Association of Albuminuria and Estimated Glomerular Filtration Rate with Functional Performance Measures in Older Adults with Chronic Kidney Disease

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Keywords

Functional impairment · Albuminuria · Chronic kidney disease

Abstract

Background: Chronic kidney disease (CKD) is increasingly common and disproportionately affects older adults. The contribution of kidney disease to the functional impairment noted in the elderly CKD population is unclear. **Methods:** This is a cross-sectional analysis of a hypertensive cohort of people aged ≥ 75 years from the Systolic Blood Pressure Intervention Trial. We evaluated estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) as predictors of 3 measures of functional status: EuroQol-5 Dimensional (EQ-5D) score, Falls Efficacy Scale (FES) score, and gait speed. Linear regression models were used to evaluate the associations between our independent variables

and outcome measures. **Results:** Our analysis included 2,620 participants, mean age of 79.9 (4.0) years. Unadjusted models showed that lower eGFR level and higher UACR level were associated with lower EQ-5D ($p < 0.001$ for both) and slower gait speed ($p < 0.001$ for both) and worse scores on FES ($p = 0.032$ and $p = 0.039$). In the fully adjusted models, higher levels of UACR remained significantly associated with lower EQ-5D scores and slower gait speed ($p = 0.011$ and $p = 0.002$, respectively). In contrast, level of eGFR was not associated with any functional outcome measures when accounting for covariates. **Conclusions:** In individuals aged ≥ 75 years, albuminuria and eGFR were associated with impairments in physical performance and self-reported functional status; however, only the association with albuminuria remained after adjusting for relevant demographics and comorbidities. Evaluation of albuminuria may provide an additional tool for identifying older individuals at risk for functional impairment.

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Introduction

Chronic kidney disease (CKD) is increasingly common in the US population, especially in older adults. It is estimated that 14% of the US population has CKD; that prevalence rises to 35% in adults over 60 years of age [1]. CKD is associated with adverse outcomes including death and cardiovascular disease (CVD), with increased risk present for individuals with early CKD as well as end-stage renal disease (ESRD) [2]. Despite its importance, research on the contribution of CKD to health-related quality of life outcomes, such as functional status, has been far less extensive. While the association of ESRD with functional status is established [3–5], it is not clear that less advanced CKD affects function, independent of its association with other chronic conditions. It is important to clarify if CKD is associated with impaired functional status, which is associated with increased healthcare utilization and mortality. This is particularly important for older patients, who make up the majority of Americans with CKD. Aging itself is a risk factor for functional impairment, thus older adults with CKD may be at greater risk for functional impairment. Additionally, older adults with CKD are at higher risk for subsequent decline in activities of daily living and community mobility compared to those without CKD [6, 7].

Studies evaluating functional impairment in patients with CKD have been limited by small cohorts, often special populations (i.e., women only) and few older participants [8, 9]. In addition, few have examined gradations of estimated glomerular filtration rate (eGFR) levels, focusing more on the cutoff of eGFR <60 mL/min/1.73 m². Other analyses, including the recent Framingham Offspring Study, have focused on the development of functional impairment in subsequent years in persons who have CKD at baseline [10, 11]. Those studies do not give us a clear understanding of CKD status and functional impairment since the level of renal function at the time that functional impairment was noted was not described. Furthermore, prior research on this subject has not evaluated the role of albuminuria, a determinant of CKD severity, in functional status. We therefore examined the cohort of older patients with hypertension enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT) for evidence of an association between markers of CKD severity and various domains of functional status including physical performance, activity limitations, and concern for falls.

Methods

Design

SPRINT was a multicenter randomized clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI), the National Institute for Diabetes and Digestive and Kidney Diseases, National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS). A thorough description of the rationale and design of SPRINT has been published [12]. In brief, the goal of SPRINT was to determine if treatment targeting a systolic blood pressure (SBP) <120 mm Hg compared to targeting SBP <140 mm Hg would reduce CVD events. SPRINT was approved by Institutional Review Boards at participating sites and all participants provided written informed consent.

