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Consequences of CKD on Functioning

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Abstract

CKD is highly prevalent in the U.S. and throughout the world,¹ with approximately 13% of adults affected.² In addition, according to recent estimates, almost half of patients with CKD stage 3-5 are 70 years of age or older.² In the United States, the number of prevalent ESRD cases continues to rise in patients aged over 65. In light of the demographic characteristics of patients with CKD and ESRD, there has been considerable focus on associations between CKD and cardiovascular outcomes.³ Until recently, less attention had been paid to other consequences of CKD in general and among older individuals with CKD in particular, but there is now solid evidence linking CKD with impairments of physical function, cognitive function, and emotional function and quality of life. This review will summarize available literature on these topics, focusing specifically on physical functioning and frailty; cognitive function; emotional health, including depression and anxiety; and health-related quality of life.

Keywords

Chronic kidney disease; physical function; frailty; cognitive function; depression; health-related quality of life

Physical Functioning and Frailty in CKD

It has been clear for some time that patients with ESRD^{4,5} and CKD not requiring dialysis^{6,7} have impaired maximal oxygen consumption during maximal exercise testing, and more recent studies have also examined other tests of physical performance. One of the larger studies of patients with CKD found that Vo_{2peak} was 54 ± 20 % of sedentary age-predicted values among 32 patients with eGFR 30 ± 17 ml/min/1.73m². These individuals also performed poorly on several tests of performance of day-to-day activities, with maximal gait speed over a short distance that was approximately 85% of population norms and sit-to-

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stand performance 79% of expected.⁸ A Swedish study of physical fitness in CKD patients found that the mean peak values of handgrip strength were $78.0 \pm 24.8\%$ of the age- and sex- matched reference values for men and $84.0 \pm 22.2\%$ for women. The proportion of patients who failed to rise from a chair without using their arms was higher among individuals with lower eGFR, and no patients with $eGFR < 12 \text{ ml/min/1.73m}^2$ were able to perform the maneuver.⁹

Data from community cohorts have been analyzed to address individuals with earlier stages of CKD. In the prospective University of Alabama at Birmingham Study of Aging, community-dwelling older adults with CKD, defined as $eGFR < 60 \text{ ml/min/1.73m}^2$ by the MDRD formula, had higher adjusted odds of decline in both basic (OR 2.46; 95% CI 1.19 to 5.12) and instrumental activities of daily living (ADL) (OR 1.83; 95% CI 1.06 to 3.17) compared to those without CKD.¹⁰ In data from the Health, Aging, and Body Composition Study, $eGFR$ less than $60 \text{ ml/min/1.73m}^2$ was independently associated with the development of difficulty in walking one-quarter of a mile or climbing 10 steps.¹¹ In a follow-up to that study, participants in the highest quartile of cystatin C concentration (1.13 mg/L) experienced a significantly higher risk of developing functional limitation (HR 1.70; 95% CI 1.40 to 2.07) than those in the lowest quartile ($< 0.86 \text{ mg/L}$).¹¹

It was not surprising that investigators in the Heart and Soul Study¹² found that exercise capacity, defined as metabolic equivalents (METs) achieved at peak exercise, was reduced in patients with $eGFR < 60 \text{ ml/min/1.73m}^2$ (OR 6.7; 95%CI 3.8 to 11.8 for low exercise capacity, defined as $< 5 \text{ METs}$) compared to those with $eGFR > 90 \text{ ml/min/1.73m}^2$. However, more novel was their finding that participants with $eGFR$ of $60\text{-}90 \text{ ml/min/1.73m}^2$ were also more likely to have low exercise capacity (OR 2.3; 95% CI 1.4 to 3.8), suggesting that maximal exercise tolerance may become impaired even in the early stages of CKD. Furthermore, the proportion of participants with poor exercise capacity was 45% among those with cystatin C concentration in the highest quartile ($> 1.3 \text{ mg/L}$) compared with 12% among those in the lowest quartile ($< 0.92 \text{ mg/L}$, adjusted OR 3.2; 95%CI 1.6 to 6.5, $p=0.001$).¹³ Leikis and colleagues also demonstrated¹⁴ that as renal function declined over 2 years, there was a corresponding decrease in exercise performance even when hemoglobin was maintained.

More recent studies have focused on frailty, which is described in the geriatric literature as a multidimensional construct characterized as a state of reduced functional capacity in the elderly that predicted risk of disability, hospitalization, institutionalization, and death.¹⁵ The most widely cited index used to define the frailty phenotype includes unintentional weight loss, muscle weakness (grip strength), self-reported fatigue or exhaustion, low physical activity, and slow walking speed.¹⁶ Analysis from the Cardiovascular Health Study, in which the measure was developed, showed that community-dwelling elderly individuals with CKD, defined as a serum creatinine level of 1.3 mg/dL in women and 1.5 mg/dL in men, were three times as likely to be frail compared to those with normal renal function.¹⁷ The frailty phenotype was associated with 2.5-fold (95% CI 1.4 to 4.4) higher risk of death or dialysis therapy when compared with nonfrail CKD participants followed for 2.5 year in the Seattle Kidney Study.¹⁸ Using a modification of previously validated frailty criteria, investigators reported that the prevalence of frailty was 20% among participants in the Third National

Health and Nutrition Examination Survey (NHANES) with eGFR less than 45 ml/min/1.73m² compared with 1.5% in those without CKD. The likelihood of frailty was significantly higher among individuals at all stages of CKD. Participants with more severe CKD were more likely to be frail, and both frailty and CKD were independent predictors of mortality.¹⁹ After dialysis initiation, two-thirds of the incident dialysis patients participating in the United States Renal Data Systems (USRDS) Dialysis Morbidity and Mortality Study were frail.²⁰ Older patients, women, and patients with diabetes mellitus were more likely to be frail, and frailty was associated with 2-3 fold higher risk of death.

