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Exercise and Cognitive Function in Patients with End-Stage Kidney Disease

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Abstract

In this review we summarize the research pertaining to the role of exercise in preventing cognitive decline in patients with end-stage kidney disease (ESKD). Impairment in cognitive function, especially in executive function, is common in patients with ESKD, and may worsen with maintenance dialysis as a result of retention of uremic toxins, recurrent cerebral ischemia, and high burden of inactivity. Cognitive impairment may lead to long-term adverse consequences, including dementia and death. Home-based and intradialytic exercise training (ET) are among the non-pharmacologic interventions identified to preserve cognitive function in ESKD. Additionally, cognitive training (CT) is an effective approach recently identified in this population. While short-term benefits of ET and CT on cognitive function were consistently observed in patients undergoing dialysis, more studies are needed to replicate these findings in diverse populations including kidney transplant recipients with long-term follow-up to better understand the health and quality of life consequences of these promising interventions. ET as well as CT are feasible interventions that may preserve or even improve cognitive function for patients with ESKD. Whether these interventions translate to improvements in quality of life and long-term health outcomes, including dementia prevention and better survival, are yet to be determined.

INTRODUCTION

Aging of Population of Patients with End-Stage Kidney Disease (ESKD)

End-stage kidney disease (ESKD) is a growing public health challenge in the United States, with more than 640,000 adults suffering from this devastating chronic condition.¹ With a growing prevalence of obesity, hypertension, and diabetes, it is estimated that there will be >1 million ESKD patients by 2025.¹ However, the burden of ESKD is not equally distributed across the age spectrum. There has been a continuous increase in the number of older adults (age ≥ 65 years) initiating hemodialysis (HD) in the US, and in 2014, 49.6% of patients initiating HD were older adults.¹ Additionally, patients undergoing HD are living longer; the number of HD patients aged 85 and older has increased from 5,073 in 1996 to 24,231 in 2014.¹ As kidney transplant (KT) has become a growing treatment option for older

adults, and as patients live longer with a functioning graft, these demographic shifts have also been observed among KT recipients.²

Measures of Global Cognitive Function in Studies of ESKD

While large cohort studies of patients with ESKD rarely conduct a neurocognitive battery to assess multiple cognitive domains, such as attention, memory, language, visuospatial ability, and executive function, global cognitive function is often assessed using brief screening tools in prospective cohort studies.^{3–6} The most commonly studied tool to measure cognitive function in patients with ESKD is the Modified Mini-Mental State Exam (3MS), a validated measure of global cognitive function^{7–9} based on responses to 15 components covering domains including temporal and spatial orientation, multi-stage commands, and recall; scores for the 3MS range from 0 to 100, where lower scores indicate worse cognition. The Montreal Cognitive Assessment (MoCA) is another brief screening tool of global cognitive function that is increasingly being recognized as a better tool for its improvements in sensitivity in detecting mild cognitive impairment, but has only recently been studied in ESKD patients.⁶

Global Cognitive Function among Patients with ESKD

Dialysis patients have a high burden of global cognitive impairment even at younger ages,^{10–12} and patients undergoing HD of all ages have worse cognitive function than individuals of the same ages in the general population.^{4,13} In a cohort study of 324 adults aged 18 years and older initiating HD (mean age=55), the average (SD) 3MS score for global cognitive function was 89.8 (7.6),⁴ which parallels scores of the most cognitively vulnerable group of community-dwelling older adults aged 60 years and older.¹⁴ Many patients already have partially compromised cognition at dialysis initiation,^{15–17} which further declines while undergoing treatment,^{10,18–20} and often fluctuates from month to month.²¹ In fact, only 13% of prevalent HD patients were reported to have normal cognition²² and clinicians often fail to recognize declining cognition among patients who are undergoing HD²³ or KT.⁶ In fact, physicians were found to only accurately identify HD patients and KT recipients 57%²³ and 66%⁶ of the time, respectively. Yet, patients undergoing peritoneal dialysis (PD) have better cognitive functioning compared to those undergoing HD.²⁴ Notably, however, chronic kidney disease patients with cognitive impairment are less likely to initiate PD and are more likely to have venous catheters at dialysis initiation.²⁵

Among those undergoing KT, the prevalence of cognitive impairment is as high as 58% based on the MoCA.²⁶ After restoration of kidney function, recipients may experience short-term improvements in cognitive function,^{3,27–32} regardless of age, sex, race, and frailty status.³ Despite these observed short-term improvements, a recent 4-year study of cognitive trajectories among KT recipients of all ages has demonstrated that some subgroups, particularly frail KT recipients, experience declines in cognitive functioning in the longer term, to the extent of reaching cognitive levels that were below their pre-KT levels on average.³