Participants

The senior SPRINT subgroup, which consisted of individuals aged ≥75 years of age at enrollment, was included in this analysis. The senior subgroup was one of the 3 subgroups targeted during enrollment. The complete SPRINT cohort was made up of participants aged ≥50 years and at risk for cardiovascular event based on either clinical CVD or subclinical CVD or high risk for CVD, including eGFR 25–59 mL/min/1.73 m² or Framingham risk score for 10 year CVD risk ≥15%. SPRINT exclusion criteria included a known history of stroke, diabetes mellitus, >600 mg/day of albuminuria, or >1 g/day of proteinuria based on 24 h collection or if not available a spot urine ratio within the last 6 month, or eGFR <20 mL/min/1.73 m².

Data Collection

At the randomization visit, participants completed a self-administered survey, including demographic data. Other items included socioeconomic status, tobacco and alcohol use, self-reported medical conditions, and the EuroQol-5 Dimensional (EQ-5D) measure of health-related quality of life. At this same visit, SPRINT staff measured height, weight, and blood pressure, performed a brief physical examination including a timed 4 m walk to measure gait speed for those aged ≥75 years, collected urine and blood for laboratory analysis, and recorded an electrocardiogram. A random subset of participants plus all seniors randomized after January 8, 2013, also completed the Falls Efficacy Scale (FES).

Outcome Measures

We used 3 measures to gain a comprehensive view of functional status: the EQ-5D, FES, and gait speed. We used the EQ-5D to measure health-related quality of life concentrating on functional status. It includes 5 questions on mobility, ability to perform self-care, ability to perform usual daily activities, pain/discomfort, and anxiety/depression. EQ-5D is commonly used to measure health-related quality of life; however, it focuses on function in 3 out of the 5 questions and pain level is also likely to influence functional status. We used standard methods to summarize the EQ-5D, with scores ranging from –0.11 (i.e., worse than death) to 1.0 (perfect health) [13]. The FES includes 7 items that are scored on a 4-point Likert scale and summarized by simple addition to yield a score ranging from 7 to 28 with higher scores indicating increased concern for falls [14]. Increased scores are associated with falls, decreased functional activity, and limitations in social activity [15, 16]. We used gait speed as a measure of physical performance. Population studies show normal gait speeds range from 0.78 to 0.96 m/s among individuals aged >70 years [17].

Measures of CKD

The SPRINT Central Lab measured creatinine in serum or urine on a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) using a creatinase enzymatic method, which has been standardized against the isotope dilution mass spectrometry procedure. Urine albumin was measured by nephelometry using the Siemens ProSpec nephelometer and a rabbit-derived anti-human albumin antibody. We calculated the urine albumin/creatinine ratio (UACR) using a spot urine sample obtained at the baseline visit and measured in milligrams of albumin/gram of creatinine (mg/g). We calculated eGFR in mL/min/1.73 m² using the serum creatinine level obtained at the baseline visit. We used the 4-variable MDRD equation for our primary analysis and repeated the analysis after recalculating eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation; the results were similar for the fully adjusted models [18].

Statistical Analysis

We present baseline characteristics as means (SD) or frequencies, unless otherwise noted. We compared baseline characteristics between persons with eGFR ≤60 vs. >60 mL/min/1.73 m² using 2 sample *t* tests for continuous variables and chi-square tests for categorical variables. We then used linear regression models to evaluate the cross-sectional associations between our independent variables and outcome measures. Indicator variables were used to model categories of eGFR (<44, 44–59, and >60 mL/min/1.73 m²) and UACR (≤30, 31–299, and >300 mg/g). The first model adjusted for eGFR or UACR categories without further adjustment. Additional models adjusted for demographic covariates (age, gender, race, body mass index, smoking, and drinking status), and comorbidities (coronary artery disease, congestive heart failure, peripheral vascular disease, arthritis, low back pain, depression, SBP and diastolic blood pressures, and orthostatic hypotension). The final model also included UACR for the eGFR-based model and eGFR for the UACR-based model. Adjusted means for the levels of eGFR and UACR were calculated as part of the multivariable analyses. Diagnostic tests and graphics were completed for all model assumptions. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