A few studies have examined functional outcomes after the start of dialysis among the elderly. Using a national registry of nursing home residents, Kurella Tamura and colleagues²¹ examined the effect of dialysis initiation on functional status, measured by the degree of dependence in activities of daily living (ADL) on the Minimum Data Set-Activities of Daily Living (MDS-ADL). By 12 months after initiation of dialysis, 58% had died, and predialysis functional status had been maintained in only 13%. Initiation of dialysis was associated with a sharp decline in functional status indicated by an increase of 2.8 points (95% CI 2.5 to 3.0) in the MDS-ADL score independent of age, sex, race, and functional status before the initiation of dialysis. Jassal et al.²² also demonstrated a loss of independent function 1 year after initiation of long-term dialysis in ESRD patients aged over 80 years with multiple coexisting conditions (mean modified Charlson score of 5.1±2.5). At the start of dialysis, 78% of the cohort was independent (residing in the home without assistance), but after 1 year, this percentage had decreased to 23%. Moreover, within the first 6 months, more than 30% of patients had functional loss requiring community or private-caregiver support, or transfer to a nursing home.

Although the extent to which initiation of dialysis directly affects frailty status remains unclear from the aforementioned studies, it does not appear that frailty and disability improve after the start of dialysis. Rather, available evidence suggests that physical functioning begins to decline in the early stages of CKD and continues unabated if not specifically addressed. Exercise interventions can improve physical functioning,^{23, 24} and rehabilitation programs can improve disability among patients with ESRD,²⁵ but these programs have not been widely implemented in the U.S.

Cognitive dysfunction

Patients with CKD and ESRD have a higher prevalence of cognitive dysfunction than the general population even when accounting for age, diabetes, cardiovascular risk, and other comorbidities.^{26,27} Furthermore, several studies have established that dementia and mild cognitive impairment are associated with higher mortality among patients with ESRD. Kurella *et al.* reported a RR of mortality of 1.48 (95% CI 1.32 to 1.66) among HD patients with dementia compared to those without dementia.²⁸ A separate prospective cohort study in patients treated with dialysis without a history of dementia or prior stroke also showed an adjusted HR for all-cause mortality of 2.53 (95% CI 1.03 to 6.22) at 7 years comparing mild to moderate cognitive impairment with no deficits.²⁹

Although cognitive testing is not routinely performed among patients with CKD and ESRD, the prevalence of cognitive impairment is estimated to be 30-70% in this population.^{30,31} In a cross-sectional study of 338 patients treated with hemodialysis aged 55 years or older conducted by Murray *et al.*, only 2.9% had a prior history of cognitive impairment. However, when tested for memory, executive function, and language performance, 13.1% had mild impairment, 36.1% moderate impairment, and 37.3% severe impairment; only 12.7% had normal function.³²

Although the prevalence of dementia in hemodialysis patients has been known to be high for years,³³ the prevalence and importance of mild cognitive impairment (MCI) has been less appreciated. Studies in the CKD population have varied according to which neuropsychological tests they used, with the Mini Mental State Examination (MMSE),³⁴ the Modified Mini-Mental State (3MS), the Trailmaking Test B (or Trails B), and the Montreal Cognitive Assessment (MoCA) being most common. The 3MS measures global cognitive function and is more sensitive for MCI than the MMSE.³⁵ The Trails B measures executive function, visuospatial ability, and concentration.³⁶ Apart from type of testing, studies also vary with regard to adjustment for depression, vascular risk factors, and prior CVA,³⁷ as well as to the timing of cognitive testing during, before, or after dialysis.³⁸⁻⁴⁰ Timing of cognitive testing relative to dialysis has been shown to affect scores, with better results either on the day after dialysis or immediately before dialysis and lower test scores during and within one hour after dialysis sessions.⁴¹ In a study of 51 male participants, 24 with CKD and 27 receiving HD, although all 51 patients scored >28 on the MMSE (implying normal cognition), 76% were diagnosed with MCI based on more comprehensive neuropsychological testing.⁴² In a hemodialysis-specific study, the optimal MoCA cut-off score, determined using receiver operating characteristics (ROC) analysis, was 24, which had 77% sensitivity and 79% specificity for mild cognitive impairment, whereas an MMSE score of 28, used in the general population, had 55% sensitivity and 75% specificity.⁴³

Association of GFR and albuminuria with cognitive dysfunction

The majority of studies point to a strong association between eGFR and cognitive dysfunction.⁴⁴ Cognitive impairment is more prevalent and more severe among individuals with lower eGFR, and the burden and severity are higher in ESRD as compared to earlier stages of CKD.^{31,45} A cross-sectional study of 923 patients with CKD without prior dementia or ESRD showed that eGFR of <60 ml/min/1.73 m² (by MDRD equation) was related to lower cognitive performance even after adjusting for cardiovascular disease risk factors.⁴⁶ In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, which involved 23,405 participants with CKD, each 10 ml/min/1.73 m² decrement in GFR was associated with an 11% higher risk of cognitive impairment (OR 1.11, 95% CI 1.0-1.2).⁴⁷