Executive Function among Patients with ESKD

Among the cognitive domains, executive function is most profoundly affected in adult ESKD patients.⁵ As a cognitive domain responsible for mental flexibility, set shifting, and complex problem solving, severe executive function impairment impedes HD patients' ability to comply with their dialysis schedule, maintain complicated medication regimens for chronic conditions, retain the capacity for independence and self-care,^{33–35} make informed decisions, and adhere to fluid and dietary restrictions,²³ leading to death.^{12,36}

In the cohort study of 324 adults described above, psychomotor speed was measured by the time it took to complete the Trail Making Test Part A (TMTA) and executive function by subtracting Part A from Part B (TMTB-TMTA); longer times to complete this task reflected worse cognitive function. The mean (SD) time it took for those patients to finish the Trails-Making Test Part A and Trails-Making Test Part B for executive function and processing speed was 55 seconds (29) and 161 seconds (83), respectively;⁴ these mean times to complete these tasks are significantly worse compared to averages found for community-dwelling adults of the same age ranges.³⁷ On average, HD patients suffer from a 3-fold higher rate of executive function impairment than the general population of the same ages.^{12,38} Furthermore, 38% of prevalent HD patients have severe impairments in executive function³⁹ and it affects HD patients of all ages.³⁹

Causes of Cognitive Impairment in Patients with ESKD

Elevated burden of stroke, subclinical cerebrovascular disease, arterial stiffness and central pressure in patients undergoing dialysis have been recognized as major catalysts impacting vulnerability to cognitive impairment.^{12,40–42} In addition, HD patients have a greater burden of white matter disease and cerebral atrophy.⁴³ Yet, even though HD patients experience declines in executive function due to aging and cardiovascular disease, HD itself further impacts the decline. Executive function is the domain of cognition which is most impacted by HD initiation,¹¹ though HD patients were often observed to experience deficits in multiple domains concurrently.⁴⁴ In a cohort of 212 participants, transition to dialysis was associated with loss of executive function.¹¹ HD independently leads to poor executive function through the retention of uremic toxins^{28,45} and by inducing recurrent cerebral ischemia.^{12,46} In terms of health behaviors, while undergoing HD, patients spend their dialysis session doing less cognitively challenging activities like sleeping (72.4%) and watching TV (87.9%), which leads to worse HRQOL, including mental HRQOL.⁴⁷

Implications of Cognitive Impairment in Patients with ESKD

Impairment in cognitive function has several implications for patients with ESKD. For one, cognitive impairment prior to initiating dialysis was associated with lower odds of maintained functional status a year after dialysis initiation.⁴⁸ Additionally, impairments in executive function in patients with ESKD may suggest early signs of dementia, particularly vascular dementia,^{49,50} and in many cases, Alzheimer's disease.^{51,52} In a national study of 356,668 older patients initiating HD, the 5-year risk of diagnosed dementia accounting for the competing risk of death and HD withdrawal was 16% for women and 13% for men; the corresponding Alzheimer's disease diagnosis risks were 2.6% for women and 2.0% for men.⁵³ These older HD patients with a dementia diagnosis were at a 2-fold higher risk of

subsequent mortality, as were those with a diagnosis of Alzheimer's disease. Additionally, older KT recipients, a group which is selected to be free of dementia and Alzheimer's disease, also have a higher burden of these conditions than community-dwelling adults, but lower than patients initiating HD.⁵⁴ These older KT recipients with a diagnosis of dementia were then at elevated risk of both graft loss and mortality.⁵⁴

While poor cognitive function has long been recognized for its adverse impact on survival in older adults generally^{55,56} and more recently this association has been observed in ESKD patients of all ages. Those who were cognitively impaired have between a 1.7- and 2.5-fold higher risk of mortality compared to their cognitively normal counterparts, independent of sociodemographic, clinical, and psychological factors.^{36,57} Additionally, mortality rates in HD patients with poor executive function are comparable to those with HD patients diagnosed dementia,⁵⁸ a highly vulnerable group of HD patients.⁵⁹ Consequences of cognitive impairment can also extend beyond a patients' time on dialysis; among KT recipients, pre-transplant cognitive impairment was associated with higher all-cause graft loss post-KT.⁶⁰

Interventions to Preserve Cognitive Function in Community-Dwelling Older Adults

Exercise training (ET), is an effective non-pharmacological intervention to preserve global cognitive function,^{61–63} with the greatest observed impact on executive function in community-dwelling older adults.^{64–69} Even prior to improving physical function and strength,⁷⁰ ET in older adults improves executive function⁶⁹ through increased: 1) cerebral blood flow;^{71,72} 2) brain volume in the prefrontal cortex and hippocampus;^{73–75} 3) brain-derived neurotrophic factor;^{76–80} and 4) engagement of neural structures. ET reduces inflammatory markers, including C-reactive protein, tumor necrosis factor alpha, and IL-6, resulting in improved brain plasticity and executive function.^{77,81} Even a single ET session changes neurophysiology and executive function.^{82–84} ET has a stronger impact on cognitive function and cortical thickness than it does on aerobic fitness.⁶³

