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Creatinine Clearance and Walking Speed and Muscle Atrophy: A Cohort Study

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Abstract

Background—Chronic kidney disease (CKD) is associated with malnutrition and inflammation. These processes may lead to loss of skeletal muscle and reduced physical performance. Associations of kidney function with muscle composition and longitudinal measures of physical performance are unknown.

Study Design—Prospective cohort study.

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Supplementary Material

Table S1: Characteristics of those with only baseline visit compared to >1 visit.

Table S2: Cross-sectional association of Clcr with physical performance and pQCT measurements.

Table S3: Cross-sectional association of eGFR_{cys} with physical performance and pQCT measurements.

Table S4: Cross-sectional association of eGFR_{cr-cys} CKD EPI with physical performance and pQCT

Table S5: Adjusted difference in mean annual change in physical performance by category of Clcr, not normalized to BSA.

Table S6: Adjusted difference in mean annual change in physical performance by category of eGFR_{cys}.

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

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Setting & Participants—We evaluated 826 community-dwelling older adults enrolled in the Invecchiare in Chianti (InCHIANTI) Study free of baseline stroke or activities of daily living disability.

Predictor—Baseline creatinine clearance (Clcr) based on a 24-hour urine collection.

Outcomes—Cross-sectional and longitudinal trajectories of physical performance measured by 7-meter usual gait speed, 400-meter fast gait speed, and knee extension strength using isometric dynamometry. Calf muscle composition assessed by quantitative CT.

Results—Mean age of participants was 74 ± 7 (SD) years with 183 having Clcr < 60 ml/min/1.73m². After adjustment each 10 ml/min/1.73m² decrement in Clcr was associated with 0.01 (95% CI, 0.004–0.017) m/s slower 7-meter usual walking speed and 0.008 (95% CI, 0.002–0.014) m/s slower 400-meter walking speed. Each 10 ml/min/1.73m² decrement in Clcr was associated with 28mm² (95% CI, 0.8–55) lower muscle area and 0.15mg/cm³ (95% CI, 0.04–0.26) lower muscle density. After adjustment, lower Clcr was associated with slower mean 7-meter ($P=0.005$) and 400-meter ($P=0.02$) walk and knee extension strength ($P=0.001$) over the course of follow-up. Over a mean follow-up of 7.1 ± 2.5 years, each 10 ml/min/1.73m² lower baseline Clcr was associated with 0.024 (95% CI, 0.01–0.037) kg/year greater decline in knee strength.

Limitations—Single baseline measurement of Clcr and 3-year interval between follow-up visits may lead to non-differential misclassification and attenuation of estimates. Conclusions: Among older adults, lower Clcr is associated with muscle atrophy, reduced walking speed and more rapid declines in lower extremity strength over time.

INDEX WORDS

physical performance; skeletal muscle composition; muscle strength; mobility impairment; muscle atrophy; longitudinal trajectory; creatinine clearance (Clcr); renal function; chronic kidney disease (CKD)

Chronic kidney disease (CKD) is associated with chronic inflammation, protein-energy wasting, and progressive loss of muscle mass and strength.^{1–4} Reduced kidney function is associated with adverse health outcomes analogous to accelerated aging. Clinical consequences of these adverse physiological processes associated with reduced kidney function include impaired ambulation, frailty, disability, and premature death.^{5–8} Patients with CKD have substantially diminished lower extremity physical performance in terms of gait.⁷ Among patients with CKD and community-dwelling older adults, lower physical performance is potentially associated with all-cause mortality.^{7,9}

Previous studies of community-dwelling older adults investigating the association of kidney function and skeletal muscle impairment are generally limited by the absence of muscle-specific imaging, cross-sectional study design, and use of serum creatinine-based glomerular filtration rate (GFR) estimating equations, which may be influenced by muscle mass.^{1,4} Nevertheless, when kidney function was estimated using cystatin C among more than 3,000 older adults from the Health, Aging, and Body Composition (Health ABC) Study, lower estimated GFR (eGFR) was associated with decreased muscle strength and slower maximal gait speed.⁴ Despite the evidence demonstrating an association between lower extremity muscle size and composition by CT with gait speed decline,¹⁰ incident mobility limitation¹¹

and mortality among older adults,^{12–14} no studies have investigated the association of kidney function with lower extremity muscle size and composition to our knowledge.

In the current study, we determine associations of creatinine clearance (Clcr) with concurrent measurements of calf muscle composition, assessed by peripheral quantitative computed tomography (pQCT), and physical performance, assessed by standardized testing, among community-dwelling older northern Italian adults aged 65 years and older from the Invecchiare in Chianti (InCHIANTI) Study. The InCHIANTI Study was designed to examine factors contributing to the decline in mobility function in later life. We specifically chose Clcr in order to account for creatinine production within an individual, reducing the potential for confounding in analyses of muscle structure and performance. We compare these associations of Clcr with calf muscle composition and physical performance to aging. We further determine associations of baseline kidney function with longitudinal changes in physical performance over 9 years.

