients: the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant. 2006;21(9):2543–2548. [PubMed: 16751655]
12. Seliger SL, Siscovick DS, Stehman-Breen CO, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol. 2004;15(7):1904–1911. [PubMed: 15213280]
13. Santos CY, Snyder PJ, Wu W-C, et al. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. Alzheimers Dement (Amst). 2017;7:69–87. [PubMed: 28275702]
14. Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58(1):353–362. [PubMed: 10886582]
15. Cheung AK, Sarnak MJ, Yan G, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int. 2004;65(6):2380–2389. [PubMed: 15149351]
16. Seliger SL, Gillen DL, Longstreth W, et al. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int. 2003;64(2):603–609. [PubMed: 12846756]
17. Drew DA, Bhadelia R, Tighiouart H, et al. Anatomic brain disease in hemodialysis patients: a cross-sectional study. Am J Kidney Dis. 2013;61(2):271–278. [PubMed: 23040011]
18. Weiner DE, Scott TM, Giang LM, et al. Cardiovascular disease and cognitive function in maintenance hemodialysis patients. Am J Kidney Dis. 2011;58(5):773–781. [PubMed: 21778003]
19. Weiner DE, Bartolomei K, Scott T, et al. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. Am J Kidney Dis. 2009;53(3):438–447. [PubMed: 19070412]
20. Barzilay JI, Fitzpatrick AL, Luchsinger J, et al. Albuminuria and dementia in the elderly: a community study. Am J Kidney Dis. 2008;52(2):216–226. [PubMed: 18468749]
21. Weiner DE, Gaussoin SA, Nord J, et al. Cognitive function and kidney disease: baseline data from the Systolic Blood Pressure Intervention Trial (SPRINT). Am J Kidney Dis. 2017;70(3):357–367. [PubMed: 28606731]
22. Griva K, Thompson D, Jayasena D, et al. Cognitive functioning pre-to post-kidney transplantation —a prospective study. Nephrol Dial Transplant. 2006;21(11):3275–3282. [PubMed: 16861731]
23. Harciarek M, Biedunkiewicz B, Lichodziejewska-Niemierko M, et al. Cognitive performance before and after kidney transplantation: a prospective controlled study of adequately dialyzed patients with end-stage renal disease. J Int Neuropsychol Soc. 2009;15(05):684–694. [PubMed: 19570307]
24. Chu NM, Gross AL, Shaffer AA, et al. Frailty and changes in cognitive function after kidney transplantation. J Am Soc Nephrol. 2019;30(2):336–345. [PubMed: 30679381]
25. Meyer TW, Hostetter TH. Approaches to uremia. J Am Soc Nephrol. 2014;25(10):2151–2158. [PubMed: 24812163]
26. Depner TA. Uremic toxicity: urea and beyond. Semin Dial. 2001;14(4):246–251. [PubMed: 11489197]
27. Souheaver GT, Ryan JJ, Dewolfe AS. Neuropsychological patterns in uremia. J Clin Psychol. 1982;38(3):490–496. [PubMed: 7050178]
28. Tamura MK, Larive B, Unruh ML, et al. Prevalence and correlates of cognitive impairment in hemodialysis patients: the Frequent Hemodialysis Network Trials. Clin J Am Soc Nephrol. 2010;5(8):1429–1438. [PubMed: 20576825]
29. Tanaka H, Sirich TL, Plummer NS, et al. An enlarged profile of uremic solutes. PloS One. 2015;10(8):e0135657. [PubMed: 26317986]
30. Sirich TL, Funk BA, Plummer NS, et al. Prominent accumulation in hemodialysis patients of solutes normally cleared by tubular secretion. J Am Soc Nephrol. 2014;25(3):615–622. [PubMed: 24231664]
31. Tamura MK, Chertow GM, Depner TA, et al. Metabolic profiling of impaired cognitive function in patients receiving dialysis. J Am Soc Nephrol. 2016;27(12):3780–3787. [PubMed: 27444566]
32. Eldehni MT, McIntyre CW. Are there neurological consequences of recurrent intradialytic hypotension? Semin Dial. 2012;25(3):253–256. [PubMed: 22353138]

33. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. Am J Kidney Dis. 2001;38(4):S11–S17.
34. Mizumasa T, Hirakata H, Yoshimitsu T, et al. Dialysis-related hypotension as a cause of progressive frontal lobe atrophy in chronic hemodialysis patients: a 3-year prospective study. Nephron Clin Pract. 2004;97(1):c23–c30. [PubMed: 15153764]
35. McIntyre CW. Recurrent circulatory stress: the dark side of dialysis. Semin Dial. 2010;23(5):449–451. [PubMed: 21039872]
36. MacEwen C, Sutherland S, Daly J, et al. Relationship between hypotension and cerebral ischemia during hemodialysis. J Am Soc Nephrol. 2017;28(8):2511–2520. [PubMed: 28270412]
37. Polinder-Bos HA, Garcia 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. [PubMed: 29496888]
38. 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. [PubMed: 30530658]
39. Watanabe A. Cerebral microbleeds and intracerebral hemorrhages in patients on maintenance hemodialysis. J Stroke Cerebrovasc Dis. 2007;16(1):30–33. [PubMed: 17689389]
40. Neumann D, Mau W, Wienke A, et al. Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course. Kidney Int. 2018;93(2):430–438. [PubMed: 29042081]
41. Abramson JL, Jurkovitz CT, Vaccarino V, et al. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC Study. Kidney Int. 2003;64(2):610–615. [PubMed: 12846757]
42. 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. [PubMed: 20930087]
43. 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. [PubMed: 17108343]
44. Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome: possible aluminum intoxication. N Engl J Med. 1976;294(4):184–188. [PubMed: 1244532]
45. Agganis BT, Weiner DE, Giang LM, et al. Depression and cognitive function in maintenance hemodialysis patients. Am J Kidney Dis. 2010;56(4):704–712. [PubMed: 20673602]
46. Rodriguez L, Tighiouart H, Scott T, et al. Association of sleep disturbances with cognitive impairment and depression in maintenance hemodialysis patients. J Nephrol. 2013;26(1):101. [PubMed: 22641565]
47. The Perindopril Protection Against Recurrent Stroke Study, Neal B, MacMahon S. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003;163:1069–1075. [PubMed: 12742805]
48. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J Clin Exp Neuropsychol. 2004;26(8):1044–1080. [PubMed: 15590460]
49. Flythe JE, Xue H, Lynch KE, et al. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol. 2014 ASN. 2014020222.
50. Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. Clin J Am Soc Nephrol. 2014;9(12):2124–2132. [PubMed: 25376764]
51. Shurraw S, Majumdar SR, Thadhani R, et al. Glycemic control and the risk of death in 1,484 patients receiving maintenance hemodialysis. Am J Kidney Dis. 2010;55(5):875–884. [PubMed: 20346561]
52. Ricks J, Molnar MZ, Kovesdy CP, et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes. Diabetes. 2012;61(3):708–715. [PubMed: 22315308]
53. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–248. [PubMed: 16034009]
54. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–1407. [PubMed: 19332456]