Cognitive training (CT)^{62,85,86} is another promising non-pharmacological intervention used to slow decline in executive function in otherwise healthy older adults. CT prevents age-related declines in key areas of cognitive function, particularly in executive function, including abstraction, working memory, verbal reasoning, and inhibition^{33,34,87–93} by improving the neural structures that mediate executive function.^{94–96} Multi-domain approaches to CT, rather than memory training alone, have been associated with broad and lasting gains in healthy older adults^{91,97,98} and benefits of CT are observable up to 10 years post-training.⁸⁹

CT and ET are among the few effective non-pharmacological interventions to impact executive function in community-dwelling older adults. Combined CT and ET over 3 months improves executive function^{70,76,90,99} and is more effective than either CT or ET alone in older adults.^{76,94} Combined CT and ET enhances synaptic connections between brain cells and improves brain plasticity.^{100,101}

Exercise Interventions in Patients Undergoing HD

Over the past 30 years, there have been several RCTs of exercise in ESKD demonstrating ET effectively improves physical function,^{102–104} and impacts treatment-related symptoms,¹⁰⁵ dialysis efficacy,¹⁰⁶ inflammation,¹⁰³ bone mineral density,^{103,107} quality of life,¹⁰⁸ peak oxygen consumption,^{109,110} anxiety,¹¹¹ and exercise capacity.^{112,113} Compliance and adherence to ET interventions are typically highest when the intervention is delivered during the dialysis session, and there is a general consensus that intradialytic ET is safe.^{114,115}

Exercise as an Intervention to Preserve Cognitive Function in Patients Undergoing Dialysis

Several studies have demonstrated the impact of various forms of ET as an effective intervention for preserving cognitive function in patients undergoing dialysis (Table 1). The Exercise Introduction to Enhance Performance in Dialysis (EXCITE) trial, for example, was a 6-month randomized, multicenter trial aimed at testing whether a home-based, personalized exercise program, including 6-min walking distance and 5-time sit-to-stand testing managed by dialysis staff, would improve functional status in adult patients of all ages on dialysis. The study demonstrated that the self-reported cognitive function and quality of social interaction component scores of the Kidney Disease Quality of Life Short Form (KDQOL-SF) improved dramatically in the exercise arm compared with the control arm.¹¹⁶ In subsequent analyses of the EXCITE trial that assessed the effect and tolerance of the program on older dialysis patients (aged 65 years and older) specifically, the intervention arm demonstrated preserved self-reported cognitive function overtime (using the KDQOL), while the control arm, on average, experienced declines in self-reported cognitive function.¹¹⁷

Most recently, two pilot studies assessed the impact of different types of intradialytic exercise on cognitive function.^{72,118} One pilot randomized controlled trial of 30 adult HD patients aged 18 years and older assessed the impact of 4 months of intradialytic cycling for aerobic exercise on cerebral blood flow and cognitive function. The study found that the ET group (N=15) demonstrated improvement in cognitive function and basilar maximum blood flow velocity compared to a control group (N=15), as well as a greater proportion of arteries with increased flow velocity.⁷²

Another pilot randomized controlled trial of 20 HD patients of all ages assessed the impact of 3 months of intradialytic CT (tablet-based brain games) (N=7), ET (foot peddlers) (N= 6), or standard of care (SC) (N=7) on measured cognitive function using the 3MS and TMTA/B.¹¹⁸ Patients with SC experienced decline in psychomotor speed and executive function by 3 months of follow-up; this decline was not seen among those with CT or ET. This pilot trial is being expanded to a 2-by-2 factorial RCT to test whether there is a synergistic effect of combined CT and ET ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03616535) # NCT03616535).

FUTURE RESEARCH

The field has only begun to scratch the surface on short-term impacts of ET, as well as CT, on cognitive outcomes in patients with ESKD. More studies are needed to explore those and

other strategies dedicated to preserving cognitive function in KT candidates and recipients. Questions also remain as to whether these non-pharmacologic training strategies can extend the benefits to impact cognitive function in such a way that translates to improvements in activities of daily living and long-term outcomes such as dementia progression and survival (Figure 1).

