Published in final edited form as:

Am J Kidney Dis. 2012 December ; 60(6): 912–921. doi:10.1053/j.ajkd.2012.05.017.

A Prospective Study of Frailty in Nephrology-Referred Patients With CKD

Baback Roshanravan, MD, MSPH¹, Minesh Khatri, MD², Cassianne Robinson-Cohen, MS³, Greg Levin, MS⁴, Kushang V. Patel, PhD⁵, Ian H. de Boer, MD, MS¹, Stephen Seliger, MD, MS⁶, John Ruzinski, BS¹, Jonathan Himmelfarb, MD¹, and Bryan Kestenbaum, MD, MS¹

¹University of Washington Kidney Research Institute, Department of Medicine, Division of Nephrology, Seattle, WA

²Columbia University Department of Medicine, Division of Nephrology, New York, New York

³University of Washington Kidney Research Institute, Department of Epidemiology, Seattle, WA

⁴University of Washington Kidney Research Institute, Department of Biostatistics, Seattle, WA

⁵Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, MD

⁶University of Maryland, Division of Nephrology, Baltimore, MD

Abstract

Background—Frailty is a construct developed to characterize a state of reduced functional capacity among older adults. However, there are limited data describing the prevalence or consequences of frailty among middle-aged CKD patients.

Study Design—Observational study

Setting & Participants—336 non-dialysis-dependent stage 1–4 CKD patients with eGFR < 90ml/min/1.73m² (by the CKD-EPI [CKD Epidemiology Collaboration] serum creatinine–based equation) or evidence of microalbuminuria enrolled in the Seattle Kidney Study, a clinic-based cohort study. Findings were compared to community dwelling older adults in the Cardiovascular Health Study.

Outcome—Prevalence and determinants of frailty in addition to its association with the combined outcome of all-cause mortality or renal replacement therapy.

© 2012 The National Kidney Foundation, Inc. Published by Elsevier Inc. All rights reserved.

Address correspondence to: Baback Roshanravan MD MSPH, Kidney Research Institute, University of Washington Nephrology Division; Box 359606, 325 9th Avenue, Seattle, WA 98104. PHONE: (206) 744-4932; FAX: (206) 744-2252; broshanr@u.washington.edu.

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

Supplementary Material

Table S1: Comparison of missing and study participants.

Table S2: Association of kidney function and other clinical characteristics with the prevalence of frailty.

Table S3: Risk of death or maintenance dialysis among individual frailty components, the frailty construct and individual comorbidities.

Item S1: Supplementary methods.

Note: The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Measurements—We defined frailty according to established criteria as 3 of the following characteristics: slow gait, weakness, unintentional weight loss, exhaustion, and low physical activity. We estimated kidney function using serum cystatin C concentrations (eGFR_{cys}) to minimize confounding due to relationships of serum creatinine levels with muscle mass and frailty.

Results—The mean age of the study population was 59 years and mean eGFR_{cys} was 51 ml/min/ 1.73m^2 . The prevalence of frailty (14.0%) was twice that of the much older non-CKD reference population ($P<0.01$). The most common frailty components were physical inactivity and exhaustion. After adjustment including diabetes, eGFR_{cys} categories of <30 and $30\text{--}44$ ml/min/ 1.73m^2 were associated with a 2.8 (95% CI, 1.3–6.3) and 2.1 (95% CI, 1.0–4.7)-fold greater prevalence of frailty compared to $\text{GFR}_{\text{cys}} \geq 60$ ml/min/ 1.73m^2 . There were 63 events during a median of 987 days of follow-up. After adjustment, the frailty phenotype was associated with an estimated 2.5 (95% CI, 1.4–4.4)-fold greater risk of death or dialysis.

Limitations—Cross-sectional study design obscures inference regarding temporal relationships between CKD and frailty.

Conclusion—Frailty is relatively common among middle-aged CKD patients and is associated with lower eGFR_{cys} as well as increased risk of death or dialysis.

Frailty is a construct that was originally designed by gerontologists to describe cumulative declines across multiple physiologic systems that occurs with aging. The frailty phenotype incorporates disturbances across interrelated domains to identify individuals who have diminished functional reserve, which places them at risk for adverse health outcomes.^{1,2} Across diverse populations the frailty phenotype is consistently associated with future risks of disability, institutionalization, hospitalization, and premature death.^{3–5} The prevalence of frailty is strongly associated with advancing age; nonetheless even among very old adults strategies such as exercise conditioning has been shown to counteract physical frailty.⁶

Chronic kidney disease (CKD) is a state of accelerated metabolic aging, as evidenced by accumulation of advanced glycation end products, oxidative stress, chronic inflammation, insulin resistance, vascular calcification, and osteoporosis.^{7–10} Given that many of these physiologic mechanisms and conditions are associated with frailty in older people, it is conceivable that frailty might be highly prevalent among middle-aged and younger CKD patients and may serve as a useful construct to summarize cumulative burden of physiologic impairments that occur in this setting. Indeed, individuals who have CKD often present with signs and symptoms that may be consistent with the frailty syndrome.^{11–13}

Previous studies of frailty in CKD have been conducted either in community-based studies,¹⁴ in which the prevalence and severity of CKD are low, or in chronic dialysis patients,¹⁵ among whom metabolic disturbances are most severe. Moreover, previous studies have focused exclusively on older CKD individuals and employed nonstandardized methods to describe the frailty phenotype.¹⁶ The prevalence, determinants, and long-term consequences of frailty among middle aged CKD patients not treated with dialysis are unknown.

