Editorial

Frailty and Cognitive Impairment in ESRD: Brain-Body Connections

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Clin J Am Soc Nephrol 10: 2104–2106, 2015. doi: 10.2215/CJN.11321015

More than 50 years after Belding Scribner and colleagues made maintenance hemodialysis feasible for treatment of ESRD, it is easy to lose sight of the key role of rehabilitation in the care of ESRD patients that Dr. Scribner envisioned: "If the treatment of chronic uremia cannot fully rehabilitate the patient, the treatment is inadequate" (1).

Early studies suggested that—contrary to Dr. Scribner's vision—most patients treated with maintenance hemodialysis had poor functional status (2). Contemporary 21st century dialysis care involves an increasingly elderly population with a high comorbidity burden, often initiating hemodialysis after an acute-care hospitalization. Contemporary studies have documented substantial impairment of physical (3) and cognitive function (4), even in patients with ESRD who are well dialyzed. Certainly, barriers to functional recovery and rehabilitation in this population are substantial.

A major contribution to the understanding of functional decline in the general population has been the concept of frailty developed from longitudinal aging studies. Frailty refers to a specific phenotype of aging characterized by "...decreased reserve and resistance to stressors...resulting from cumulative declines across multiple physiologic systems...causing vulnerability to adverse outcomes" (5). Frailty is related to but also distinct from other aging–related outcomes, such as disability, and in fact, it may be conceptualized as a risk factor or intermediate stage between health and frank disability and death. As originally conceived by Fried *et al.* (5), frailty was characterized by five domains, including (*1*) shrinkage (unintentional weight loss and sarcopenia), (*2*) muscular weakness, (*3*) exhaustion and lack of endurance, (*4*) slow gait, and (*5*) physical inactivity. One commonly applied definition considers frailty to be present if a patient has at least three of these five characteristics (5).

Keeping in mind these characteristics, it will not surprise those who treat patients with ESRD that frailty is highly prevalent in this population, and it is associated with a greater risk of morbidity and mortality independent of age and comorbidity (6). The frailty phenotype is also more common among patients with stages 1–4 CKD and predicts a greater risk of mortality and progression to ESRD (7). Others have reported a greater frequency of frailty in the general population in relation to lower GFR (8).

Although initially applied to concepts of physical performance and activity, more recently, frailty has been linked to declines and deficits in cognitive performance. Numerous studies have shown associations between frailty and lower cognitive function and cognitive decline in general elderly populations (9). There are multiple inter–related mechanisms that may mediate these associations, including chronic inflammation, nutritional patterns, vascular disease (including subclinical microvascular disease), depression, and endocrine deficiencies. Given the high frequency of cognitive impairment in ESRD, there is a plausible role for frailty in the development of cognitive impairment in this population.

In this issue of the *Clinical Journal of the American Society of Nephrology*, McAdams-DeMarco *et al.* (10) examine these associations in a well characterized prospective cohort of 324 patients on incident hemodialysis from the Baltimore region participating in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD Study. The study population was broadly representative, including community–dwelling adult patients on incident hemodialysis among 27 units who were without dementia, severe mental illness, or severe cognitive impairment at baseline. Frailty was measured in accordance with the definition by Fried *et al.* (5), including objective measures of weakness and slow gait. Cognition was quantified by a limited battery of validated tests of general cognition (Modified Mini Mental Status Examination), psychomotor and processing speed (Trail-Making Test, Part A), and set shifting and complex attention (Trail-Making Test, Part B). Cognitive performance was assessed at baseline and after 1 year of follow-up.

McAdams-DeMarco *et al.* (10) report that 34% of participants met criteria for frailty; an additional 37.6% were characterized as intermediately frail, defined as meeting one or two frailty criteria. This frequency is similar to that reported previously by Johansen *et al.* (11) in patients on prevalent hemodialysis from the San Francisco area. It is nearly five times the frailty prevalence reported by Fried *et al.* (5) among the general community–dwelling elderly population, and it is especially notable in light of the relatively younger age (mean age of 54.8 years old) of the predominately black and urban ESRD study population in the study by McAdams-DeMarco *et al.* (10). Other than a greater

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prevalence of cerebrovascular disease, there were only modest differences in comorbidity between the frail and the nonfrail; interestingly, obesity was nearly twice as common among the frail compared with the nonfrail (10). A similar association between obesity and frailty was noted in patients with stages 1–4 CKD (7). These associations would seem to contradict the conceptualization of frailty as a wasting disorder and suggest a potentially novel aspect of frailty in renal disease: simultaneous sarcopenia and obesity, with other frailty components more prominent in the setting of only minimal or early wasting.