55. Barzilay JI, Gao P, O'Donnell M, et al. Albuminuria and decline in cognitive function: the ONTARGET/TRANSCEND studies. Arch Intern Med. 2011;171(2):142–150. [PubMed: 21263104]
56. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. Jama. 2019;321(6): 553–561. [PubMed: 30688979]
57. Rouch L, Cestac P, Hanon O, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. CNS Drugs. 2015;29(2):113–130. [PubMed: 25700645]
58. Kurella Tamura M, Unruh ML, Nissenson AR, et al. Effect of more frequent hemodialysis on cognitive function in the frequent hemodialysis network trials. Am J Kidney Dis. 2013;61(2):228–237. [PubMed: 23149295]
59. Gupta A, Lepping RJ, Yu AS, et al. Cognitive function and white matter changes associated with renal transplantation. Am J Nephrol. 2016;43(1):50–57. [PubMed: 26894920]
60. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. J Am Soc Nephrol. 2014;26(4):957–965. [PubMed: 25234925]
61. Charlton RA, Barrick T, McIntyre D, et al. White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. Neurology. 2006;66(2):217–222. [PubMed: 16434657]
62. 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. [PubMed: 26712807]
63. Drew DA, Weiner DE, Tighiouart H, et al. Cognitive decline and its risk factors in prevalent hemodialysis patients. Am J Kidney Dis. 2017;69(6):780–787. [PubMed: 28131531]
64. Nasreddine ZS, Phillips NA, Béadirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–699. [PubMed: 15817019]
65. Tiffin-Richards FE, Costa AS, Holschbach B, et al. The Montreal Cognitive Assessment (MoCA)a sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. PloS One. 2014;9(10):e106700. [PubMed: 25347578]
66. Drew DA, Tighiouart H, Scott TM, et al. Cognitive performance before and during hemodialysis: a randomized cross-over trial. Nephron Clin Pract. 2013;124(3–4):151–158. [PubMed: 24335582]
67. Hedayati SS, Minhajuddin AT, Afshar M, et al. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. JAMA. 2010;303(19):1946–1953. [PubMed: 20483971]
68. Rojas GJ, Villar V, Iturry M, et al. Efficacy of a cognitive intervention program in patients with mild cognitive impairment. Int Psychogeriatr. 2013;25(5):825–831. [PubMed: 23414646]
69. Liu-Ambrose T, Best JR, Davis JC, et al. Aerobic exercise and vascular cognitive impairment: a randomized controlled trial. Neurology. 2016;87(20):2082–2090. [PubMed: 27760869]
70. 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. [PubMed: 25771249]
71. Angevaren M, Aufdemkampe G, Verhaar H, et al. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2008;2 10.1002/14651858.CD005381.pub2.

Clinical Vignette:

Mr S first started receiving hemodialysis 7 years ago. He is an avid sports fan and would always eagerly discuss the weekend scores and highlights. During the past year, you have noticed a change in your interactions with him. Though he still brings up the latest game, the conversation does not go any further than the score. He has started to gain increasing amounts of weight between dialysis sessions, which is difficult to remove due to worsening cramping. You are unsure if he is taking his medications outside of the dialysis unit as his monthly phosphorus level creeps higher. When asked to bring in all his medicine bottles, he readily agrees but never carries through with the request. His sister, who sometimes comes to the unit with him, pulls you aside and says she is concerned that he isn't able to take care of himself at home. He shrugs off these concerns, telling you that she is "just worrying about nothing."

In Practice is a focused review providing in-depth guidance on a clinical topic that nephrologists commonly encounter. Using clinical vignettes, these articles illustrate a complex problem for which optimal diagnostic and/or therapeutic approaches are uncertain.

Box 1.

Strategies for the Care of Individuals With CKD and Cognitive Impairment (Expert Opinion)

- Frequent follow-up visits
- Integrated care between technicians, dieticians, nurses, and physicians
- Written instructions
- Family involvement in care, education, and decision making
- Discussion of advanced directives and life goals with patient and family
- Medication therapy management (eg, “pill counts”)
- Consideration of palliative care and/or hospice referral with or without withdrawal from dialysis if advanced dementia

Abbreviation: CKD, chronic kidney disease.