In this study we determine the prevalence of frailty in a cohort of CKD patients not treated with dialysis using established methodology. We then delineate associations of frailty with kidney function and disability, and estimate associations of individual frailty components and the frailty phenotype with risk of death or initiation of chronic dialysis.

METHODS

Study population

The Seattle Kidney Study (SKS) is a clinic-based prospective cohort study of non-dialysis-dependent CKD patients based in Seattle, Washington. The SKS was designed to evaluate long-term complications of CKD with an emphasis on physical functioning measurements. The SKS began recruiting in 2004 from outpatient Nephrology clinics at Harborview Medical Center (HMC) and the Veterans Affairs Puget Sound Medical Center (VAMC). General SKS eligibility criteria are age >18 years and CKD stages I-IV_{CKDEPI} not currently requiring dialysis. The presence of CKD was defined as an estimated GFR by the serum creatinine based CKD-EPI equation (eGFR_{cr}) of < 90 mL/min/1.73 m² or the presence of albuminuria (urine albumin-creatinine ratio of >30 mg/g from a 12 hour urine collection). Exclusion criteria are an expectation that the patient will start renal replacement therapy or leave the area within 3 months, kidney transplant, dementia, institutionalization, participation in a clinical trial, non-English speaking, or inability to undergo the informed consent process. Institutional review boards at the University of Washington and Veterans Affairs Puget Sound Health Care System approved the SKS and all participants provided written informed consent.

For the purpose of this study, we analyzed SKS participants who were alive and not on dialysis at the time the study initiated frailty assessments in August 2006 (Figure 1). From a total of 462 potential SKS participants, we excluded 100 who did not complete frailty assessment and 26 who were ineligible, leaving 336 participants for analysis (Figure 1). Compared to participants who did not complete frailty assessment, subjects who were included in the study were on average younger (59 *versus* 66 years), had greater eGFR by the nonstandardized cystatin C CKD-EPI equation (51 *versus* 41 mL/min/1.73m²), and a lower proportion of diabetes (51% *versus* 72%) and ADL disability (6% *versus* 28%; Table S1, available as online supplementary material).

Assessment of frailty

We defined frailty using slight modifications of criteria originally established by Fried *et al* for exhaustion, physical activity, and self-reported weight loss (Table 1 and Item S1), which were based on data from the Cardiovascular Health Study (CHS), a community-based study of adults aged 65 and older. We defined frailty as the presence of at least three of the following five conditions: unintentional weight loss, weakness, exhaustion, slow gait, and inactivity. We defined an intermediate frailty phenotype as having one or two of these conditions. We defined weight loss by an unintentional 10-pound weight loss over the previous 6 months based on responses to the SKS questionnaire compared to over 12 months in the CHS. We measured grip strength in each participant's dominant hand using a Takei dynamometer and analyzed the maximal reading from three consecutive efforts. We defined weakness by grip strength less than the lowest sex and body mass index (BMI) specific 20th percentile score in CHS.^{1,17} We performed usual gait speed assessments twice per subject walking at their normal pace over a 4-meter course and analyzed the faster of the two in meters per second. We defined a slow walk as gait speed less than the lowest sex and height specific 20th percentile in CHS.^{1,17} We scored the 4-item energy/fatigue domain of the SF-36 short-form health survey and defined exhaustion as a score less than the lowest 20th percentile for adults >65 years old from the SF-36 normogram sample compared to a positive responses to either exhaustion item on the Center for Epidemiologic Studies Depression scale (CES-D) in the CHS. We assessed physical activity from self-reported exercise habits similar to a prior study of frailty in participants with end stage renal disease.¹⁵ Participants who reported never exercising or exercising less than once weekly

were considered to be physically inactive compared to CHS which defined physical activity as the lowest sex-specific quintile kcal/week.

Measurement of covariates

Prevalent diseases were defined based on participant responses to the SKS questionnaire, medication use, laboratory findings, and hospitalizations that occurred after initial SKS enrollment, but prior to frailty assessment (see Item S1 for prevalent disease definitions). Medication use was assessed by the inventory method at the HMC study site and using the electronic pharmacy database at the VAMC study site; missing medication data were completed by chart review. At each study visit, SKS study coordinators measured blood pressure and collected serum, plasma, and 12-hour timed urine samples on the same day as the frailty assessment. Three seated blood pressure measurements were recorded 5 minutes apart using an automated sphygmomanometer and the average of the last two readings were used for analysis. Samples were centrifuged for 20 minutes at 3300 RPM, transferred to cryovials, and stored at -80°C . General chemistries were measured from frozen serum using a Beckman-Coulter DXC autoanalyzer. We measured serum cystatin C and C-reactive protein (CRP) concentrations using a Siemens Nephelometer that utilized a particle-enhanced immunonephelometric assay (N Latex Cystatin C).¹⁸ Calibration of cystatin C was performed using manufacturer's standards along with daily quality controls to ensure a coefficient of variation (CV) $<15\%$. All samples were analyzed using assays from the same lot. The intra- and inter-assay CV for cystatin C measured from 20 serum samples run in triplicate was 2.59% and 1.08%, respectively. We measured urinary albumin concentration by immunoturbimetry and urinary creatinine concentration by the Modified Jaffe Method.