McAdams-DeMarco *et al.* (10) further report a prevalence of cognitive impairment at baseline of 7.5%–15.0%, depending on the cognitive test used. Frail patients on hemodialysis had significantly lower performance on all three tests of cognition, even after adjustment for potential confounders, with smaller deficits noted in those with intermediate frailty. The magnitude of these differences was clinically meaningful, with a 12-second (or roughly 22%) slower performance on the Trail-Making Test, Part A and a 33-second (roughly 20%) slower performance on Trail-Making Test, Part B compared with nonfrail patients. Furthermore, when patients were considered as cognitively impaired versus nonimpaired, impairment was more than twice as common among frail patients on hemodialysis as among the nonfrail (10).

Among 171 participants with 1-year follow-up data, performance on the test of global cognitive function but not the other tests was significantly lower among frail compared with nonfrail patients (10). However, there was no association of baseline frailty with the 1-year longitudinal change in any of the cognitive scores after adjustment for confounders.

Comparing results of studies of frailty in patients with ESRD or CKD is challenged by the different methods used to define and quantify frailty. Although McAdams-DeMarco *et al.* (10) used the cutpoints established by Fried *et al.* (5) for low grip strength and slow gait, these thresholds were derived in patients >65 years old and may not be applicable for the mostly middle–aged adults in this study. Likewise, differences in the ascertainment of exhaustion and inactivity complicate the comparison of results across studies. A strength of this study is the use of direct measurements of gait and strength in contrast to prior studies, which used self-report; these self–reported frailty measures have been shown to poorly correlate with directly observed objective measures (11).

There are unique challenges to the study of frailty and/or cognitive function in patients on hemodialysis; McAdams-DeMarco *et al.* (10) no doubt were faced with these challenges when designing their study. The cognitive assessments used in this study were well validated and widely used but included only three tests, with no or limited assessment of many functional domains, such as visual memory, visuospatial function, and language fluency. There are logistic and feasibility challenges to the use of extensive cognitive batteries in ESRD study populations, including participant fatigue and resistance to longer testing by patients already committed to three times per week dialysis treatments. Loss to follow-up is a common limitation of longitudinal studies in patients on hemodialysis because of mortality, hospitalization, and dropout, in part from increasing morbidity and disability. The nearly 50% loss to follow-up in this study was a limitation in interpreting longitudinal associations in this study, although McAdams-DeMarco *et al.* (10) did note that dropout was not different between the frail and the nonfrail. The lack of associations with longitudinal change in cognitive function may represent limited statistical power, represent unmeasured bias because of dropout, or in fact, reflect the absence of a strong causal relationship.

Nevertheless, even accounting for these limitations, the study represents an important contribution and perhaps, reconceptualization of cognitive functional impairment in ESRD, suggesting a complex interplay with physical frailty (10). The implications for treatment and prevention of cognitive impairment in ESRD are less clear and likely more indirect and long term. Prior efforts to improve cognition or prevent decline through frequent hemodialysis did not result in clear benefits (12). Likewise, it seems unlikely that a wholly pharmacologic approach will be of benefit, especially given the limited efficacy of drugs for dementia and cognitive impairment in the general population. Given the growing recognition of the inter-relatedness of cognitive impairment with physical weakness, sarcopenia, and frailty, perhaps a more holistic approach should be considered. Such an approach would consider multiple possible interventions, including treatment of depression, avoidance of central nervous system—depressing medications, nutritional support, cognitive training, and increasing physical activity and physical exercise. This approach of necessity requires careful coordination between providers from multiple disciplines beyond nephrology, including mental health, nutrition, geriatric medicine, and physical medicine and rehabilitation.

Before such crossdisciplinary interventions can be attempted in our dialysis units, however, the ESRD care team needs information on their patients' cognitive and physical functions. Fortunately, none of the measures used by McAdams-DeMarco *et al.* (10) in this study require specific technical expertise or expensive equipment. However, they do require a modest time commitment by health care staff, which may be the most significant barrier in this era of restricted dialysis reimbursement. Nevertheless, we should consider the admonition by Dr. Scribner a half-century ago: the ultimate goal of treatment of ESRD should be rehabilitation. If we neither test for functional impairment nor attempt to ameliorate it, then we cannot fulfill this goal.

Disclosures

Dr. Seliger is supported by NIDKK grant R01-DK090401.

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Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Frailty and Cognitive Function in Incident Hemodialysis Patients," on pages 2181–2189.