SPRINT investigators enrolled 9,361 participants at 102 clinics over a 2.3 year period. After applying age exclusion, our study population included 2,620 participants, most of whom were male (62%). Their mean age was 79.9 (4.0) years. See Table 1 for baseline characteristics of the cohort. As intended, participants included large numbers of individuals who had CKD (*n* = 1,161, 44%). In our cohort, the median (25th–75th percentile) eGFR was 62.54 mL/min/1.73 m² (50.70–75.22) and the median (25th–75th percentile) UACR was 13.16 mg/g (7.24–32.35).

EuroQol-5 Dimensional

The mean (SD) EQ-5D score was 0.85 (0.13). In the unadjusted analysis (Model 1), mean EQ-5D scores were similar amongst participants with an eGFR >44 to <60

and ≥60 and were slightly higher compared to the scores of participants with eGFR ≤44 (*p* < 0.001; Table 2). EQ-5D scores declined as level of albuminuria increased (*p* < 0.001; Table 3). After adjustment for baseline demographics as potential confounders (Model 2), both lower eGFR and higher UACR remained associated with lower EQ-5D scores (*p* = 0.007 and *p* < 0.001; Tables 2, 3). However, after fully adjusting for demographics and comorbidities (Model 3), eGFR was no longer associated with EQ-5D score (*p* = 0.443) while UACR remained significantly associated (*p* = 0.040; Tables 2, 3, respectively). Graphical results of Model 3 are available online as online supplemental Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000455388).

Gait Speed

The mean (SD) gait speed was 0.87 (0.22) m/s. In the unadjusted analysis (Model 1), mean gait speed increased among participants as eGFR increased (*p* < 0.001) and decreased as UACR increased (*p* < 0.001; Tables 2, 3, respectively). After adjustment for baseline demographics (Model 2) and comorbidities (Model 3), level of eGFR was no longer associated with gait speed (*p* = 0.063 and *p* = 0.520). UACR remained significantly associated with gait speed after adjusting for the additional demographics (Model 2) and comorbidities (Model 3; *p* < 0.001 and *p* = 0.003; Table 3). Graphical results of Model 3 are available online as online supplemental Figure 2.

Falls Efficacy Scale

The mean (SD) FES score was 9.12 (3.34). In the unadjusted analysis (Model 1), higher (worse) FES scores were associated with lower level eGFR (*p* = 0.032) and higher UACR (*p* = 0.039; Tables 2, 3, respectively). The associations with eGFR and FES scores did not persist in the adjusted models (Model 2, *p* = 0.173; Model 3, *p* = 0.181). The association between UACR and FES scores remained after adjusting for baseline demographics (*p* = 0.020; Model 2) but not when including comorbidities (*p* = 0.122; Model 3). Graphical results of Model 3 are available online as online supplemental Figure 3.

Discussion

In a cohort of older adults with hypertension, we found that increased level of albuminuria was associated with slower gait speed, a measure of physical function, and worse EQ-5D score, a measure of health-related quality