A priori, we decided to use cystatin C-based estimates of GFR for this study due to the relationship between serum creatinine level and muscle mass and frailty. We used the CKD-EPI equation that incorporates nonstandardized cystatin C level, age, sex, and race to calculate eGFR: $\text{eGFR}_{\text{cys}} = 127.7 \times \text{CysC}^{-1.17} \times \text{age}^{-0.13} \times (0.91 \text{ if female}) \times (1.06 \text{ if black})$.¹⁹ Cystatin C- and serum creatinine-based equations provide similar precision and accuracy compared to gold-standard radioisotope dilution methods.^{19,20} We also evaluated eGFR using the original serum creatinine-based CKD-EPI equation^{20a} (which uses IDMS-traceable serum creatinine level) as a secondary exposure (denoted eGFR_{cr}).

Assessment of disability

Physical function was assessed by asking about difficulties with 15 tasks of daily life including activities of daily living (ADLs), instrumental activities of daily living (IADLs), and mobility tasks.²¹ Mobility tasks include the ability to walk from room to room, to walk up on flight of stairs, and to walk half a mile. In keeping with previous studies, we categorized ADLs, IADLs, and mobility disabilities as the presence of one or more disability versus none.¹

Follow-up and outcomes

Study coordinators contacted participants by telephone every six months and in person every year through annual study examination to assess renal outcomes of chronic renal replacement therapy or kidney transplant. Coordinators assessed vital status using medical record review, contact with family members, and the social security death index.

Statistical Analyses

We calculated the unadjusted prevalence of frailty as the number of frail individuals divided by the total number of individuals in the study population. We indirectly compared the unadjusted prevalence of frailty in SKS to that of the CHS reference population using a Z-

test for proportions and we estimated 95% confidence intervals by referencing the binomial distribution. We categorized eGFR_{cys} and eGFR_{cr} using *a priori* accepted categories of 60, 45–59, 30–44 and <30 ml/min/1.73m². We used Poisson regression with robust variance estimation to estimate cross-sectional associations of kidney function with the prevalence of frailty (yes *versus* no) after adjustment for potential confounding variables. We prefer Poisson regression to logistic regression when the outcome of interest is not rare in order to best model the relative risk. We used a Cox proportional hazards model with robust standard variance estimation to estimate associations of frailty components with the time to death or dialysis after adjustment for potential confounding variables. Sensitivity analysis was performed excluding those from the analysis who started dialysis less than 90 days after the study enrollment.

We investigated groups of potential confounding factors using nested multivariate models: model one adjusted for age, sex, and race (white *versus* non-white); model two added diabetes, BMI, prevalent cardiovascular disease (CVD), and log(CRP). We performed a sensitivity analysis using a third model, which added education, systolic blood pressure, albumin and hemoglobin. Given 12% missing data for education we performed multiple imputation for this variable using chained equations.²² We tested for a multiplicative interaction among eGFR_{cys}, albuminuria, and frailty by including a product term in the model (eGFR_{cys} × log(albuminuria)) and testing its significance with the Wald test. Parallel analyses were performed using eGFR_{cr}. All analyses were conducted using Stata 11.2 (Stata Corporation, College Station, Texas).

RESULTS

Characteristics of the cohort

Among the entering cohort the mean age was 59 ±13 years (25th–75th percentile, 51–67 years), 81% of participants were male, 26% were African American, and 51% percent had prevalent diabetes (Table 2). The median eGFR_{cys} for the cohort was 46 (25th–75th percentile, 32–63) ml/min/1.73m².

Prevalence of frailty

There were 47 SKS participants who met criteria for frailty, resulting in an unadjusted prevalence of 14.0% (95% confidence interval, 10.5%–18.2%; Table 1). The unadjusted prevalence of intermediate frailty was 51.8%. In contrast, the unadjusted prevalence of frailty was 7.0% among the reference CHS population (mean age, 74 years) that was used to create the frailty definition (p <0.001). Among male and female SKS participants, the prevalence of frailty was 13% and 17%, respectively. Among diabetics the prevalence of frailty was 18% compared with 10% for non-diabetics. The most common frailty components in the SKS cohort were inactivity (35.1%), exhaustion (31.8%) and slowness (25.9%).

Characteristics of frail individuals

Frail participants in SKS were more likely to be African American, more likely to have prevalent diabetes, heart failure, and angina, and more likely to be obese (Table 2). Weight was a major distinction between frail (mean BMI, 34.7 ±9.8 [SD]) *versus* non-frail (mean BMI, 30.8 ±6.8) study participants. Frail individuals also had lower eGFR_{cys} and a greater urine albumin-creatinine ratio compared to those who were not frail. Consistent with diminished kidney function, frail individuals had lower hemoglobin and albumin concentrations and higher serum CRP and phosphorus concentrations. In contrast, the mean age of frail *versus* non-frail participants in SKS was similar (58.0 versus 58.9 years).

Association of kidney function with frailty

The prevalence of frailty for eGFR_{cys} categories ≥ 45 ml/min/1.73m² was 8.1% (Figure 2a). Prevalence estimates increased sharply to 21.6% and 18.7% for eGFR_{cys} categories of 30–44 and <30 ml/min/1.73m², respectively. After adjustment for age, sex and race, the relative prevalence of frailty for eGFR_{cys} categories of 30–45 and <30 ml/min/1.73m² were 3.3 (95% CI, 1.5–7.4) and 2.6 (95% CI, 1.1–5.9), respectively, compared to an eGFR_{cys} ≥ 60 ml/min/1.73m² (Table 3). After further adjustment for diabetes, prevalent cardiovascular disease, and CRP, the prevalence estimates were reduced, but the trend across eGFR_{cys} categories remained statistically significant (p-for-trend = 0.01). When participants were stratified according to both kidney function and albuminuria status a higher prevalence of frailty was observed for both measures of reduced kidney function in combination (p-for-interaction = 0.06) (Figure 2b). A parallel sensitivity analysis using eGFR_{cr} did not demonstrate an association of eGFR_{cr} with frailty (Table S2).