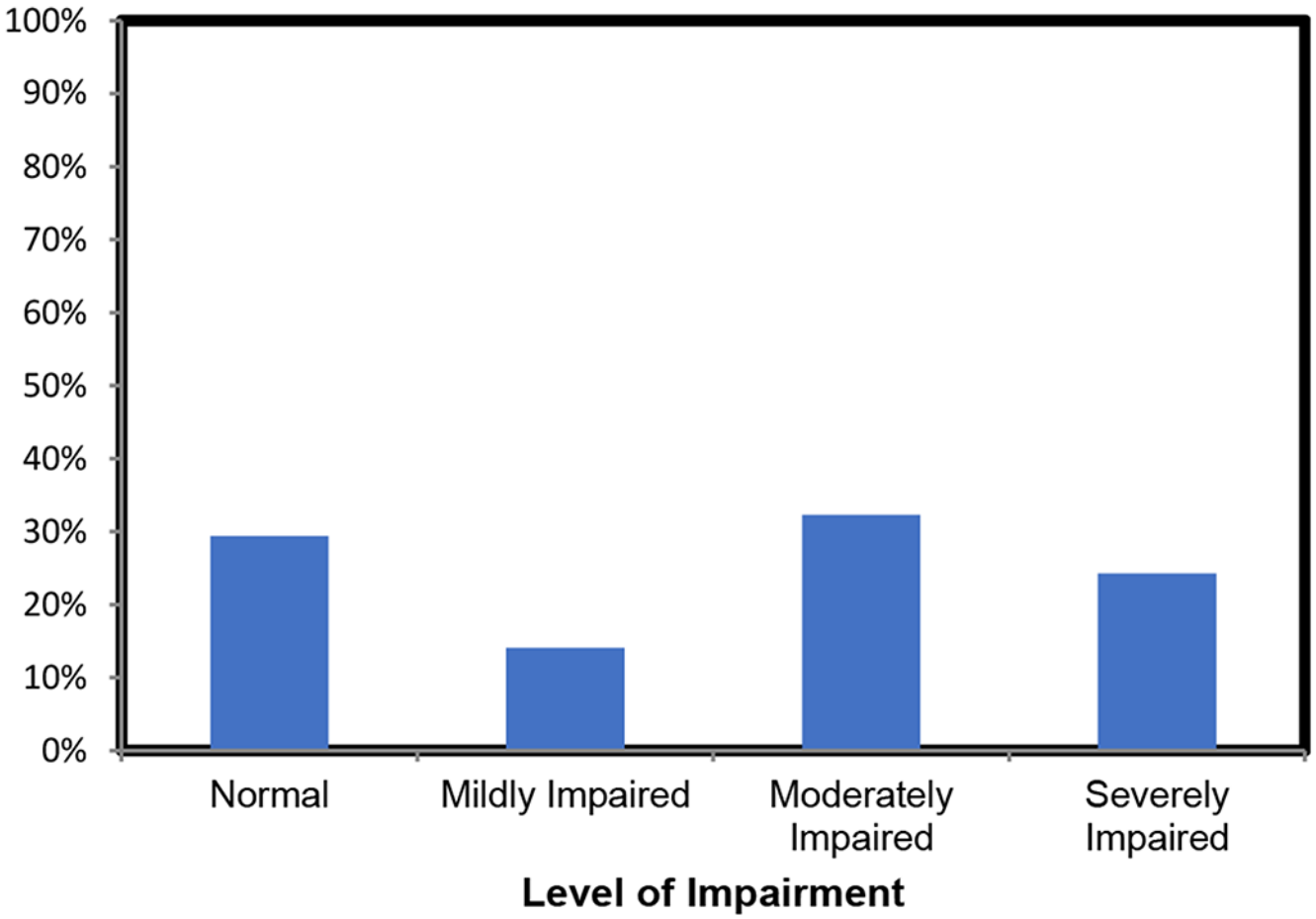

Figure 1.