Table 1. Baseline characteristics of SPRINT cohort by CKD status

	Overall (n = 2,620), % or mean (SD)	Non CKD (n = 1,459), % or mean (SD)	CKD (n = 1,161), % or mean (SD)	p value
Age, years	79.85 (3.99)	79.39 (3.73)	80.42 (4.23)	<0.001
Gender, female	993 (37.9)	555 (38)	438 (37.7)	0.869
Race				0.067
African American	448 (17.1)	269 (18.4)	179 (15.4)	
Caucasian	1,954 (74.6)	1,061 (72.7)	893 (76.9)	
Hispanic	171 (6.5)	98 (6.7)	73 (6.3)	
Other	47 (1.8)	31 (2.1)	16 (1.4)	
Smoking				0.375
Never	1,231 (47)	701 (48)	530 (45.7)	
Past	1,301 (49.7)	712 (48.8)	589 (50.7)	
Current	84 (3.2)	43 (2.9)	41 (3.5)	
Drinking status				0.071
Non-drinker	1,240 (47.3)	676 (46.3)	564 (48.6)	
Light drinker	482 (18.4)	260 (17.8)	222 (19.1)	
Moderate drinker	501 (19.1)	294 (20.2)	207 (17.8)	
Heavy drinker	262 (10)	162 (11.1)	100 (8.6)	
Coronary artery disease	515 (19.7)	242 (16.6)	273 (23.5)	<0.001
Congestive heart failure	117 (4.5)	41 (2.8)	76 (6.5)	<0.001
Peripheral vascular disease	218 (8.3)	96 (6.6)	122 (10.5)	<0.001
Arthritis	1,620 (61.8)	860 (58.9)	760 (65.5)	<0.001
Low back pain	1,186 (45.3)	668 (45.8)	518 (44.6)	0.594
Moderate to severe depression	88 (3.4)	35 (2.4)	53 (4.6)	0.002
SBP	141.61 (15.73)	141.65 (15.44)	141.56 (16.1)	0.887
Diastolic blood pressure	71.19 (10.93)	71.82 (10.5)	70.4 (11.41)	0.001
Orthostatic hypotension	248 (9.5)	112 (7.7)	136 (11.7)	<0.001
Body mass index, kg/m ²	27.76 (4.73)	27.7 (4.67)	27.84 (4.81)	0.475
Serum creatinine	1.13 (0.35)	0.92 (0.16)	1.4 (0.34)	<0.001
eGFR, mL/min/1.73 m ²	63.36 (18.25)	76.11 (12.79)	47.34 (9.22)	<0.001
UACR, mg/g Cr	55.21 (191.15)	35.71 (155.37)	79.28 (225.47)	<0.001
EQ-5D	0.85 (0.13)	0.85 (0.13)	0.84 (0.13)	0.009
FES	9.12 (3.34)	9.04 (3.18)	9.22 (3.55)	0.455
4 m walk, mean	0.87 (0.22)	0.88 (0.22)	0.85 (0.22)	0.002

* CKD based on eGFR <60 mL/min/1.73 m², eGFR, estimated glomerular filtration rate.

of life with a focus on function. This association remained even after adjusting for relevant covariates. In contrast, the level of eGFR was associated with our functional outcome measures when unadjusted; however, after adjusting for relevant covariates, the associations were no longer significant. Our study suggests that kidney disease as noted by increased level of albuminuria is associated with functional impairment in older adults.

Our study adds to the evidence that in persons with CKD, there are impairments in function. However, in contrast to previous research, we did not find that eGFR level (above 20 mL/min/1.73 m²) alone was associated with functional impairment after adjusting for demographics and relevant covariates. We note that previous

research demonstrating an association of eGFR and functional status was in select patient populations, such as patients with coronary artery disease, a disease which may modify susceptibility to functional impairment [8, 9]. Furthermore, we evaluated the association between current eGFR and functional impairment in contrast to other studies that evaluated the subsequent development of functional impairment associated with a baseline eGFR [10, 11]. Evaluating the subsequent development of functional limitations does not provide the severity of CKD at the time of impaired function as CKD may have progressed during follow-up. Additionally, previous studies did not include albuminuria as a risk factor for functional impairment. Since decline in eGFR is higher in those