Sensitivity analysis adding hemoglobin, albumin, systolic blood pressure, education, and antidepressant use to the model modestly attenuated the strength of association between eGFR_{cys} and frailty. In this analysis, the relative prevalence for eGFR_{cys} categories of 30–45 and <30 ml/min/1.73m² were 2.38 (95% CI, 0.98–5.79) and 2.14 (95% CI, 0.83–5.51), respectively compared with eGFR_{cys} ≥ 60 ml/min/1.73m² (p-for-trend = 0.06).

Association of frailty with disability

Disabilities in activities of daily living, instrumental activities of daily living, and mobility were each more common among frail *versus* non-frail study participants (Figure 3). The proportions of frail individuals who had at least one ADL, IADL, and mobility disability were 15%, 60%, and 40%, respectively. In comparison, the proportions of non-frail individuals with at least one ADL, IADL, and mobility disability were 5% (p=0.009), 28% (p<0.001), and 18% (p=0.001), respectively.

Association of frailty components with death or dialysis

Median follow-up time was 967 days; range 1 day to 4.8 years. Thirty-five participants initiated dialysis while 30 participants died before dialysis for a total of 65 participants (19%). The median time to death was 794 days (range, 27 days to 4 years). The median time to initiation of dialysis was 514 days (range, 1 day to 3.9 years). The unadjusted rate of the combined endpoint was 63 per 1000 person-years among those who had no frailty components compared to 181 per 1000 person-years among those who had 3 or more frailty components. After adjustment for age, sex, BMI, eGFR_{cys}, diabetes and cardiovascular disease, the frailty phenotype was associated with a 2.5 (95% CI, 1.4–4.4) fold greater risk of death or dialysis. Among the individual frailty components, weight loss, physical inactivity and slow gait speed were most strongly associated with the combined endpoint (Figure 4 & Table S3). Risk of death or dialysis appeared to be 1.5 fold greater among those with diabetes (95% CI, 0.9–2.87; p=0.2) and 1.6 fold greater among those with cardiovascular disease (95% CI, 0.9–2.7; p=0.1), but these associations did not reach statistical significance (Table S3).

DISCUSSION

Among a cohort of CKD patients not requiring dialysis, the prevalence of the frailty phenotype was 14%. This prevalence estimate is two-fold greater than that of the reference population used to establish the frailty phenotype, which was on average 15 years older. The most common frailty components among CKD individuals were low physical activity, exhaustion, and slow gait speed. After adjustment for diabetes and other co-morbidities, frailty was strongly associated with obesity and reduced kidney function, but not with age.

In particular, the prevalence of frailty was substantially greater for $\text{eGFR}_{\text{cys}} < 45 \text{ ml/min/1.73m}^2$. The frailty phenotype in CKD was associated with disability across multiple domains. Furthermore the frailty phenotype was associated with greater risk of death or dialysis after adjustment for diabetes and other co-morbidities. These findings suggest that the frailty construct is useful as a measure for global co-morbid disease burden in persons with CKD.

The original frailty construct characterized a wasting disorder of older age with weight loss as a diagnostic criterion.¹ When the classic definition of frailty was applied to a middle-aged CKD population, frail individuals were found to be generally obese and physically inactive with frequently reported symptoms of exhaustion. In parallel with obesity, we found evidence for skeletal muscle dysfunction among CKD individuals, demonstrated by the relatively high prevalence of low grip strength and slow walking speed that were similar to those of much older adults in the general population. These findings suggest a phenotype of altered body composition in CKD in which fat mass is increased and effective skeletal muscle mass and function is reduced.

There are many physiologic consequences of CKD and obesity that may increase risk of frailty. Kidney disease is known to adversely affect muscle structure and metabolic function via mechanisms of chronic inflammation, protein-energy wasting, and insulin resistance^{23–26} all of which overlap with physiologic impairments associated with frailty.^{27,28} Pathophysiologic processes and complications of obesity are intertwined with those of kidney disease.^{29,30} Obesity and metabolic syndromes have been shown to contribute to an elevated risk of progressing to ESRD.³¹ Purported mechanisms of renal and muscle dysfunction in obesity include oxidative stress and endothelial dysfunction mediated in part by insulin resistance, inflammatory adipokines and cytokines.^{32,33} Despite the elevated BMI in obese individuals, the percent muscle mass has been demonstrated to be lower and associated with poor muscle quality.³⁴

Previous associations of obesity with frailty suggest a biological link through heightened inflammation, insulin resistance, and decreased muscle quality.^{34,35} CKD and obesity culminate in a final common pathway towards frailty - sarcopenia, which links the metabolic effects of CKD to functional consequences. Furthermore, the distinguishing characteristics of frailty in our study, exhaustion, inactivity, and weakness, suggest an adverse impact of non-dialysis CKD on sarcopenic obesity, a process previously described in both the general and dialysis populations.^{36,37} Our findings strengthen and extend previously reported associations of CKD with frailty suggesting that the malnutrition-inflammation complex of CKD may predispose to frailty in a younger cohort without stereotypic features of hypercatabolic wasting prior to the onset of dialysis.

