Review Article

Aging and Chronic Kidney Disease: The Impact on Physical Function and Cognition

Shuchi Anand,1 Kirsten L. Johansen,2,3 and Manjula Kurella Tamura1,4

1Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California.
2Nephrology Section, Department of Veterans Affairs Medical Center, San Francisco, California.
3Division of Nephrology, Department of Medicine, University of California, San Francisco.
4Geriatric Research and Education Clinical Center, Palo Alto Veterans Affairs Health Care System, California.

Address correspondence to Manjula Kurella Tamura, MD MPH, Division of Nephrology, Stanford University School of Medicine, 777 Welch Road, Suite DE, Room D100, Palo Alto, CA 94304. Email: mktamura@stanford.edu

Evidence has recently been building that the presence of chronic kidney disease (CKD) is an independent contributor to decline in physical and cognitive functions in older adults. CKD affects 45% of persons older than 70 years of age and can double the risk for physical impairment, cognitive dysfunction, and frailty. To increase awareness of this relatively new concept of CKD as a risk factor for accelerated aging, we review studies on the association of CKD with physical function, frailty, and cognitive function. We also present a summary of the proposed mechanisms for these associations.

Key Words: Chronic kidney disease—Frailty—Physical function—Cognitive function.

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OLDER adults with chronic kidney disease (CKD) face a high risk for physical disability and cognitive decline. Prospective studies in older adults with CKD have quantified this risk as approximately double that of the age-matched general population (1,2).

Experts debate the clinical significance of mild CKD among older adults, especially because an isolated reduction in estimated glomerular filtration rate (eGFR) may simply reflect age-related decline in kidney function without measurable risk for progression to end-stage renal disease. But even early stages of CKD add 5 or more years to the aging process, substantially lowering the likelihood of “successful” aging without serious comorbidity, physical disability, or cognitive impairment (3). These data take on particular relevance when we consider that 45% of adults older than 70 years of age are classified as having CKD using the National Kidney Foundation definition (ie, eGFR below 60 ml/min/1.73 m² or presence of kidney damage, which is typically albuminuria) (4).

In this review, we summarize the studies examining CKD as a risk factor for impairment in physical function, cognitive decline, and frailty in older adults. We will also discuss proposed mechanisms for the association. Our review focuses primarily on older adults with CKD not requiring dialysis therapy. Table 1 highlights cohort studies that have examined the relationships among CKD and physical and cognitive functions.

Epidemiology

CKD and Impaired Physical Activity and Function

For the purposes of this review, we will use physical function as a broad term: one that encompasses self-care tasks such as the activities of daily living (ADL) or instrumental activities of daily living, leisure time activities such as attending a wedding, and performance tests such as the get up and go test (5). The term disability specifically indicates impairment in self-care tasks. Physical activity refers to the use of muscles to expend energy above basal rates and is a function of both exercise capacity and voluntary effort (6).

Older adults receiving dialysis report physical activity levels below the fifth percentile of age-matched controls (7), but few studies have addressed physical activity among older adults with CKD. The Heart and Soul Study enrolled 1,024 participants with stable coronary heart disease who underwent an objective evaluation of maximal exercise capacity via treadmill testing. Participants were 67 years old on average. On cross-sectional analysis, the odds of low exercise capacity (below five metabolic equivalents of task at maximal exertion) were sixfold higher for participants with eGFR below 60 ml/min/1.73 m² (8). Not only did the study report a substantially lower maximal exercise capacity among individuals with CKD, but the relationship also appeared to be graded, with lower eGFR associated with...
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Notes: ADL = activities of daily living; CKD = chronic kidney disease; eGFR = estimated glomerular filtration; IADL = instrumental activities of daily living; MDRD = Modification of Diet in Renal Disease study equation.

*Ranges in the sample size represent different analytic cohorts for each analysis.*
worse exercise capacity—a finding borne out in an alternate analysis from this study that used cystatin C rather than serum creatinine to estimate eGFR (9) and in another smaller study of persons with CKD (10).