METHODS

Study Population

The InCHIANTI Study is a prospective, community-based cohort study of factors contributing to the decline in mobility function in later life. Participants were randomly selected using multistage stratified sampling methods from two towns in the Chianti geographic area of Italy (Greve in Chianti and Bagno a Ripoli, Tuscany, Italy). The baseline examination took place from September 1998 through March 2000, and longitudinal examinations occurred every 3 years until May 2009. Full details of the study design and data collection methods have been previously published.^{15–17} The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee.

For cross-sectional analyses, we studied participants who were free of stroke and disability in their activities of daily living (ADLs) at baseline and who completed an adequate 24-hour urine collection (Figure 1). For longitudinal analyses we studied those who had 1 follow-up assessment.

Exposure Measurement

Participants completed serum creatinine measurements and a 24-hour urine collection at baseline. The Clcr was standardized to body surface area calculated using the Mosteller formula.¹⁸

Serum creatinine concentrations were measured on a Roche/Hitachi analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) and urine creatinine concentrations were measured on an ADVIA Centaur Immunoassay system (Bayer Diagnostics). Serum creatinine measurements were standardized to isotope-dilution mass spectrometry. We considered 24-hour urine collections to be inadequate if 24-hour urine creatinine excretion was <10 or <8 mg/kg lean body mass in men and women, respectively.

Cystatin C was measured in the Laboratory of Clinical Biochemistry Research, University of Vermont College of Medicine, Colchester, VT, using the Dade Behring Nephelometer II System (Dade Behring Inc., Deerfield, IL, USA) and utilizing a particle-enhanced immunonephelometric assay (N Latex Cystatin C kit; Dade Behring Inc., Deerfield, IL, USA).

Physical Performance Outcome Measures

Gait speed and knee extension strength were assessed at each follow-up. For the 7-meter walk, participants were asked to stand with both feet touching the starting line and then begin walking at their usual pace after verbal command. Walking time was measured using an optoelectronic system that included two photocells connected to a recording chronometer. The faster of two trials was used in the analysis. For the 400-meter walk, participants were asked to walk as fast as they could throughout the test; only one timed 400-meter walk was performed.¹⁹ Isometric knee extension strength was measured using a handheld dynamometer according to a standardized assessment protocol.²⁰ The maximal strength from two trials on the right leg was used for analysis.

pQCT Outcome Measures

Cross-sectional muscle and fat areas of the right calf were measured using a recent generation scanner (XCT 2000; Stratec, Pforzheim, Germany) to assess lower extremity muscle and composition. The pQCT technology has been shown to be highly reproducible.²¹ Data presented here were derived from standard 2.5-mm thick transverse scans obtained at 66% of the tibial length starting from the tibiotarsal joint. Previous studies have demonstrated this region to represent the largest outer calf diameter with small variability across individuals.²¹ The muscle density (in mg/cm³), muscle cross-sectional area (CSA) (in mm²), and fat CSA (in mm²) were ascertained using the BonAlyse software version 3.1 (BonAlyse Ltd, Jyväskylä, Finland). Density thresholds of 15 mg/mm³ and 180 mg/mm³ were used to separate fat from muscle tissue and muscle from bone tissue, respectively. Muscle density was calculated from x-ray attenuation and represents a measure of fatty degeneration of muscle tissue.

Comorbidities and Other Variables

Comorbidities were ascertained at baseline using a combination of self-report, medical records, and a clinical medical examination and included coronary artery disease (angina and acute myocardial infarction), stroke (and/or transient ischemic attack), diabetes, and chronic obstructive pulmonary disease. Diabetes was defined as fasting blood glucose of 126 mg/dL, glycosuria, self-report, or medication use. Physical activity in the year before the baseline interview was assessed by interviewer-administered questionnaire.²² One of the following response categories that incorporated duration, frequency, and intensity of physical activity could be chosen for the past year: sedentary (mostly sitting/some walking), light-moderate (light exercise 2–4 hr/wk or moderate exercise 1–2 hrs/wk), and moderate-high (>3 hr/wk moderate exercise). Smoking was classified as either current smoker (within 3 years of the interview) or never/former smoker. We adjusted for total daily consumption of animal protein (grams/day) obtained from self-reported questionnaire in our models with Clcr as the primary exposure.^{23–25}