In the Chronic Renal Insufficiency Cohort Cognitive Study (CRIC COG), comprising 825 adults aged 55 years and older enrolled in the CRIC, those with eGFR <60 ml/min/1.73 m² had significantly lower odds of having a cognitive testing score 1 SD or more below the mean on a battery of tests as compared to those with eGFR from 45-59 ml/min/1.73 m². Those with eGFR 30-44 ml/min/1.73m² performed worse, and those with eGFR <30

ml/min/1.73 m² had the highest odds of poor performance. After adjustment for age, sex, race, education, DM, HTN, BMI, and depression, the graded association between eGFR and cognitive function was preserved in all tested domains except verbal fluency.²⁶

Individuals with lower eGFR are also at higher risk of decline in cognitive function over time, and cognitive impairment can also become apparent relatively early in the course of CKD if patients undergo cognitive testing. In the Northern Manhattan Study,⁴⁸ a population-based, prospective cohort study of patients without prior stroke, those with a Cockcroft-Gault estimated creatinine clearance (eCrCl) of <60 ml/min performed worse than those with eCrCl from 60-90 ml/min on the Telephone Interview for Cognitive Status Score (TICS-m). Patients in both categories of CKD performed worse than those with a eCrCl of >90 ml/min. Furthermore, each 0.1 mg/dL higher serum creatinine concentration corresponded to an average decline of 0.04 in the TICS-m score per year over a mean follow-up of 2.9 years. By way of comparison, each year of age was associated with a decline of 0.023 per year over the same follow-up, such that patients with eCrCl of 60-90 ml/min declined approximately three times faster than those without CKD.⁴⁸

In the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg (INVADE), there was no difference in baseline cognitive impairment according to eGFR category (>60, 45-60, and < 45 ml/min/1.73 m²) among 3679 elderly men and women. However, the incidence of new cognitive impairment was 5.8, 9.9, and 21.5% respectively, in these groups, suggesting that worse CKD was associated with more rapid decline in cognitive function.⁴⁹

Davey *et al.* conducted a 5-year longitudinal study with 17 separate cognitive tests among community-dwelling individuals (mean age 62.1 years) without any history of dementia, stroke, or ESRD. More rapid decline in eGFR was associated with more rapid decline in cognition, including global cognitive functioning, visual memory, and abstract reasoning domains. A decline in eGFR of 6 ml/min/1.73 m² per year corresponded to approximately the same decline in cognition over 5 years as might be expected with over 11 to 12 years in the absence of a decline in eGFR.⁵⁰ The Health, Aging, and Body Composition Study showed a similar graded association between eGFR and cognition at baseline as well as risk for decline in cognition over time. Compared to patients with eGFR 60 ml/min/1.73m², the odds ratio for developing cognitive impairment was 1.32 (95% CI 1.03 – 1.69) for those with eGFR 45-59 ml/min/1.73 m² and 2.43 (95% CI 1.38 – 4.29) for those with eGFR <45 ml/min/1.73 m².⁵¹

The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD-MIND) substudy examined the association of albuminuria (≥ 30 mg albumin/g Cr in spot urine) and four indices of cognitive function, including executive function among 2,977 patients with HbA1c >7.5%. Participants with albuminuria were more likely to perform poorly on the SDST and on a verbal memory test, with scores equivalent to ~3.6 years of aging.⁵² Barzilay *et al.* followed ACCORD-MIND participants and characterized them as having no, persistent, progressive (development of new albuminuria), or remitting albuminuria (resolution of albuminuria).⁵³ Patients with persistent albuminuria had the poorest performance on cognitive tests at baseline, whereas those with no albuminuria

performed best.⁵³ Over an average of 3.3 years of follow-up, the largest change in cognitive function testing was in the SDST, and persistent and progressive albuminuria were associated with 7.2 and 3.2 years of cognitive aging per year of actual aging, respectively, independently of change in eGFR.

Association of dialysis modality and dose with cognitive function

The association of dialysis modality with cognitive function is not clear. One study found less cognitive impairment among patients treated with peritoneal dialysis than among those on hemodialysis based on neuropsychological testing.⁵⁴ Another study using EEG-based parameters related to attention and cognition⁵⁵ reported that EEG responses were worse among patients on hemodialysis than those on PD before the dialysis session but not after dialysis, suggesting that dialysis may correct metabolic factors affecting cognition.⁵⁶ A more recent study comparing matched HD and PD patients did not find statistically significant differences in processing speed.⁵⁷ A larger study that included 145 prevalent dialysis patients, of whom 17% were treated with home hemodialysis patients and 47% with PD, did not find any association between dialysis modality and cognitive function on a battery of neuropsychological tests. Of note, home hemodialysis patients were analyzed in the same group as in-center hemodialysis patients, which may have biased towards a healthier HD group.²⁹ In general, the possibility of selection bias based on modality choice in these observational studies, with more cognitively intact patients selecting PD, cannot be discounted.⁵⁸

Dose of dialysis has not been directly associated with cognitive function. In cross-sectional data from the Frequent Hemodialysis Network (FHN) Trials,⁴⁰ there were no independent associations among urea clearance, dietary protein intake, nutritional markers, hemodynamic measures, or other dialysis therapy associated markers and global cognition or executive function. In the interventional parts of the studies, frequent hemodialysis did not improve cognitive dysfunction using the Trails B, the MMSE, and the 3MS, or other tests compared to standard dialysis. However, the studies were not blinded, and the sample sizes relatively small.⁵⁹ Another study examining dialysis adequacy showed no association between dialysis dose (single pool Kt/V) and cognitive decline, but the range of spKt/V was relatively narrow, from 1.25 to 1.79.³⁹ Interestingly, a longitudinal study of patients receiving renal allografts did show that patients with impaired cognitive function prior to transplant improved after transplantation such that post-transplant test scores were not appreciably different from healthy norms.⁶⁰ Although we are not including children in this review, we note that the presence of neurocognitive deficits even in children^{61, 62} also supports a possible effect of CKD or its sequelae on neurologic function.