Cognitive impairment in dialysis patients. A comprehensive battery of neurocognitive tests was administered in the first hour of hemodialysis to 314 patients and cognitive impairment was defined using methodology based on that described by Murray et al.[8] Only 30% of hemodialysis patients had intact cognitive performance, while more than half had moderate or severe cognitive impairment. Extracted from data reported in Sarnak et al.[3]

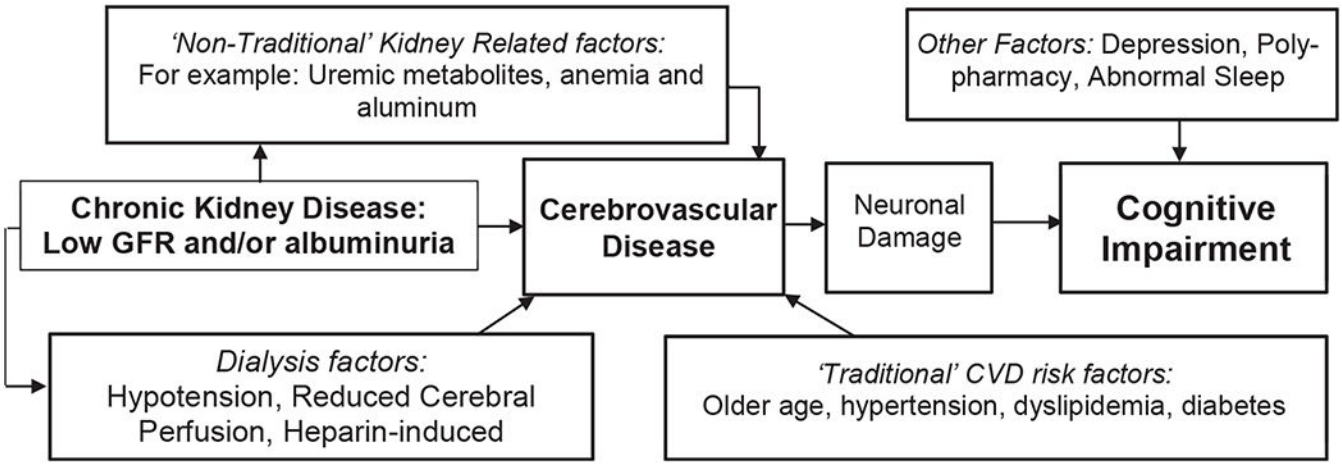

Figure 2.

Proposed pathophysiology of chronic kidney disease-related cognitive impairment.

Abbreviations: CVD, cardiovascular disease; GFR, glomerular filtration rate.