All major domains of physical function—ability, leisure time activity, and performance—are also impaired to a greater degree among older adults with CKD than in the age-matched general population. The Cardiovascular Health Study, a community-based cohort of 5,888 persons 65 years or older, assessed disability among its participants in a cross-sectional analysis (11). The prevalence of a limitation in ADL was nearly double among the participants with CKD (12% vs 7% in participants without CKD). The prevalence was higher among participants with eGFR below 40 ml/min/1.73 m² compared with participants with eGFR between 40 and 60 ml/min/1.73 m² (15% vs 8%). On multivariate analysis, the association was not statistically significant. Similarly, although 17% and 23% of adults aged older than 65 without CKD reported difficulty with ADL and instrumental activities of daily living, respectively, in the National Health and Nutrition Survey, the corresponding prevalence was 25% and 36% for persons with eGFR below 60 ml/min/1.73 m² (12). The increase in risk for disability was not significant after multivariate adjustment. Notably, a greater proportion of older adults with CKD in this study reported impairment in leisure time activities such as attending social events or going to the movies on both adjusted and unadjusted analyses, but the association was not graded. In a similarly large group (n = 13,179) of adults aged older than 75 years in the United Kingdom, those with eGFR below 30 ml/min/1.73 m² had a 2.2-fold higher odds of impairment in ADLs and those with eGFR between 30 and 44 ml/min/1.73 m² had a 1.6-fold higher odds of impairment in ADLs, compared with those with eGFR above 60 ml/min/1.73 m² (13).

The Health Aging and Body Composition study measured physical performance—400-m walk, lower extremity performance, and grip and knee extension strength—in 3,075 persons aged 70–79 years (14). In cross-sectional analysis, scores on all three measures were worse among individuals with lower levels of kidney function, using both cystatin C measurements and creatinine-based eGFR. For example, participants with eGFR below 60 ml/min/1.73 m² took 20 extra seconds to complete their 400-m walk and had a 1.9-kg lower grip strength. On follow-up, participants in the highest quartile of cystatin C experienced a 40% higher hazard of developing limitation in physical performance (15). Of note, the relationship was not graded, that is, the incidence of impairment was not increased for participants in the second or third quartile of cystatin C. One strength of this analysis was the use of cystatin C (as opposed to serum creatinine) to estimate eGFR, thereby avoiding confounding by muscle mass, which could be higher among those who exercise and would also raise serum creatinine.

Prospective analyses from the Heart and Estrogen/Progestin Replacement study examined the association between changes in kidney function and changes in physical activity measured by the Duke Activity Status Index in 2,761 women with an average age of 67 years. Those with eGFR below 30 ml/min/1.73 m² had 10-point lower physical activity scores at baseline (16). On 4-year follow-up, participants with declines in eGFR of 15 ml/min/1.73 m² or more experienced a larger decline in their physical activity, in comparison with participants with stable eGFR. Similarly, the Singapore Longitudinal Aging Study of 1.315 community-dwelling adults aged older than 55 noted lower instrumental activities of daily living scores at baseline and twofold greater odds for decline during a period of 4 years among participants with eGFR below 60 ml/min/1.73 m² compared with those with eGFR at or above 60 ml/min/1.73 m² (1). However, when eGFR was used as a continuous predictor, the association was not statistically significant.

Thus, several cross-sectional studies and three prospective cohorts have demonstrated that functional impairment is more common and more likely to develop among older adults with CKD. However, although the cross-sectional studies point to higher prevalence of functional impairment even among persons with early stages of CKD, there is a suggestion of a “threshold” effect based on prospective data, such that a higher risk of developing functional impairment only appears when CKD reaches a moderate stage or is progressing rapidly.

At the same time, older adults who maintain physical activity may delay progression of CKD. In a prospective analysis from the Cardiovascular Health Study, participants in the upper quintile of leisure time physical activity experienced a 29% lower relative risk of rapid kidney function decline as defined by more than 3 ml/min/1.73 m² per year fall in eGFR during a period of 7 years (17). By self-report, these participants were expending more than 2,000 calories per week in leisure time physical activity at baseline, the equivalent of walking approximately 90 min/day or swimming laps for 3 hours per week. The authors created a score that combined walking pace and leisure time physical activity. Participants with the highest score also experienced a lower risk for loss of kidney function, even after stratification by baseline eGFR.