Etiology of cognitive dysfunction

The pathophysiology of dementia and cognitive impairment in CKD has not been fully elucidated, but is likely multifactorial (Figure). In addition to possible toxic/metabolic causes of cognitive dysfunction, cerebrovascular disease (CVD) may contribute. CVD is more common in all stages of CKD relative to the general population, particularly among patients receiving maintenance dialysis.^{37, 63, 64} The relative risk of stroke among dialysis patients compared to the general population ranges from 4.4 – 9.7 after adjusting for age.⁶⁵

Although some of the higher risk can be accounted for by shared risk factors, higher prevalence of traditional risk factors such as diabetes, hypertension, cardiovascular disease, and prior stroke, does not fully explain the inordinately high risk of stroke in CKD and ESRD patients. In addition to stroke, cerebral atrophy and other white matter lesions have also been encountered on brain MRI of patients treated with dialysis, and white matter lesions have been linked to cognitive dysfunction, even without a history of stroke.⁶⁶

Patients with ESRD appear to have altered remodeling of vasculature and increased arterial stiffness, which could be related to volume overload and abnormalities in calcium and phosphate metabolism.⁶⁷ Hemodynamic variability experienced by HD patients may be an exacerbating factor, leading to perfusion mismatches and in turn to higher risk of stroke or other forms of brain injury.^{68,69}

Fazekas *et al.* performed a study in which magnetic resonance imaging (MRI) and neuropsychological testing were performed on 30 patients on HD and 30 patients matched for age, sex, and presence of HTN, CAD, and DM.⁷⁰ HD patients had significantly worse cognitive function than controls, as well as higher grades of brain atrophy and a higher prevalence of all types of vascular lesions than the controls. Marked cognitive impairment was associated with atrophy, but not with vascular lesions in the dialysis group.

In a cross-sectional study of 45 maintenance dialysis patients and 67 controls without known kidney disease, Drew and colleagues found that hemodialysis patients had more white matter disease and cerebral atrophy compared with controls, as well as a high prevalence of unrecognized infarcts.⁶⁶ A study in 335 elders in Boston receiving home health care found that albuminuria was associated with worse executive function when controlling for traditional cardiovascular risk factors and eGFR, and was also associated with higher volume of white matter hyperintensity, suggesting a role for microvascular disease in the cognitive dysfunction and MRI abnormalities of individuals with CKD.⁷¹ A study of 600 older individuals with vascular risk factors found that CKD was associated with a higher risk of incident dementia even after adjusting for MR findings, including cerebral atrophy, lacunar infarction, and white matter hyperintensities, implying that there may be damage not visible with traditional MRI techniques.⁷² In fact, studies using more sensitive MRI techniques have shown that patients with ESRD have increased axonal demyelination compared to healthy, age-matched controls.⁷³ Taken together, these studies demonstrate correlations between anatomic abnormalities and cognitive dysfunction in the dialysis population. Few studies have addressed treatment of cognitive dysfunction in the CKD population, so management of metabolic disturbances and dementia-specific treatments used in the general population are the rule.

Impact of CKD on Emotional Functioning and Quality of Life

Patients with CKD are at risk for developing or worsening preexisting psychological illness such as depression and anxiety. They face stressors that can affect their emotional state, such as adjustment to strict dietary and fluid restriction and concern about initiation of dialysis, as well as fear of burdening caregivers. The heavy burden of symptoms among patients with CKD and ESRD, including pain, fatigue, and impaired well-being, may also contribute.^{74, 75}

Depression

Magnitude of the Problem

Depression is one of the most common psychiatric illnesses in the CKD population. Although the actual prevalence of depressive symptoms among CKD patients is presumably underestimated, it has been reported to be nearly three times higher than the 2-10% commonly reported in the general population⁷⁶ and also higher than among patients with other chronic diseases such as diabetes mellitus⁷⁷ and congestive heart failure.⁷⁸ The reported prevalence clearly depends on the screening techniques used to identify depression. Data from the Chronic Renal Insufficiency Cohort (CRIC) study revealed that the prevalence of depressive symptoms varied according to level of kidney function, with lower eGFR associated with higher odds of depression.⁷⁹ In contrast, Hedayati and colleagues found that the point prevalence of major depression was approximately 20% and did not vary significantly among different stages of CKD.⁸⁰ Palmer and co-workers⁸¹ conducted a meta-analysis of depressive symptoms determined by clinician-administered questionnaire across all stages of CKD and reported that dialysis patients experienced the highest rate of depressive symptoms (39.3%). The prevalence of depressive symptoms in patients with CKD (a mix of stages 1-5) and kidney transplant recipients were 26.5% and 26.6%, respectively. The prevalence of depression in CKD patients was markedly lower, 20.3%, when assessed by specified diagnostic criteria using structured clinical interview.⁸¹