Statistical Analysis

Multivariable linear regression was used to estimate cross-sectional associations of Clcr with study outcomes of usual gait speed over 7 meters, fast gait speed over 400 meters, isometric knee extension strength, and pQCT measures of muscle density, calf muscle CSA, and fat CSA. The Clcr was modeled as a categorical variable with Clcr ≥ 90 ml/min as the referent category and continuously standardized to either a 10 ml/min decrement or 1-standard deviation decrement. Models were adjusted for age, gender, height and weight, study site, smoking status (current, vs. never or former), education (none, elementary school, secondary school, and high school or greater), diabetes (yes, no), coronary artery disease (yes, no) and total daily consumption of animal protein. We performed complete case analysis in all models. Because physical activity is a potential intermediate in the causal pathway linking Clcr with our outcomes of interest, we chose to adjust for physical activity in our sensitivity analysis. The Wald test was used to obtain 95% confidence intervals (CIs) and p-values for model covariates and to evaluate potential interactions by gender and diabetes. Since diabetes has been shown to impact physical performance, we tested for an additive interaction between the combination of CKD and diabetes on gait speed compared to the sum of CKD alone and diabetes alone.²⁶ Additive interaction between diabetes and dichotomous CKD (defined as Clcr <60 vs Clcr ≥ 60 ml/min/1.73 m²) for 7-meter walking pace (the most complete measure) was tested using the Wald Test. Pearson's correlations coefficient between the pQCT measures were calculated. We specifically tested whether associations of kidney function with pQCT outcomes differed by gender.

Linear mixed effects models with participant age as the time scale were constructed to estimate associations of baseline Clcr with changes in knee extension strength and usual gait speed over time. Given the relatively small number of participants who had Clcr <45 ml/min/1.73 m² and available follow-up visits, Clcr categories of <45 and 45–59 ml/min/1.73 m² were combined for the longitudinal analyses. The interaction of longitudinal age (the age at the time of each examination) by Clcr was used to estimate the rate of change in each outcome variable over time. We included a quadratic term for age in longitudinal models of usual walking pace based on the observed functional form of this characteristic with aging. For longitudinal models, we estimated the adjusted mean difference in annual decline of each characteristic for each category of Clcr. We tested for trends across Clcr category by including Clcr as a grouped linear variable in the multivariate models.

Sensitivity analyses were performed using non-standardized Clcr and eGFR calculated with the 2012 CKD-EPI (CKD Epidemiology Collaboration) cystatin C (eGFR_{cys}) and creatinine–cystatin C equations (eGFR_{cr-cys}).²⁷ All statistical analysis was performed using STATA version 12 (StataCorp LP, College Station, TX).

RESULTS

Sample Characteristics

There were 826 InCHIANTI participants who were free of baseline ADL disability and stroke/transient ischemic attack and who completed baseline walking speed assessment and adequate urine collection (figure 1). Mean age was 74 ± 6.5 (standard deviation) years; 56%

of the cohort were women and 12% had diabetes. Mean Clcr was 78 ± 23 ml/min/1.73m². There were 183 participants with Clcr < 60 ml/min/1.73m² (table 1). Participants who had lower Clcr were on average older, more likely to be female, and had lower levels of education and physical activity. Those with lower baseline Clcr had less frequent visits (table 1). Participants missing follow-up were on average older, less educated, more sedentary, and had worse kidney function (table S1, available as online supplementary material).

Baseline Physical Performance

Mean 7-meter usual walking pace and 400-meter fast walking pace were 1.17 ± 0.27 m/s and 1.23 ± 0.24 m/s, respectively. Mean knee extension strength was 16.5 ± 6 kg. After adjustment for age, sex, study site, height, weight, smoking, education, diabetes, and prevalent coronary disease, Clcr <45 ml/min/1.73m² was associated with an estimated 0.11 (95% CI, 0.05–0.18) m/s slower 7-meter usual walking speed and a 0.072 (95% CI, 0.01–0.14) m/s slower 400-meter fast walking speed (table 2) compared to Clcr ≥ 90 ml/min/1.73m². CKD (defined as Clcr <60 ml/min/1.73m²) was associated with a 0.068 (95% CI, 0.031–0.104) m/s slower gait speed compared to Clcr ≥ 60 ml/min/1.73m². When modeled linearly, each 10 ml/min/1.73m² decrement in Clcr was associated with an estimated 0.01 (95% CI, 0.004–0.017) m/s slower 7-meter usual walking speed and a 0.008 (95% CI, 0.002–0.014) m/s slower 400-meter fast walking speed (table 2 and figure 2). No association was noted between Clcr and knee extension strength. After adjustment, each 1-year older age was associated with an equivalent 0.017 (95% CI, 0.02–0.015) m/s slower 7-meter walking speed and 400-meter walk speed.