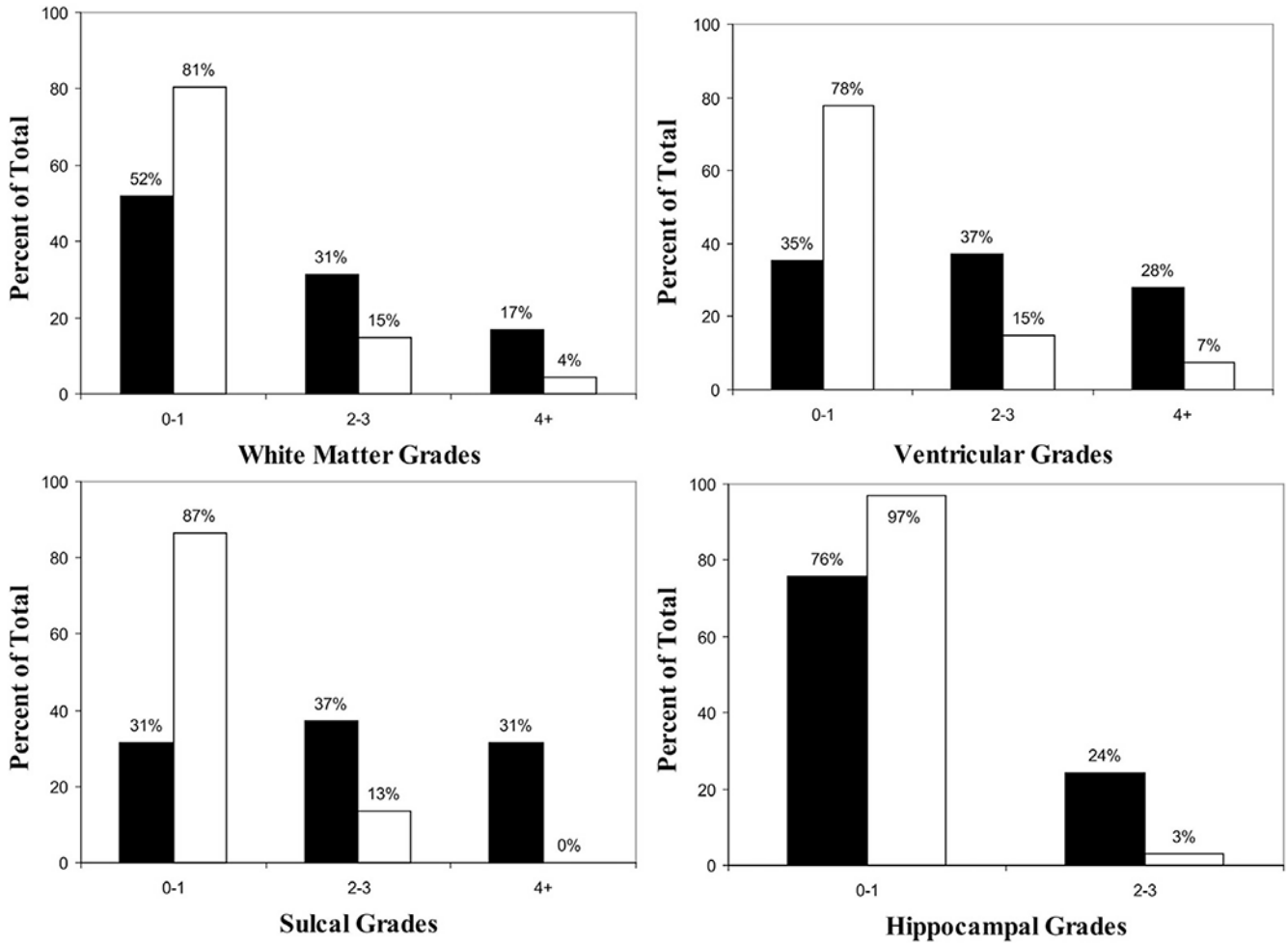

Figure 3.

Distribution of brain magnetic resonance imaging (MRI) white matter disease and cerebral atrophy grades for individuals receiving maintenance hemodialysis versus individuals without known chronic kidney disease. Hemodialysis patients consistently displayed more severe white matter damage and more cerebral atrophy than controls. Black = hemodialysis group, white = control group without reported kidney disease. Higher grades correspond to more white matter disease or greater atrophy. Reproduced from Drew et al,[17] with permission of the National Kidney Foundation.