In addition to the negative experience of having depressive symptoms, they are also associated with adverse medical outcomes. CKD patients with depression have worse overall quality of life, significantly faster eGFR decline with rapid progression to ESRD⁸², as well as higher risk of hospitalization and death.⁸³⁻⁸⁶ Longitudinal data from chronic hemodialysis patients observed that worse scores on the Patient Health Questionnaire (PHQ)-9 depression instrument were related to reductions of 1.09, 4.52, and 0.64 points in quality of life evaluated by the physical and mental component summary of Short form 12, and Global Quality of life score, respectively.⁸⁷ Using data collected from participants of the Symptom Management Involving End-Stage Renal Disease (SMILE) Trial, depressive symptoms were independently associated with both missed and shortened dialysis sessions, with incidence rate ratios [IRR] of 1.21; 95% CI 1.10 to 1.33 and 1.08; 95% CI 1.03 to 1.14, respectively, as well as with more emergency department visits (IRR 1.24; 95% CI 1.12 to 1.37).⁸⁸ Indeed, patients receiving hemodialysis who have a clinical diagnosis of depression have a higher hazard of death or hospitalization (HR 2.07, 95% CI 1.10 to 3.90) compared with those without depression after adjustment for age, gender, race, dialysis vintage, and comorbidities.⁸⁹ Among patients treated with PD, the median survival was significantly shorter among patients with depressive symptoms compared to non-depressed patients.⁹⁰

Screening and diagnostic tools

Various screening questionnaires have been validated against Diagnostic and Statistical Manual of Mental Disorders (DSM)-based structured interviews in CKD and dialysis populations (Table 1). Most of these screening tools are not time-consuming and could be easily used in CKD clinics and dialysis facilities. Therefore it has been suggested that screening for depression should be incorporated into routine clinical practice in these

settings. The Beck Depression Inventory (BDI) has been extensively studied, and Hedayati and colleagues suggested that the optimal cutoff score for diagnosis of depression was 14 (sensitivity 62%, specificity 81%) in patients receiving hemodialysis,⁹¹ whereas they suggested a lower BDI cutoff value 11 (sensitivity 89%, specificity 88%) in stage 2 to 5 CKD.⁹² The higher cutoff values for the ESRD population are necessary because of overlapping somatic symptoms of uremia and depression: loss of energy, fatigue, decreased appetite, and difficulty concentrating. Importantly, in order to affirm the diagnosis of depression and grade the disease severity in patients who screen positive using questionnaire-based criteria, particularly among ESRD patients, a physician-administered interview such as the Structured Clinical Interview for DSM criteria (SCID)⁹³ with the Mini International Neuropsychiatric Interview (MINI)⁹² is suggested before initiating treatment.

Management

A multidisciplinary team approach including psychiatrists, psychologists or social workers should be taken in the treatment of depression. Combined pharmacological and nonpharmacological treatment (psychological counseling) is the mainstay of treatment of depression in patients with CKD and ESRD. A randomized trial of 12 weekly sessions of cognitive behavioral therapy (CBT) in 85 depressed hemodialysis patients demonstrated that the intervention group experienced significant improvement compared to usual treatment in mean BDI scores (24.2 ± 9.7 to 14.1 ± 8.7 vs 27.3 ± 10.7 to 21.2 ± 9.7 , $p < 0.001$, respectively).⁹⁴ Cukor and colleagues conducted a randomized crossover trial in 59 ESRD patients comparing chairside CBT during dialysis treatment *versus* a wait-list control group that received usual standard of care, including formal psychological or psychopharmacologic treatment by their primary nephrologists and found that CBT intervention significantly reduced the rate of diagnosis of depression by SCID (89.5% of participants were considered non-depressed at the end of treatment compared with 37.5% in the wait-list group, $p = 0.01$) and subjective depression scores (mean BDI score change -11.7 ± 1.5 vs -4.8 ± 1.4 , $p < 0.001$, respectively).⁹⁵ Exercise training programs may also be an option for reducing depressive symptoms in dialysis populations, as long as the intervention is of sufficient duration – typically at least six months⁹⁶⁻⁹⁸. Social support has also been shown to decrease depressive symptoms, specifically increasing optimism and self-esteem among ESRD patients.⁹⁹

In pharmacologic treatment of depression among patients with advanced CKD and ESRD, consideration is needed regarding the appropriate medication dose, potential adverse effects, and drug-drug interactions. Despite the high prevalence of depression, a majority of patients are left untreated¹⁰⁰, perhaps as a result of medication-related concerns of patients or providers. In a cross-sectional analysis of the African American Study of Kidney Disease and Hypertension (AASK) cohort study, only 20% of patients with depressive symptoms diagnosed by BDI scores over 14 were prescribed antidepressants.¹⁰¹

Most antidepressant medications are highly protein bound and are not effectively removed by HD or PD.¹⁰² These medications commonly undergo hepatic metabolism, but the active metabolites are excreted via the kidney. Hence the dosing should be cautiously adjusted according to eGFR level, with careful monitoring for potential adverse drug effects (Table 2). Use of tricyclic antidepressants, serotonin modulators, and monoamine oxidase inhibitors

should be limited because of cardiac and central nervous system side effects, including prolonged QTc, arrhythmia, anticholinergic effects, and orthostatic hypotension.¹⁰³ Selective serotonin re-uptake inhibitors (SSRIs) are considered the first-line agents for patients with stage 3-5 CKD if treatment with an antidepressant is indicated.^{104, 105} There have been several studies of these agents in patients with ESRD¹⁰³, but most were of short duration and had small sample sizes. Blumenfeld et al.¹⁰⁶ studied the efficacy and safety of fluoxetine in hemodialysis patients with major depression by randomly assigning patients to fluoxetine vs placebo for an eight-week period. The treatment group experienced a significant improvement in depression at 4 weeks that was not sustained at 8 weeks. All side effects reported were minor, and no patients discontinued study drugs due to adverse events. Koo and coworkers¹⁰⁷ reported that treatment with paroxetine 10 mg/day plus concurrent psychotherapy for 8 weeks in ESRD patients decreased the severity of depressive symptoms assessed by Hamilton Depression Rating Scale (from 16.6±7.0 to 15.1±6.6, $p<0.01$). Citalopram is frequently prescribed, and there is minimal change in pharmacokinetics of this drug in patients with ESRD.¹⁰⁸ Treatment with 50 mg/day of sertraline (another SSRI) for 12 weeks was associated with a decrease in BDI score from 22.4 to 15.7, $p<0.001$ in patients on PD.¹⁰⁹ However, well-designed studies are limited regarding the efficacy and safety profile of antidepressant medications in patients with CKD not requiring dialysis. The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) study¹¹⁰ is an ongoing double-blinded placebo-controlled trial that aims to recruit 200 participants to investigate whether treatment with sertraline improves severity of depression, overall ability to work and maintain close relationships, and quality of life in patients with stage 3-5 CKD. The results of this trial will generate novel information regarding the efficacy and safety of antidepressant agents in the treatment of depression in patients with advanced CKD.