Our study has several limitations. First, the cross-sectional study design obscures inference regarding temporal relationships between CKD and frailty. Longitudinal follow up, however confirms that the frailty construct is associated with higher risk of mortality or progression to dialysis. Second, generalizability of our findings may be limited due to study of only two clinic sites characterized by a high proportion of male CKD patients. Further studies are needed to confirm these findings in women with CKD. Nonetheless, the fact that physical frailty is more common in community dwelling older adult women than men^{1,38} may suggest that our estimates are conservative. Third, estimates of frailty among those with $\text{eGFR}_{\text{cys}} < 30 \text{ ml/min/1.73m}^2$ was similar to $\text{eGFR}_{\text{cys}} 30–44 \text{ ml/min/1.73m}^2$. This is likely the result of random sampling error and the lower number of participants in the lowest eGFR_{cys} category. In addition, there are multiple non-GFR factors associated with cystatin C in addition to BMI and CRP, such as proteinuria and white blood cell count, that may contribute to residual confounding.^{39,40} Nonetheless, frailty was more closely associated

with eGFR_{cys} than for creatinine-based estimates, which showed no association. This may be a consequence of confounding by muscle mass on the association between creatinine-based estimates of GFR and frailty consistent with findings from the Health, Aging, and Body Composition study demonstrating a U-shaped association between creatinine-based eGFR and physical performance.⁴¹ Fourth, our findings cannot reliably separate whether frailty in individuals with CKD is attributable to the complex burden of co-morbid illnesses found in even moderately reduced kidney function or results from direct complications of kidney failure. Given the known overlap of cardiovascular disease with frailty and biologic effects of uremia on skeletal muscle impairment it is likely that both processes contribute. Finally there was large amount of individuals missing completed frailty assessments. However, the observation that individuals with missing frailty assessments had worse kidney function and a greater co-morbid burden suggests that the estimate of frailty prevalence may be conservative. Nonetheless these findings point out the high degree of multi-domain functional impairment in the CKD setting as a means to inform clinicians and researchers as to the nature of problem and encourage further investigations in this area.

In summary we document a high prevalence of frailty among a middle-aged cohort of individuals with CKD and demonstrate an increased risk of mortality or chronic renal replacement therapy associated with the frailty phenotype. Further studies are needed to probe potential pathophysiologic mechanisms and to elucidate potential health consequences of the frailty phenotype in individuals with CKD. Such research could lead to successful treatment strategies in frail persons with CKD. One particular strategy may be resistance exercise conditioning, which has been shown to counteract muscle weakness and physical frailty in older adults.⁶ Similarly a small randomized-controlled trial of resistance training and low-protein diet in persons with CKD demonstrated improvements in muscle mass, strength, nutritional status, and decreased IL-6 compared with low-protein diet alone.^{42,43} Resistance exercise-induced increase in muscle mitochondrial content was associated with decreased inflammation in CKD and insulin sensitivity in diabetics.^{44,45} A more recent study suggests that exercise-induced autophagy is one potential mechanism leading to improved glucose tolerance.⁴⁶ The potential benefit of early exercise intervention on counteracting the consequences of the adverse metabolic environment of kidney failure among frail persons with CKD on outcomes of disability or progression to dialysis or death, however, remains to be investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank study coordinators Noah Citron and Georgia Galvin and study manager Ernie Ayers for their contributions to the study. Support: This work was supported by an NIH RO1 HL070938 (Drs Himmelfarb and Kestenbaum), NIH RO1 DK087726 (Dr de Boer), by support from the Kidney Research Institute, NIH T32 (Dr Roshanravan), and by an unrestricted grant from the Northwest Kidney Center Foundation. This research was supported in part by the Intramural Research Program of the National Institute on Aging, NIH (Dr Patel). This study is the result of work supported by resources from the VA Puget Sound Health Care System, Seattle, WA

References

1. Fried L, Tangen C, Walston J. Frailty in older adults: evidence for a phenotype. *J of Gerontol*. 2001; 56A(3):M146–M156.
2. Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci*. Oct; 2009 64(10):1049–1057. [PubMed: 19567825]