**CKD and Frailty**

Experts have proposed various definitions of frailty (18), all of them designed to identify a group of older adults vulnerable to mortality, morbidity, and functional decline in settings of acute stress—stemming from low physiologic reserve. Frailty can precede disability (5). The definition proposed by Fried and coworkers (19) based on analyses from the Cardiovascular Health Study has been most widely applied in research studies related to CKD, although others have proposed definitions that may be more clinically accurate.
applicable (20). The Cardiovascular Health Study definition identifies a person as frail if he or she meets three of the following criteria: weight loss, weakness, poor energy or exhaustion, slowness, and low physical activity. For participants identified as frail, the risk of falls and worsening mobility during a period of 3 years was 30% and 50% higher, respectively; the risk of worsening ADL disability and mortality was double that of nonfrail participants (19).

The prevalence of frailty overall among the Cardiovascular Health Study cohort was 7%. When restricted to patients with CKD, the prevalence of frailty was 15%, highest among participants with eGFR below 40 ml/min/1.73 m² (20%) and, in particular, black women with CKD (11). The adjusted odds of frailty for participants with CKD were 1.5 times that of the general population. In analyses from the Women’s Health and Aging Studies including 620 women between 70 and 79 years old, Chang and coworkers (21) found that CKD was one of the most common conditions identified among frail women.

Using a modified Cardiovascular Health Study definition of frailty, Wilhelm-Leen and coworkers (22) examined the prevalence of frailty among 10,256 National Health and Nutrition Survey participants with CKD (average age was 49 years) and evaluated whether frailty was associated with risk of death. The prevalence of frailty was 20% among participants with eGFR below 45 ml/min/1.73 m² (compared with 1.5% in participants without CKD). Frailty and CKD were both independent predictors of mortality. However, there was no synergistic interaction between the two, such that presence of frailty among CKD and among those without CKD was associated with about a twofold higher risk for mortality. Among the 336 participants in the Seattle Kidney Study with CKD (average age 59 years) followed for 2.5 years, those with frailty had 2.5-fold higher risk for mortality compared with those without CKD (23). Thus, although the prevalence of frailty among older adults with CKD is double that of age-matched controls, its impact in terms of the increase in risk for mortality is similar in magnitude to that in persons without CKD.

**CKD and Impaired Cognitive Function**

There is a high prevalence of cognitive impairment among older adults with CKD. For example, in a sample of 23,000 black and white U.S. adults with a mean age of 65, cognitive impairment, ascertained by a brief cognitive screen, was present in 12% of adults with eGFR below 60 ml/min/1.73 m² (24). In prospective studies, CKD is also associated with a higher incidence of dementia and cognitive decline. Seliger and coworkers (25) demonstrated a higher risk for incident dementia among older adults with CKD in the Cardiovascular Health Study. CKD, defined according to sex-specific serum creatinine cut points, was associated with a 37% higher risk for clinically defined dementia during a median 6-year period of follow-up.

Several other prospective studies have demonstrated an independent and severity-dependent relationship between CKD and risk for cognitive decline. In the Health Aging and Body Composition study, participants with eGFR below 60 ml/min/1.73 m² had lower baseline scores on Modified Mini-Mental State Examination (3MS) compared with participants with eGFR above 60 ml/min/1.73 m² (2). The decline in these scores in the 4 years of follow-up was also two points more among participants with eGFR below 45 ml/min/1.73 m² compared with participants with eGFR above 60 ml/min/1.73 m². In addition, participants with eGFR between 45–60 ml/min/1.73 m² and below 45 ml/min/1.73 m² had a graded, increased incidence of cognitive impairment defined as a 3MS below 80 or decline in score by more than 5 points (adjusted odds ratios [ORs] 1.3 and 2.8, respectively). A similar magnitude of increased risk for cognitive impairment (adjusted OR 2.1) was reported for participants with eGFR below 45 ml/min/1.73 m² in the Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg (INVADE) study (26). Of the 886 older adults participating in the Rush Memory and Aging project, those with eGFR below 60 ml/min/1.73 m² experienced a faster decline in cognitive function, particularly in the memory domains (as opposed to visuospatial abilities or perceptive speed), compared with participants without CKD (27). The authors quantified this increased risk: for a 15 ml/min/1.73 m² lower eGFR at baseline, the increase in rate of cognitive decline was equivalent to being 3 years older at baseline in their model.