Other emotional disorders

Anxiety is also commonly encountered among CKD and ESRD patients, but this problem has been substantially less well studied than depression. In fact, anxiety has a negative impact on quality of life and several physical conditions (e.g., migraine headache, allergic conditions, respiratory diseases).¹¹¹ In a cross-sectional study, Lee et al. reported that the prevalence of anxiety was 24.8%, 29.9%, and 34.3% in CKD stage 3, 4, and 5, respectively, and did not differ significantly across CKD stages.¹¹² (By comparison, the prevalence of anxiety in the general population is estimated to be approximately 18%.¹¹³) A systematic review of the prevalence of symptoms of anxiety in maintenance dialysis patients reported that approximately 38% (range 12% to 52%) of patients were affected.¹¹⁴ Although screening for depression is increasing, data on screening for anxiety are scarce. Cukor and colleagues¹¹⁵ found that 71% of hemodialysis patients were diagnosed as having anxiety disorder using the gold standard SCID, whereas only 45.7% of participants met a criterion of anxiety by the Hospital Anxiety and Depression Scale (HADS). These findings suggested that there is poor agreement for anxiety diagnosis between questionnaires and formal interviews. More accurate screening tools are necessary to improve the diagnosis before comparing medical outcomes after treatment of anxiety disorder in patients with ESRD.

Benzodiazepines have been commonly prescribed for treatment of acute episodes of anxiety.¹¹⁶ No dose adjustment is required for renal impairment because benzodiazepines

are metabolized mainly by the liver. However, this drug class should be avoided due to high rates of side effects, such as prolonged sedation, delusions, and hallucinations. Alprazolam and diazepam have higher free serum drug levels in patients with ESRD. Lorazepam is also not recommended for use in patients with CKD.¹⁰⁸

Impact of CKD on Quality of Life

Quality of life is a broad, multidimensional concept that includes an individual's perception of subjective general well-being, in the context of the culture and value systems in relation to their goals, expectations, standards, and concerns.¹¹⁷ Health-related quality of life (HRQoL) is defined by the Centers for Disease Control and Prevention as quality of life and its relationship with health – either physical or mental – comprising health risks and conditions, functional status, social support, and socioeconomic status.¹¹⁸ HRQoL is often compromised in patients with CKD.¹¹⁹

There are numerous valid and reliable tools for evaluating HRQoL. Many experts recommend using disease-specific tools in conjunction with established generic instruments. The most widely used instrument in ESRD clinical practice and research is the Kidney Disease Quality of Life (KDQoL), which incorporates generic and disease-specific scores.¹²⁰ The Medical Outcomes Survey 36 item-Short Form (SF-36) is a generic instrument developed for use in many populations with 8 dimensions of HRQoL that can be summarized into Physical Component Summary (PCS) and Mental Health Component Summary (MCS) scores. The KDQoL also contains disease-specific scales including symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, cognitive function, work status, sexual function, quality of social interaction, and sleep. Multi-item measures of social support, dialysis staff encouragement and patient satisfaction and a single-item overall rating of health are also included.¹²¹ Lower scores for the three major components of KDQoL (PCS, MCS, and the kidney disease component summary [KDSC]) were associated with significantly higher risk of death (adjusted RR per 10-point lower score were 1.13 for MCS [95% CI 1.09 to 1.17], 1.25 for PCS [95% CI 1.20 to 1.30], and 1.11 for KDSC [95% CI 1.08 to 1.13]) and first hospitalization (adjusted RR 1.06 [95% CI 1.04 to 1.08], 1.15 [95% CI 1.12 to 1.39], and 1.07 [95% CI 1.05 to 1.09] for MCS, PCS, and KDSC, respectively) among over seven thousand dialysis patients recruited into the Dialysis Outcomes and Practice Pattern Study (DOPPS).¹²²

HRQoL in patients with CKD

Although there is growing evidence of an association between HRQoL and mortality risk in ESRD patients, few studies have examined HRQoL in patients with earlier stages of CKD. A cross-sectional study in 535 patients with CKD stage 2-5 observed that HRQoL, assessed using the SF-36, was significantly impaired compared to matched controls, and there was a graded association between higher stage of CKD and worse HRQoL.¹²³ However, this study should be interpreted with caution because there were relatively few patients with early stages of CKD (eGFR >50 ml/min/1.73m²) and no patients with eGFR between 30 and 50 ml/min/1.73m². A prospective large-scale study by Mujais and colleagues showed that HRQoL using the KDQoL-SFTM was proportionally lower with greater severity of CKD

stage. Further, HRQoL significantly declined over time with the maximal decrement in Physical Function score, which fell by a mean of -3.23 ± 0.64 points per year, $p < 0.0001$.¹²⁴ Female gender, presence of diabetes, and cardiovascular co-morbidities were associated with lower HRQoL. Another study by Molsted et al.¹²⁵ also documented that CKD patients had lower SF-36 scores than the general population and that the most pronounced impairment was in the Physical Function and Role Physical scales.