3. Cawthon P, Marshall L, Michael Y, et al. Frailty in older men: prevalence, progression, and relationship with mortality. *Journal of the American Geriatrics Society*. 2007; 55(8):1216–1223. [PubMed: 17661960]
4. Woods N, LaCroix A, Gray S, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society*. 2005; 53(8):1321–1330. [PubMed: 16078957]
5. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc*. Dec; 2008 56(12):2211–2116. [PubMed: 19093920]
6. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. Jun 23; 1994 330(25):1769–1775. [PubMed: 8190152]
7. Landau M, Kurella-Tamura M, Shlipak MG, et al. Correlates of insulin resistance in older individuals with and without kidney disease. *Nephrol Dial Transplant*. Jan 19.2011
8. El-Abbadi M, Giachelli CM. Mechanisms of vascular calcification. *Adv Chronic Kidney Dis*. Jan; 2007 14(1):54–66. [PubMed: 17200044]
9. Linden E, Cai W, He JC, et al. Endothelial dysfunction in patients with chronic kidney disease results from advanced glycation end products (AGE)-mediated inhibition of endothelial nitric oxide synthase through RAGE activation. *Clin J Am Soc Nephrol*. May; 2008 3(3):691–698. [PubMed: 18256374]
10. Ensrud KE, Lui LY, Taylor BC, et al. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med*. Jan 22; 2007 167(2):133–139. [PubMed: 17242313]
11. Jhamb M, Argyropoulos C, Steel JL, et al. Correlates and outcomes of fatigue among incident dialysis patients. *Clin J Am Soc Nephrol*. Nov; 2009 4(11):1779–1786. [PubMed: 19808226]
12. Cruz MC, Andrade C, Urrutia M, Draibe S, Nogueira-Martins LA, de Sessa RC. Quality of life in patients with chronic kidney disease. *Clinics (Sao Paulo)*. 2011; 66(6):991–995. [PubMed: 21808864]
13. Gyamiani G, Basu A, Geraci S, et al. Depression, Screening and Quality of Life in Chronic Kidney Disease. *Am J Med Sci*. May 27.2011
14. Shlipak M, Stehman-Breen C, Fried L, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis*. 2004; 43(5):861–867. [PubMed: 15112177]
15. Johansen K, Chertow G, Jin C, Kutner N. Significance of frailty among dialysis patients. *J Am Soc Nephrol*. 2007; 18(11):2960–2967. [PubMed: 17942958]
16. Wilhelm-Leen ER, Hall YN, M KT, Chertow GM. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med*. Jul; 2009 122(7):664–671. e662. [PubMed: 19559169]
17. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. Jul; 2010 39(4):412–423. [PubMed: 20392703]
18. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest*. Feb; 1999 59(1):1–8. [PubMed: 10206092]
19. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. Mar; 2008 51(3):395–406. [PubMed: 18295055]
20. Kwong YT, Stevens LA, Selvin E, et al. Imprecision of urinary iothalamate clearance as a gold-standard measure of GFR decreases the diagnostic accuracy of kidney function estimating equations. *Am J Kidney Dis*. Jul; 2010 56(1):39–49. [PubMed: 20537455]
- 20a. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009; 150(9):604–612. [PubMed: 19414839]
21. Fitti JE, Kovar MG. The Supplement on Aging to the 1984 National Health Interview Survey. *Vital Health Stat*. Jun.1987 121:1–115.
22. Royston P. Multiple imputation of missing values. *The Stata Journal*. 2004; 4(3):227–241.

23. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* Feb; 2008 73(4):391–398. [PubMed: 18094682]
24. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. *J Cachex Sarcopenia Muscle.* Mar; 2011 2(1):9–25.
25. Adey D, Kumar R, McCarthy JT, Nair KS. Reduced synthesis of muscle proteins in chronic renal failure. *Am J Physiol Endocrinol Metab.* Feb; 2000 278(2):E219–225. [PubMed: 10662705]
26. Siew ED, Ikizler TA. Insulin resistance and protein energy metabolism in patients with advanced chronic kidney disease. *Semin Dial.* Jul-Aug; 2010 23(4):378–382. [PubMed: 20701717]
27. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med.* Nov 11; 2002 162(20):2333–2341. [PubMed: 12418947]
28. Vanitallie TB. Frailty in the elderly: contributions of sarcopenia and visceral protein depletion. *Metabolism.* Oct; 2003 52(10 Suppl 2):22–26. [PubMed: 14577059]
29. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol.* Oct; 2006 6(10):772–783. [PubMed: 16998510]
30. Stompor T, Sulowicz W, Dembinska-Kiec A, Janda K, Wojcik K, Zdzenicka A. An association between body mass index and markers of inflammation: is obesity the proinflammatory state in patients on peritoneal dialysis? *Perit Dial Int.* Jan-Feb; 2003 23(1):79–83. [PubMed: 12691512]
31. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med.* Jan 3; 2006 144(1):21–28. [PubMed: 16389251]
32. Tesauro M, Canale MP, Rodia G, et al. Metabolic syndrome, chronic kidney, and cardiovascular diseases: role of adipokines. *Cardiol Res Pract.* 2011; 2011:653182. [PubMed: 21403882]
33. Schrager MA, Metter EJ, Simonsick E, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. *J Appl Physiol.* Mar; 2007 102(3):919–925. [PubMed: 17095641]
34. Villareal D, Banks M, Seiner C, Sinacore D, Klein S. Physical Frailty and Body Composition in Obese Elderly Men and Women. *Obes Res.* 2004; 12(6):913–920. [PubMed: 15229329]
35. Blaum C, Qian LX, Elisabete M, Richard D, Linda P. The Association Between Obesity and the Frailty Syndrome in Older Women: The Women's Health and Aging Studies. *J Am Geriatr Soc.* 2005; 53(6):927–934. [PubMed: 15935013]
36. Narici MV, Maffulli N. Sarcopenia: characteristics, mechanisms and functional significance. *Br Med Bull.* 2010; 95:139–159. [PubMed: 20200012]
37. Honda H, Qureshi AR, Axelsson J, et al. Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. *Am J Clin Nutr.* Sep; 2007 86(3):633–638. [PubMed: 17823427]
38. Garre-Olmo J, Calvo-Perxas L, Lopez-Pousa S, de Gracia Blanco M, Vilalta-Franch J. Prevalence of frailty phenotypes and risk of mortality in a community-dwelling elderly cohort. *Age Ageing.* Mar 27. 2012
39. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int.* Mar; 2009 75(6):652–660. [PubMed: 19119287]
40. Muntner P, Winston J, Uribarri J, Mann D, Fox CS. Overweight, obesity, and elevated serum cystatin C levels in adults in the United States. *Am J Med.* Apr; 2008 121(4):341–348. [PubMed: 18374694]
41. Odden M, Chertow G, Fried L. Cystatin C and measures of physical function in elderly adults. The Health, Aging, and Body Composition (HABC) Study. *American Journal of Epidemiology.* 2006; 164:1180–1189. [PubMed: 17035344]
42. Castaneda C, Gordon PL, Parker RC, Uhlin KL, Roubenoff R, Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis.* Apr; 2004 43(4):607–616. [PubMed: 15042537]
43. Castaneda C, Gordon PL, Uhlin KL, et al. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. *Ann Intern Med.* Dec 4; 2001 135(11):965–976. [PubMed: 11730397]