Table 2. EQ-5D, mean gait speed, and FES (adjusted means [SE]) at baseline by eGFR categories

	eGFR, mL/min/1.73 m ²			<i>p</i> value
	≤44	>44–<60	≥60	
EQ-5D, <i>n</i>	372	781	1,449	
Model 1	0.82 (0.01)	0.85 (0.01)	0.85 (0.00)	<0.001
Model 2	0.82 (0.01)	0.84 (0.01)	0.84 (0.01)	0.007
Model 3	0.73 (0.01)	0.75 (0.01)	0.73 (0.01)	0.443
Mean gait speed, <i>n</i>	355	755	1,392	
Model 1	0.83 (0.01)	0.86 (0.01)	0.88 (0.01)	<0.001
Model 2	0.77 (0.02)	0.79 (0.01)	0.80 (0.01)	0.063
Model 3	0.74 (0.02)	0.75 (0.02)	0.76 (0.02)	0.520
FES, <i>n</i>	109	253	495	
Model 1	9.89 (0.34)	8.93 (0.21)	9.04 (0.15)	0.032
Model 2	9.95 (0.48)	9.23 (0.39)	9.42 (0.36)	0.173
Model 3	11.08 (0.59)	10.54 (0.56)	10.93 (0.51)	0.181

Model 1: unadjusted.

Model 2: model 1 with age, gender, race, body mass index, smoking status, and drinking status.

Model 3: model 2 plus coronary artery disease, congestive heart failure, peripheral vascular disease, arthritis, low back pain, depression, SBP, diastolic blood pressure, DBP, orthostatic hypotension, and UACR.

Table 3. EQ-5D, mean gait speed, and FES (adjusted means [SE]) at baseline by UACR categories

	UACR, mg/g Cr			<i>p</i> value
	≤30	>30–<300	≥300	
EQ-5D, <i>n</i>	1,846	566	91	
Model 1	0.85 (0.00)	0.84 (0.01)	0.81 (0.01)	<0.001
Model 2	0.84 (0.01)	0.83 (0.01)	0.80 (0.02)	<0.001
Model 3	0.74 (0.01)	0.74 (0.01)	0.71 (0.02)	0.040
Mean gait speed, <i>n</i>	1,782	540	85	
Model 1	0.88 (0.01)	0.83 (0.01)	0.84 (0.02)	<0.001
Model 2	0.81 (0.01)	0.77 (0.02)	0.77 (0.03)	<0.001
Model 3	0.77 (0.02)	0.74 (0.02)	0.74 (0.03)	0.003
FES, <i>n</i>	615	185	33	
Model 1	9.04 (0.13)	9.09 (0.24)	10.55 (0.57)	0.039
Model 2	9.19 (0.37)	8.94 (0.41)	10.61 (0.63)	0.020
Model 3	10.65 (0.52)	10.33 (0.53)	11.49 (0.69)	0.122

Model 1: unadjusted.

Model 2: model 1 with age, gender, race, body mass index, smoking status, and drinking status.

Model 3: model 2 plus coronary artery disease, congestive heart failure, peripheral vascular disease, arthritis, low back pain, depression, SBP, diastolic blood pressure, DBP, orthostatic hypotension, and eGFR.

with increased albuminuria [19], it is possible that previous findings, similar to our results, actually reflected the importance of albuminuria in functional outcomes. Finally, the lack of association with eGFR may be due to the decreased accuracy of creatinine-based GFR estimates in the elderly [20]. In our cohort, the severity of CKD may

not be accurately reflected with our creatinine-based eGFR in those aged ≥75 years.

While albuminuria is known to relate to severity and prognosis of CKD, our results indicate it may also be a marker for decreased functional status, at least in a hypertensive population without diabetes. In a recent report, a

higher degree of albuminuria but not eGFR was associated with increased risk for serious falls among Medicare beneficiaries aged ≥ 65 years, even after adjustment for demographic, comorbid, and fall risk factors [21]. This is consistent with our results as slower gait speed is associated with increased falls risk [22]. Furthermore, in two large trials focused on participants with diabetes or vascular disease, albuminuria was associated with worse performance on cognitive assessments at baseline and in follow-up [23, 24]. These authors hypothesized that microvascular pathology could lead to both albuminuria and cerebral white matter disease. Similarly, our results could reflect that albuminuria is a marker of vascular endothelial pathology that is associated with the increased inflammatory state of CKD. Such microvascular pathology could also lead to skeletal muscle damage and impaired physical performance. Observational analysis has demonstrated that persons with albuminuria have a higher risk for sarcopenia, further supporting a link between physical performance and albuminuria [25].