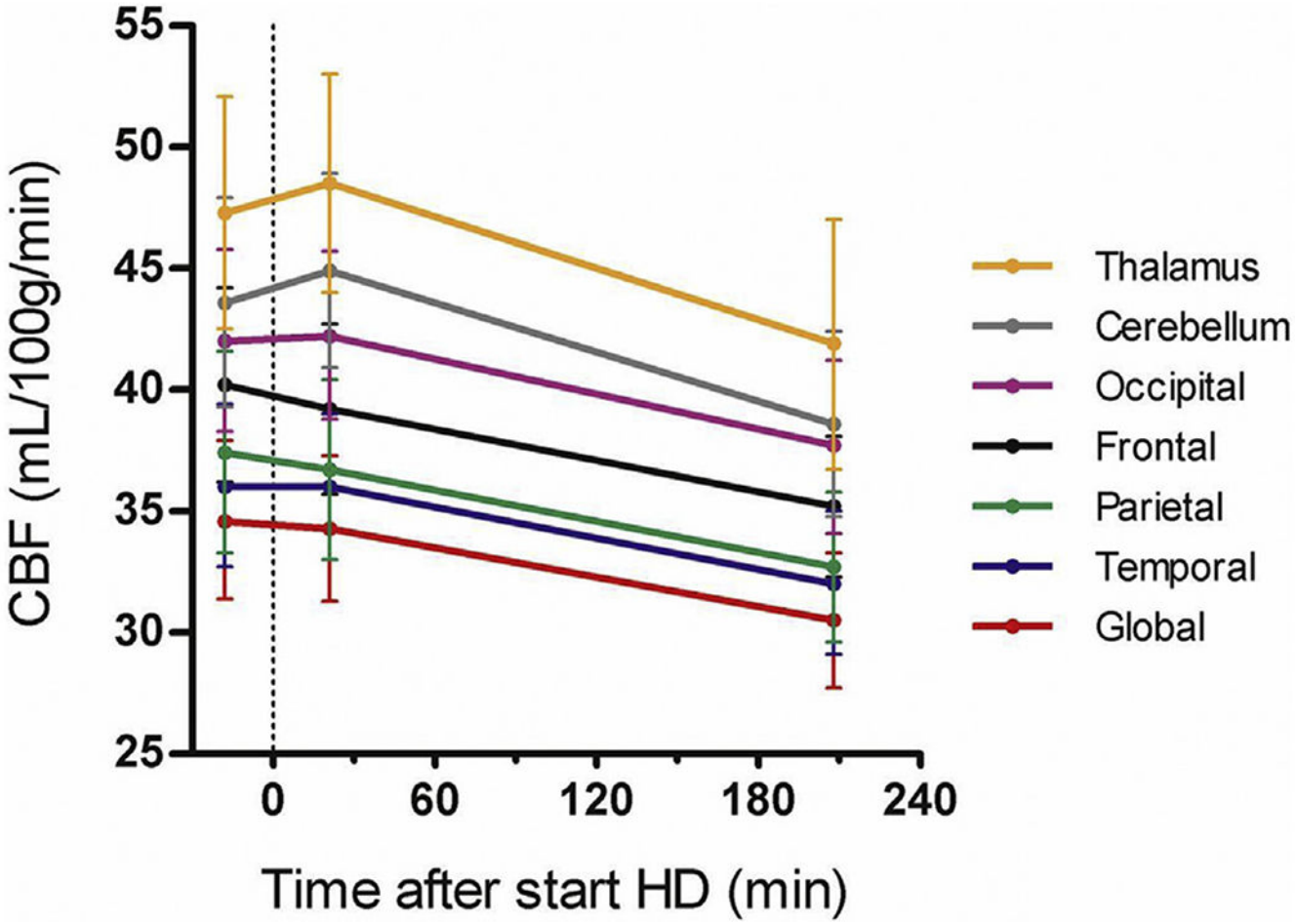

Figure 4.

Hemodialysis (HD) consistently induced a decrease in cerebral blood flow (CBF) in elderly patients during the course of an HD treatment. The decrease in blood flow was observed across multiple different brain regions, as measured using positon emission tomography–commputed tomography. Image ©2018 American Society of Nephrology; reproduced from Polinder-Bos et al[37] with permission of the copyright holder.

Table 1.

Potential Interventions to Reduce the Incidence of Cognitive Impairment in Individuals With CKD

Intervention	Population Targeted	Evidence in CKD
Control of traditional CVD risk factors	CKD	Extrapolation from general population
ACE inhibitor or angiotensin receptor blocker[55]	CKD	Post hoc analysis of RCTs
Intensive blood pressure control[56]	CKD	RCT with CKD participants
Interventions to reduce hemodynamic instability including intradialytic cooling[60]	Dialysis	Dialysis RCT
Kidney transplantation[22,23,59]	Kidney failure	Multiple cohort studies with transplant participants
Treatment of depression[45,67]	CKD and dialysis	Extrapolation from CKD and dialysis cohort studies
Improved sleep hygiene[46]	CKD and dialysis	Extrapolation from dialysis cohort study
Cognitive/brain training[68,70]	CKD and dialysis	RCTs in general population
Avoiding sedating medications & polypharmacy	CKD and dialysis	Expert opinion
Exercise[69–71]	CKD and dialysis	RCTs in general population

Abbreviations: ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; CVD, cardiovascular disease; RCT, randomized controlled trial.