It is encouraging that these interventions can indeed have such a profound effect on health and quality of life, as was demonstrated in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, an ongoing multi-center trial of healthy community-dwelling older adults followed for 20+ years.^{89,93,119} The likelihood of success among patients with ESKD may be especially hopeful given the high burden of cognitive impairment, and therefore, greater room for improvement in the face of these interventions; cognitive screening as part of a comprehensive geriatric assessments may help identify those ESKD patients who may benefit most from ET and/or CT.^{120,121}

CONCLUSIONS

Among patients with ESKD, cognitive impairment is common across multiple domains, with the greatest deterioration in executive function, a key domain that often declines with onset of vascular dementia. Transition to dialysis and maintenance dialysis often catalyzes the decline in cognitive function due to retention of uremic toxins, recurrent cerebral ischemia, and high burden of inactivity during dialysis sessions, which may in turn lead to long-term adverse consequences, such as dementia and mortality. Home-based and intradialytic ET, as well as CT, are non-pharmacologic interventions that successfully preserve cognitive function in patients with ESKD. Despite short-term benefits on cognitive function, further research is needed to better understand the long-term consequences of exercise interventions, and whether those benefits may extend to health and quality of life domains in patients undergoing dialysis and KT recipients.

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BOX 1. PRACTICAL TIPS FOR NEPHROLOGISTS

- Once a patient is identified as having cognitive impairment, clinicians should consider exercise and cognitive training, as these remain the two most promising interventions to preserve and improve cognitive function in patients with end stage kidney disease (ESKD).
- Clinicians should consider using global cognitive assessment tools to screen patients with ESKD at least once every 6 months.
- The Modified Mini-Mental State Exam (3MS) is a common brief screening tool used to assess cognitive impairment and measure global cognitive function.
- The Montreal Cognitive Assessment (MoCA) is increasingly being recognized as a better tool as it is more sensitive to capturing ESKD patients with mild cognitive impairment.

BOX 2. AREAS FOR FUTURE RESEARCH

- Future randomized controlled trials should consider exploring the effect of exercise training programs, and potentially cognitive training programs, as non-pharmacologic interventions for preserving cognitive function and potentially improving long-term health and quality of life outcomes in end-stage kidney disease.
- Future trials should inform the development of novel interventions to preserve cognitive function for kidney transplant recipients.

Figure 1. Conceptual Framework of Non-pharmacologic Interventions on Short- and Long-term Outcomes in Patients with End-Stage Kidney Disease.
Black arrows represent impact.

Table 1.
Summary of studies examining non-pharmacologic interventions to preserve cognitive function in patients with end-stage kidney disease undergoing dialysis.

3MS= Modified Mini-Mental State Exam for global cognitive function; CT=cognitive training; ET=exercise training; HD= hemodialysis; KDQOL-SF= Kidney Disease Quality of Life Short Form questionnaire with cognitive function subcomponents; MMSE= Mini-Mental State Exam; NA= not available; SC=standard of care; TMTA and TMTB = Trails Making Tests Parts A and B for processing speed; TMTB – TMTA = Trail Making Test B minus Trails Making Test A for executive function.

Reference	Population characteristics	Intervention Description	Measures of Cognition	Findings
Baggetta et al. 2018 ¹¹⁷	Older HD & PD patients aged 65+ years from the Exercise Introduction to Enhance Performance in Dialysis (EXCITE) trial (n=115, mean age=NA)	Home-based, personalized exercise program: 6-min walking distance & 5-time sit-to-stand testing (Duration of exposure: 6 months)	KDQOL-SF	Self-reported cognitive function declined in the control arm ($P=0.04$) and remained stable in the active arm ($P=0.78$)
Manfredini et al. 2017 ¹¹⁶	Adult dialysis patients in the Exercise Introduction to Enhance Performance in Dialysis (EXCITE) trial (n=296, mean age=NA)	Home-based, personalized exercise program: 6-min walking distance & 5-time sit-to-stand testing (Duration of exposure: 6 months)	KDQOL-SF	Walking exercise (intervention) vs. normal activity (controls) experienced improvements in self-reported cognitive function ($P=0.04$) and quality of social interaction ($P=0.01$)
McAdams-DeMarco et al. 2018 ¹¹⁸	Adult HD patients of all ages participating in a pilot randomized controlled trial (n=20, mean age=50.8)	Intradialytic CT (tablet-based brain games), ET (foot peddlers), or standard of care (SC) (Duration of exposure: 3 months)	3MS TMTA TMTB	Patients with SC experienced psychomotor speed and executive function decline by 3 months; this decline was not seen in both intervention arms (CT or ET, all $P>0.05$).
Stringuetta et al. 2018 ⁷²	Adult HD patients of all ages participating in pilot randomized controlled trial (n=30, mean age=NA)	Intradialytic ET (cycling) (Duration of exposure: 4 months)	MMSE Transcranial Doppler	Patients with ET improved in cognitive function ($P=0.001$) and basilar maximum blood flow velocity ($P=0.029$) compared to control group. ET group also had greater proportion of arteries with increased flow velocity ($P=0.038$).