One approach to improving HRQoL among patients with CKD has been treatment of anemia using erythropoietin stimulating agents (ESA). A large multi-center cross-sectional study in stage 3-5 CKD by Finkelstein and co-workers¹²⁶ showed that higher hemoglobin levels were associated with significantly higher scores on the SF-36 PCS and general health score of the KDQoL-SF™. The maximal increase in HRQoL per incremental increase in hemoglobin appears to occur in the range of 10-12g/dL, with blunted improvements in HRQoL above this level. The most improved domains are physical symptoms, vitality, energy, and performance.¹²⁷ An open-label study among patients with CKD naïve to ESA with a baseline hemoglobin of 9.1 ± 0.1 g/dL also demonstrated a mean improvement in the KDQoL subscales of burden of kidney disease ($+9.8 \pm 3.2$ points), symptoms ($+4.2 \pm 1.6$), and overall health ($+9.8 \pm 3.3$, all $p < 0.05$) after anemia correction to a hemoglobin of 11.3 g/dL after 8 weeks.¹²⁸ However, the decision to initiate ESA therapy should be individualized based on the risks related to ESA therapy, the presence of anemic symptoms, the rate of fall of hemoglobin concentration, and prior response to iron therapy.¹²⁹

Since there is strong evidence to suggest that emotional problems such as depressive symptoms or anxiety affect HRQoL, it is logical to consider that treatment of these conditions might improve HRQoL. However, it is unclear whether this is the case.^{101, 130, 131}

HRQoL in dialysis patients

A national, prospective cohort study, the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study¹³² examined the difference in self-reported HRQoL and overall health status between patients on HD and PD using the CHOICE Health Experience Questionnaire (CHEQ). This study included 928 incident dialysis patients and reported that HD and PD patients did not differ with respect to the unadjusted or adjusted change in overall health status by CHEQ after 1 year of dialysis. HD patients had better improvement in two general SF-36 domains: Physical Function (5.1 points higher, $p < 0.05$) and General Health (4.1 points higher, $p < 0.05$) than PD patients. However, the results were mixed for ESRD specific domains. PD was significantly better than HD (8.1 points greater) for finances, whereas HD was better than PD for sleep (8.1 points higher) and for overall quality of life (4.3 points higher, all $p < 0.05$). One small randomized trial conducted to compare mean quality-adjusted life-year (QALY) and survival among incident HD and PD patients reported statistically equivalent mean QALY scores in the first two years after the start of dialysis.¹³³ Liem et al.¹³⁴ conducted a meta-analysis to compare SF-36 scores among patients on renal replacement therapy and reported that the unadjusted scores of all SF-36 dimensions did not significantly differ between patients on HD and PD. Recently, a systematic review by Purnell et al.¹³⁵ concluded that patients receiving HD and PD experienced similar rates of

life participation outcomes, including physical functioning, social and recreational activities, freedom, travel, as well as ability to work.

Previous studies have demonstrated that interventions that may improve HRQoL in dialysis patients include correction of anemia,^{136, 137} treatment of depression,¹⁰⁹ structured exercise programs,^{97, 138} and alterations in dialysis regimens. The Frequent Hemodialysis Network (FHN) Trial evaluated changes in HRQoL in patients undergoing HD six times per week compared to patients who continued on a conventional dialysis regimen and showed a significant improvement of the PCS score of SF-36 with frequent dialysis.¹³⁹ However, no dimensions of the SF-36 were changed in patients receiving nocturnal HD performed three times per week for 7-8 hours a night, whereas they deteriorated in the conventional group (bodily pain from 64.9±29.6 to 57.1±28.8, $p=0.03$; mental health from 69.2±23.9 to 65.1±23.1, $p=0.04$; vitality from 68.7±24.3 to 64.4±25.2, $p=0.01$).¹⁴⁰ In the London Daily/Nocturnal Hemodialysis Study¹⁴¹, quotidian HD patients reported significant improvement in renal disease-specific QOL indicators including the numbers of dialysis symptoms, recovery time from dialysis, as well as the General Health and Vitality subscales of SF-36. One of the most striking changes in patients undergoing daily or nocturnal HD was the faster time to recovery after dialysis sessions, which dropped from 327 to 16 minutes after 12 months of short daily HD and 2 minutes after 15-month of nocturnal HD.¹⁴² In PD patients, however, data regarding the change of dialysis regimen yielded an opposing result. HRQoL assessed by KDQoL-SF™ did not significantly improve after increasing small solute peritoneal clearance in the Adequacy of Peritoneal Dialysis in Mexico study.¹⁴³

Conclusions

Overall, CKD and ESRD are associated with impairments in physical function, cognitive function, emotional health, and health-related quality of life. In general, these issues seem to worsen as kidney disease progresses despite management of kidney disease and initiation of dialysis. These disorders may respond to traditional therapy, but in some cases adjustments are needed in the CKD. Routine screening for depression, as is recommended in the general population, could lead to more treatment and better HRQoL among patients with CKD. In addition, although vigorous exercise training has not been a sustainable model among patients with advanced CKD and ESRD, more research is needed to determine whether increasing physical activity through less vigorous means could improve physical function, depression, and cognitive function in this population – or, short of improvement, whether the seemingly inevitable decline can be mitigated.