44. Balakrishnan VS, Rao M, Menon V, et al. Resistance training increases muscle mitochondrial biogenesis in patients with chronic kidney disease. *Clin J Am Soc Nephrol.* Jun; 2010 5(6):996–1002. [PubMed: 20498251]
45. Phielix E, Meex R, Moonen-Kornips E, et al. Exercise training increases mitochondrial content and ex vivo mitochondrial function similarly in patients with type 2 diabetes and in control individuals. *Diabetologia.* 2010; 53:1714–1721. [PubMed: 20422397]
46. He C, Bassik MC, Moresi V, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature.* Jan 26; 2012 481(7382):511–515. [PubMed: 22258505]

\$watermark-text

\$watermark-text

\$watermark-text

Figure 1.

CONSORT diagram of Seattle Kidney Study participants included in this study.

Abbreviations: GFR = Glomerular filtration rate (estimated by the serum creatinine-based CKD-EPI equation and given in ml/min/1.73m²), UACR = Urine albumin-creatinine ratio.

Figure 2.

(a) Prevalence of frailty and intermediate frailty by estimated glomerular filtration rate (eGFR) calculated from serum cystatin C concentration. (b) Prevalence of frailty by eGFR and urine albumin excretion (p-for-interaction=0.06). Error bars represent 95% confidence interval. Numbers under each bar graph represents number of frail subjects over total in each category of cystatin C-based eGFR and albuminuria (<300mg/g versus ≥300mg/g).

Figure 3. Disability according to frailty status. Numbers under each bar represent number of each disability. Abbreviations: ADL = activities of daily living, IADL = instrumental activities of daily living.

Figure 4.

Forest plot of adjusted hazard ratios for death or dialysis comparing individual frailty components to the frailty phenotype and co-morbidities. Error bars represent 95% confidence interval. Estimated hazard ratios are adjusted for age, sex, BMI, diabetes, cardiovascular disease, and eGFR_{cys} (cystatin C-based estimated glomerular filtration rate). DM = diabetes mellitus; CVD = cardiovascular disease.

Table 1

Operational definitions and prevalence of frailty

	CHS (mean age 76 y)		SKS (mean age 59 y)	
	Definition	Prevalence	Definition	Prevalence
Weight Loss	Self-reported 10-lb unintentional weight loss in past y	6%	Self-reported 10-lb unintentional weight loss in past 6 mo	10%
Weakness	Lowest sex and BMI specific 20 th percentile grip strength	20%	Same absolute cutoffs as CHS ^{1,17}	16%
Low Activity	Lowest sex specific 20 th percentile kcal/wk ^a	20%	Self reported exercise < 1x/wk	35%
Exhaustion	Positive response to either exhaustion item on CES-D ^b	17%	Lowest 20 th percentile exhaustion score on SF-36 [*]	32%
Slowness	Lowest sex and height specific 20 th percentile walking pace assessed over 15-ft course	20%	Same absolute cutoffs as CHS; walking pace assessed over 4-m (13.1 ft) course	26%
Frailty	--	7%	--	14%
Intermediate frailty	--	47%	--	52%

CES-D = Center for Epidemiologic Studies Depression Scale; CHS, Cardiovascular Health Study; SKS, Seattle Kidney Study; BMI, body mass index; SF-36, 36-Item Short Form Health Survey (from RAND Corp)

^aPhysical activity kcal/wk measured using Minnesota Leisure Time Activity questionnaire.

^bExhaustion items on the CES-D are "I felt that everything I did was an effort," and "I could not get going."

^{*}Percentile score on SF-36 derived from adults ≥ 65 years old used to create the standard normal (score <37.5).

Table 2

Characteristics of Seattle Kidney Study participants who completed frailty assessment