If our results are confirmed in other studies, they suggest that screening older adults with kidney disease marked by macroalbuminuria for impaired physical function could improve outcomes. For example, if screening identified reduced or rapidly declining gait speed, physical therapy could be used to reduce falls and maintain mobility and independence [26, 27].

The strengths of our study include our relevant measures of both patient reported functional status and objectively assessed physical performance along with a large cohort of older adults. Our physical performance measure is clinically important as gait speed has already been shown to be a predictor of adverse outcomes in elderly individuals, including functional declines [28], hospitalizations [29, 30], falls [22], and mortality [30–32]. A decrease of 0.1 m/s in gait speed is associated with a 6–17% decrease in survival depending on age stratum [32]. The 0.03 m/s difference in gait speed that we observed between SPRINT participants with macroalbuminuria and those with normoalbuminuria is similar to changes in gait speed that have been reported to have a meaningful impact on patient reported mobility including the ability to walk a quarter mile, and ability to climb one flight of stairs [33, 34]. Using gait speed, we were able to identify subtle differences in functional status that may progress and lead to disability and the adverse outcomes described above. Our patient reported outcome, the EQ-5D questionnaire, is a widely used and validated measure of health-related quality of life with a focus on function [35, 36]. In addition to the above outcomes, we also included a measure of the

patients' perception of risk of falling while performing routine daily activities (FES). Overall, our cohort displayed only mild concern for falls with the average score of 9 [14]. From our FES results, we were able to conclude that there was no increased concern for falls at early to moderate stages of CKD. Thus, the decrease in gait speed associated with increased albuminuria is unlikely to be attributed to an increased concern for fall or patient self-imposed limitations but may reflect a more direct effect of kidney disease on physical capabilities. This adds evidence for the importance of screening older adults with albuminuria for physical impairment, since they may not be aware of impairment or think to report the impairment until it has progressed to a more severe stage.

Our study has the following limitations. First, we cannot determine whether the association we observed between albuminuria and reduced functional status is causal. Increased albuminuria due to primary renal disease could lead to impaired function or another disease process that could both cause albuminuria and impair function status. Second, the number of participants with $\text{UACR} \geq 300$ mg/g and $\text{eGFR} \leq 44$ mL/min/1.73 m² was small and participants with albuminuria >600 mg/g were excluded, limiting our ability to determine if greater levels of albuminuria or lower eGFR would be associated with worse functional outcomes. Third, we did not extensively evaluate other clinical variables commonly seen in early kidney disease such as abnormalities in bone mineral parameters. Fourth, our cohort had participants in a clinical trial with existing CVD or risk factors for CVD, which affects its applicability to the general population. Finally, the differences we observed between different levels of albuminuria are small. Our fully adjusted results show that the EQ-5D score was 0.03 points lower among participants with macroalbuminuria than among those with normoalbuminuria. Although a meaningful difference in EQ-5D score varies based on disease state and age, the difference that we note is similar to changes seen with 10-year increases in age according to published US population norms [37]. Similarly, the difference in gait speed we observed is associated with small yet meaningful changes in patient reported mobility [33, 34].

Conclusion

We evaluated a range of functional outcomes in older adults with and without markers of CKD. Our results indicate that among older hypertensive adults, albuminuria is associated with impairments in functional status.

As SPRINT final closeout visits are completed and the data becomes available, the longitudinal relationship between albuminuria and functional status can be evaluated. Future research should confirm this association in a broader population and explore the relationship between functional impairment and other clinical variables noted in mild to moderate kidney disease. This may help identify both the appropriate time point for intervention and potential therapeutic interventions for the functional impairment noted in older adults with kidney disease.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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