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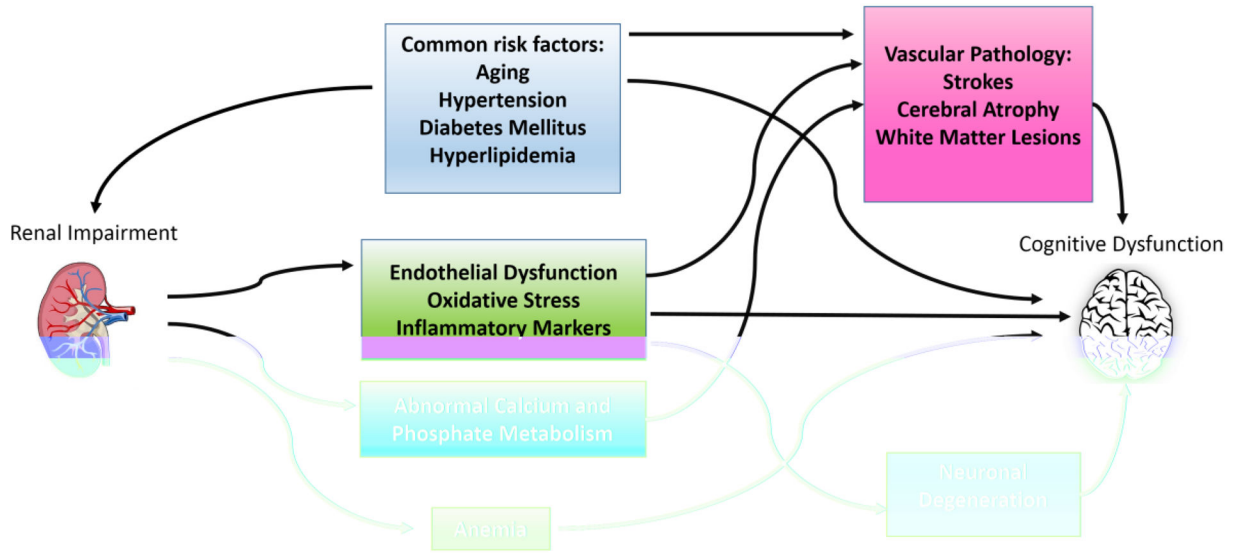


Figure.
Potential causes of cognitive dysfunction in CKD.

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Table 1

Commonly used questionnaires for depression screening in CKD and ESRD.

	Number of items	Cutoff in the general population	Cut-off in CKD	Cut-off in ESRD
BDI ^{91, 92, 144-146}	21	10	11	17 ¹⁴⁴ 16 ^{145, 146} 14 ^{91, 92}
CES-D ^{91, 147}	20	16	16	18
PHQ-9 ¹⁴⁵	9	10		10
QIDS-SR16 ⁹²	16	10	10	
MHI-5 ^{148, 149}	5	60-76		70
HDRS ¹⁵⁰	21	8		8
Zung SDS ¹⁵¹⁻¹⁵³	20	50 or SDS index 0.63		40 or SDS index 0.50

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Study of Depression; HDRS, Hamilton Depression Rating Scale; MHI-5, 5 items Mental Health Inventory (subscale of the 36-item Short-Form Health Survey Questionnaire); QIDS-SR16, 16 items Quick Inventory of Depressive Symptomatology Self-Report; PHQ-9, 9 items Patient Health Questionnaire; SDS, Self-Rated Depression Scale

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Table 2Selected psychotropic medications for treatment of depression in CKD and ESRD.^{104, 108, 154}

Medication class	Dosing in normal GFR	Dosing in CKD and ESRD	Potential class adverse effects	Comments
Selective serotonin re- uptake inhibitors	Sertraline 50- 200 mg/day Paroxetine - IR 20-50 mg/day - ER 25-62.5 mg/day Fluoxetine 20-80 mg/day Citalopram 10-60 mg/day Escitalopram 10-20 mg/day	No dose adjustment recommended, but active metabolites excreted via kidney	Increased risk of bleeding, GI side effects (e.g. nausea and vomiting), suicidal ideation	Higher citalopram doses associated with QTc prolongation in severe renal impairment
Dopamine/norepinephrine re-uptake inhibitors	Bupropion 200-450 mg/d	Use with caution with maximal dose 150 mg/day	Cardiac dysrhythmia, wide QRS complex, nausea, insomnia	Increased risk for seizures in ESRD. Drug interaction with MAOIs.
Noradrenergic and serotonergic agonist	Mirtazapine 7.5-22.5 mg/day	Dosage reduced by 50% in ESRD	somnolence, hallucination, weight gain	Drug interaction with MAOIs
Tricyclics and tetracyclics	Amitriptyline 75-150 mg/day Desipramine 100-300 mg/day Doxepin 25-300 mg/day Nortriptyline 25-75 mg/day	No dose adjustment recommended, but	QTc prolongation, orthostatic hypotension, anti- cholinergic effects	Avoid in CKD if possible given cardiac side effects
Serotonin/norepinephrine re-uptake inhibitors	Venlafaxine - IR 75-225 mg/day - ER 37.5-225 mg/day	Reduce dose by 25-50%	Hypertension, sexual dysfunction	Not removed by dialysis
Serotonin modulators	Nefazodone 100-600 mg/day Trazodone 150-600 mg/day	No dose adjustment needed	Cardiac dysrhythmia, serotonin syndrome	Avoid in cardiovascular and liver disease
Monoamine oxidase inhibitors	Phenelzine 45-90 mg/day Selegiline 5-10 mg/day	Generally avoid in CKD	Orthostatic hypotension	Significant drug-drug interactions

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; ER extended-release; IR, immediate-release; HD, hemodialysis; MAOIs, monoamine oxidase inhibitors