	% Complete	All (N = 336)	Frail	
			No (n = 289)	Yes (n = 47)
Demographic data	100			
VA Medical Center		158 (47)	139 (48)	19 (40)
Harborview Medical Center		178 (53)	150 (52)	28 (60)
Age (y)		58.7 ±13.0	58.9 ±13.1	58.0 ±12.6
Male sex		272 (81)	236 (82)	36 (77)
Race	100			
White		225 (67)	195 (67)	25 (53)
Black		86 (26)	69 (24)	17 (36)
Hispanic		10 (3)	9 (3)	1 (2)
Other		15 (4)	16 (6)	4 (9)
Education	88			
Some High School or less		43 (15)	39 (15)	4 (10)
Completed High School		162 (55)	137 (53)	25 (64)
Completed College or More		91 (30)	81 (32)	10 (26)
Current smoking	99	63 (19)	53 (19)	10 (22)
Current alcohol use	99	117 (35)	103 (36)	14 (30)
Physical examination data				
SBP (mm Hg)	100	132.5 ±19.9	132.1 ±19.3	135.1 ±23.6
Body mass index (kg/m ²)	100	31.4 ±7.4	30.8 ±6.8	34.7 ±9.8
Obese	100	174 (52)	144 (50)	30 (64)
Waist circumference (in)	98	42.2 ±6.8	41.8 ±6.5	45.1 ±8.2
Laboratory data				
eGFR _{cys} (ml/min/1.73m ²)	100	50.9 ±27.1	52.5 ±27.6	41.1 ±21.3
eGFR _{cr} (ml/min/1.73m ²)	100	46.4 ±25.5	47.2 ±25.4	41.6 ±25.9
Creatinine (mg/dL)	100	2.1 ±1.3	2.0 ±1.2	2.5 ±1.7
Urine albumin (mg/g Cr)	97	111.5 [13.9–688.7]	102 [10.0–592.9]	311.2 [52.6–1395.7]
Hemoglobin (g/dL)	90	13.0 ±2.0	13.2 ±2.0	12.2 ±1.9
Bicarbonate (mEq/L)	100	24.5 ±3.6	24.4 ±3.5	24.9 ±4.3
CRP (mg/dL)	99	2.4 [0.9 – 5.3]	2.1 [0.9 – 5]	3.8 [1.0 – 8.0]
LDL-C (mg/dL)	95	104.0 ±44.0	103.3 ±43.4	114.9 ±46.7
HDL-C (mg/dL)	100	39.6 ±15.6	39.5 ±15.4	39.8 ±16.8
Serum Albumin (g/L)	100	3.8 ±0.6	3.9 ±0.6	3.6 ±0.7
Phosphate (mg/dL)	100	3.8 ±0.8	3.7 ±0.8	4.1 ±1.0
Prevalent diseases				
Diabetes	99	170 (51)	140 (49)	30 (64)

	% Complete	All (N = 336)	Frail	
			No (n = 289)	Yes (n = 47)
Heart Failure	100	49 (15)	35 (12)	14 (30)
COPD	98	85 (26)	76 (27)	9 (20)
Myocardial infarction	100	56 (17)	46 (16)	10 (21)
Angina	100	79 (24)	63 (22)	16 (34)
PVD	100	78 (23)	66 (23)	12 (26)
Stroke	100	44 (13)	38 (13)	6 (13)
Any CVD	100	145 (43)	123 (43)	22 (47)
Cancer	79	35 (13)	28 (12)	7 (18)
Current dialysis access	100	16 (5)	12 (4)	4 (9)
Medications	99			
Statin		189 (57)	162 (57)	27 (57)
ACEi or ARB		252 (76)	217 (76)	35 (74)
Any antihypertensive		309 (93)	263 (92)	46 (98)
Antianginal		28 (8)	22 (8)	6 (13)
Erythropoietin		13 (4)	12 (4)	1 (2)
Antidepressant		110 (33)	89 (31)	21 (45)

Values for categorical variables given as (percentage); values for continuous variables given as mean $\pm$ SD or median [25th–75th percentile].

Abbreviations and definitions: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; SBP, Systolic blood pressure; PVD, Peripheral vascular disease; CVD, cardiovascular disease; VA, Veterans Administration; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; eGFR_{cys}, estimated glomerular filtration rate calculated by the CKD-EPI equation incorporating nonstandardized cystatin C level, age, sex, and race; eGFR_{scr}, estimated glomerular filtration rate calculated by the serum creatinine-based CKD-EPI equation.

Table 3

Association of kidney function with frailty prevalence in the Seattle Kidney Study

	Frail Cases (no./no. at risk)	Model 1 (n=336)	Model 2 (n=336)
eGFR _{cys}			
60 ml/min/1.73m ²	8/99	1.0 (reference)	1.0 (reference)
45–59 ml/min/1.73m ²	6/74	1.3 (0.5–3.6)	1.2 (0.4–3.3)
30–44 ml/min/1.73m ²	19/88	3.3 (1.5–7.4)	2.8 (1.3–6.3)
<30 ml/min/1.73m ²	14/75	2.6 (1.1–5.9)	2.1 (1.0–4.7)
eGFR _{cys} p-for-trend		0.01	0.01
Age (per 10y older)		0.9 (0.7–1.1)	0.9 (0.8–1.2)
Non-white race		1.8 (1.1–3.1)	1.9 (1.1–3.3)
Female		0.9 (0.5–1.6)	1.2 (0.6–2.2)
BMI (per 5-kg/m ² difference)		--	1.2 (1.0–1.4)
Diabetes		--	1.4 (0.8–2.4)
Any cardiovascular disease		--	1.0 (0.6–1.7)
Log(CRP)		--	1.2 (0.9–1.5)

Except where indicated, values shown are prevalence ratio (95% confidence interval). Model 1: estimated glomerular filtration rate, sex, age, race (white versus other). Model 2: Model 1 + BMI + Diabetes + Any cardiovascular disease (CVD) + Log C-reactive protein.

Abbreviations: BMI = body mass index; CRP, C-reactive protein; eGFR_{cys}, estimated glomerular filtration rate calculated by the CKD-EPI equation incorporating nonstandardized cystatin C level, age, sex, and race.