Even participants with mild decrement in kidney function experience modestly higher risk. For example, in an analysis from the Health Aging and Body Composition study, participants with eGFR above 60 ml/min/1.73 m² but high cystatin C levels—indicating early CKD—experienced a 1.7-fold higher incidence of cognitive impairment (28). The Cardiovascular Health Study reported similar results (3).

Although most studies have defined CKD based on eGFR alone, a few have examined the association of albuminuria with cognitive function or decline. Barzilay and coworkers pooled data on more than 25,000 participants of two clinical trials and found that baseline albuminuria was associated with higher odds of rapid cognitive function decline (adjusted OR 1.2), even after adjusting for baseline eGFR. However, two analyses have identified important caveats. In an analysis from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, Joosten and coworkers (29) reported that the higher risk was restricted to younger (<48 years) participants. Kurella Tamura and coworkers found that albuminuria was associated with incident cognitive impairment only among individuals with eGFR above 60 ml/min/1.73 m² (30).

Not all studies suggest CKD is independently associated with cognitive decline. In the Osteoporosis in Men (MrOS) study involving 5,520 men with an average age of 74, lower eGFR was not independently associated with cognitive
decline (31). Among 1,345 adults in the Rancho Bernardo study with an average age of 75, low eGFR was not independently associated with cognitive decline (32). In the Three City (3C) Study, eGFR was not independently associated with risk of dementia, but a decline in eGFR more than 4 ml/min/1.73 m² was independently associated with more than a fourfold higher risk for vascular dementia (33).

MECHANISMS

A potential link between CKD and impaired levels of physical function and cognition may exist simply because CKD is a common disease state, more likely to be found in older adults who are in ill-health and therefore also suffering from functional and cognitive limitations. For example, CKD may simply be a marker for the frail phenotype—particularly because no prospective studies have yet examined whether incidence of frailty is higher in older adults with CKD.

However, given that several prospective studies have identified CKD as an independent risk factor for incident impairment in physical and cognitive functions, two additional possibilities are reasonable to consider. First, CKD may share risk factors with these states (eg, small vessel disease) such that the development or progression of CKD parallels the development of physical or cognitive impairment. Or CKD may be a potential accelerant of decline in physical and cognitive functions through associated anemia, mineral-bone disease, or inflammation. Evidence for the latter comes from studies of patients who have received kidney transplants and presumably corrected the metabolic derangements induced by CKD. For example, Harciarek and coworkers (34) and others (35) have shown significant improvement in memory, psychomotor speed, and abstract reasoning immediately after a kidney transplant and persisting after 1 year. One study showed dramatic improvements in maximal oxygen consumption and maximal heart rate post-transplant (36). Of note, however, an increase in frequency of hemodialysis to six times weekly or conversion to longer, nocturnal hemodialysis has not been definitively shown to improve cognitive function (37) or physical function (38).

Small Vessel Disease

Small vessel disease leading to cerebral ischemia, either in the form of silent or subclinical brain infarcts or white matter lesions, increases risk for cognitive decline, dementia, and age-related disability (39). Silent brain infarcts were associated with a doubling of the risk of dementia in the Rotterdam Scan Study during the 3.6 years of follow-up (40). Similarly, the Leukoaraiosis and Disability study showed a doubling in the risk for disability during the 3-year follow-up among participants with severe white matter lesions compared with participants with mild white matter lesions (41).

Studies using MRIs have shown that persons with CKD have a higher prevalence of subclinical brain infarcts (42) and deep white matter lesions (43), even after adjusting for traditional risk factors such as smoking, hypertension, and diabetes. Kuriyama and coworkers (43) examined white matter lesions in 273 participants who underwent two MRIs in a 5-year period. Participants with white matter lesions were more likely to have CKD at baseline (adjusted OR 1.1); the odds of CKD were greater among participants who developed new white matter lesions or had progression in their severity (adjusted OR 1.4). In another study, participants with albuminuria were more likely to fall in the highest tertile of white matter intensities on MRI (44). Given that small vessel disease also contributes to the pathophysiology of CKD (45), it is possible that impaired physical function or cognition and CKD are associated because of this shared risk factor (46). Or CKD may aggravate the impact of small vessel disease, potentially by promoting salt retention, worsening hypertension control, or increasing vascular calcification (Figure 1) (42).

Anemia

Anemia commonly coexists with CKD, a comorbidity that may be particularly detrimental for older adults because its presence has been linked to a range of adverse outcomes including falls, impaired physical function, and cognitive decline (47). Results from 3-year follow-up of the Longitudinal Aging Study Amsterdam indicate that anemic older adults are at double the risk of recurrent falls (48). Scores on tests of physical performance and functional ability are also worse in this group (49,50). Cross-sectional analyses from the Women’s Health and Aging Study II (51) and from the Health and Anemia study (52) also reported an association between anemia and poorer scores on tests of executive function and selective attention performance.

Although this may lead us to speculate that anemia is a potential mediator of physical and cognitive impairments in older adults with CKD, results from clinical studies have been mixed. For example, in the Heart and Soul study, the adverse impact of anemia in terms of objective and subjective measures of physical performance was additive to
the presence of CKD (8). In other words, patients with CKD but without anemia still performed worse compared with participants without anemia or CKD. Similarly, when Kurella and coworkers (2) tested the hypothesis that anemia may be a potential mediator of worse performance on cognitive testing among participants with CKD in the Health Aging and Body Composition study, they found that adjusting for hematocrit did not substantially attenuate the association between CKD and cognitive decline (ORs prior to and after adjustment were 2.6 and 2.4). In addition, anemia would not explain the increased odds of cognitive impairment observed in persons with albuminuria without reduction in eGFR.

**Mineral-Bone Disease**

Disorders of mineral-bone metabolism leading to abnormal bone architecture and fracture may in part explain the relationship between CKD and low physical function. For example, the prevalence of hip fractures among persons with eGFR below 60 ml/min/1.73 m² was double that of the general population in National Health and Nutrition Survey III (53). In the Cardiovascular Health Study, women with eGFR below 60 ml/min/1.73 m² were at approximately 40% higher risk for incident hip fracture compared with women without CKD (54). A complex interplay of hypocalemia, hyperphosphatemia, hyperparathyroidism, vitamin D deficiency (both 25-OH and 1,25-OH vitamin D), and metabolic acidosis has been implicated in these processes (55). Bone biopsies have shown abnormal bone architecture (predominantly osteitis fibrosis cystica but also mixed and adipose bone disease) among persons with CKD who do not yet have any radiological evidence of bone disease (56). Thus, mineral-bone disease associated with CKD leads to increased risk for hip fracture, which in turn is associated with substantial physical disability (57) and could be one important mechanism for the observed indirect correlation between eGFR and physical function.

**Inflammation**

Frailty, impaired physical function, and lower levels of physical activity have been linked to the presence of inflammation. Frail persons demonstrate some of the hallmark features of chronic inflammation: unintentional weight loss, skeletal muscle loss, and physical exhaustion. In the Cardiovascular Health Study, frail persons had higher serum concentrations of C-reactive protein, factor VIII, and d-dimer than their nonfrail counterparts. Results from the InChianti study also indicated an inverse association between tests of physical performance and serum concentrations of C-reactive protein and interleukin-6 in the elderly participants (58). Finally, participants in the highest quartile of serum C-reactive protein concentrations were more than 40% less likely to meet recommended physical activity guidelines in the National Health and Nutrition Examination Survey (59).

Presumably if CKD potentiates inflammation, which in turn leads to a catabolic state of muscle breakdown and cachexia (60), then it could be implicated as a causative factor in frailty and impairment in physical function. There is some evidence to support this, as persons with CKD have been reported to have higher serum concentrations of C-reactive protein in some studies (61,62)—although the mechanisms for this association are unclear. Decreased clearance and comorbid cardiovascular disease are potential explanations.

**Conclusion**

The existing evidence supports the conclusion that CKD is a model of accelerated aging, manifested by higher risks for poor physical function, frailty, and cognitive decline. A better understanding of these associations may lead to the identification of novel pathways to prevent the development of disability and dementia in older adults. Because physical and cognitive functions are important determinants of health-related quality of life and longevity, clinicians caring for older adults with CKD should incorporate preservation of functional status as an important component of routine care. Simplification of medication regimens, support from ancillary health care workers, emphasis on maintaining physical activity, and other principles of geriatric management are particularly applicable to older adults with CKD.

**References**