There was evidence for an additive interaction of diabetes and CKD (Clcr <60 ml/min/1.73m²) with 7-meter walking speed ($P < 0.001$). Participants who had Clcr <60 ml/min/1.73m² and diabetes had an estimated 0.142 (95% CI, 0.003–0.28) m/s slower gait speed compared to those who had neither diabetes nor CKD. Use of non-standardized Clcr yielded similar results (table S2A).

Physical activity was associated with all physical performance measures ($P < 0.01$). Sensitivity analysis further adjusting for baseline physical activity showed each 10 ml/min decrement in Clcr was associated with an estimated 0.007 (95% CI, 0.001–0.014) m/s slower 7-meter usual walking speed and an estimated 0.007 (95% CI, 0.001–0.012) m/s slower 400-meter walk. Sensitivity analysis using eGFR_{cys} and eGFR_{cr-cys} was consistent with Clcr in its association with physical performance (tables S3A and S4A). After adjustment, lower baseline eGFR_{cr-cys} was associated with greater knee extension strength (table S4A).

Baseline Calf Muscle pQCT

The pQCT measurements of calf muscle were available for 814 participants. Mean calf muscle CSA and muscle density were 6177 ± 1222 mm² and 71 ± 3.5 mg/cm³, respectively. Fat CSA was negatively correlated with muscle CSA ($\rho = -0.28$) and muscle density ($\rho = -0.26$). After adjustment lower Clcr was associated with lesser calf muscle CSA and muscle density (table 3). Each 10 ml/min/1.73 m² lower Clcr was associated with an estimated 28

(95% CI, 0.8–55) mm² lower muscle CSA and a 0.15 (95% CI, 0.04–0.26) mg/cm³ lower muscle density, respectively. In comparison, each additional year of age was associated with an estimated 30 (95% CI, 20–41) mm² lower muscle CSA and a 0.15 (95% CI, 0.11–0.19) mg/cm³ lower muscle density after adjustment. CKD was associated with 177 (95% CI, 19–335) mm² greater muscle fat CSA compared with no CKD. No sex interaction was observed. Results were consistent with non-standardized Clcr (table S2B).

Physical activity was associated with muscle density and CSA ($P < 0.02$), but not fat CSA. Sensitivity analysis adjusting for baseline physical activity showed each 10 ml/min/1.73m² decrement in Clcr was associated with an estimated 0.13 (95% CI, 0.03–0.28) mg/cm³ lower muscle density. After adjusting for baseline physical activity the association of CKD with fat CSA was not attenuated, however the association with calf muscle CSA was no longer significant ($P = 0.1$).

Sensitivity analysis using eGFR_{cys} instead of Clcr did not demonstrate a significant association with calf muscle area ($P = 0.7$) or fat CSA ($P = 0.5$) (Table S3B). However, those with eGFR_{cys} < 60 ml/min/1.73m² had an estimated mean difference in muscle density of -0.81 (95% CI, -1.61 to -0.007) mg/cm³ ($P = 0.05$) compared to those with eGFR_{cys} ≥ 90 ml/min/1.73m² (categorical P for trend = 0.05). No meaningful association was noted between eGFR_{cr-cys} and calf muscle pQCT (table S4B).

Physical Performance Trajectory

Mean follow-up time among participants who completed at least 1 follow-up measurement of usual walking speed was 7.1 ± 2.5 years. Those with Clcr < 45 ml/min/1.73m² had mean follow-up of 5.8 ± 2.8 years compared with 7.6 ± 2.3 years for those with Clcr ≥ 90 ml/min ($P < 0.001$). Over the course of follow-up, lower Clcr was associated with lower adjusted mean knee extension strength (P for trend = 0.005) and slower 7-meter walking speed (P for trend = 0.02) (figure 3). After adjustment, each 10 ml/min/1.73m² lower baseline Clcr was associated with an estimated mean 0.008 (95% CI, 0.001–0.014) m/s slower 7-meter walking speed and an estimated mean 0.149 (95% CI, 0.044–0.254) kg lower knee extension strength throughout the duration of follow-up. Each 10 ml/min/1.73m² lower baseline Clcr was associated with an estimated 0.024 (95% CI, 0.01–0.037) kg/year greater decline in knee extension strength ($P = 0.001$) (tables 4 and S5, figure 3). In contrast, Clcr was not associated with longitudinal changes in usual or fast walking speed in this cohort.

After sensitivity analysis further adjusting for baseline physical activity, each 10 ml/min lower baseline Clcr was associated with an estimated 0.022 (95% CI, 0.008–0.037) kg/year greater decline in knee extension strength.

No association was observed between eGFR_{cys} and longitudinal changes in usual or fast gait speed and knee extension strength (table S6).

DISCUSSION

In summary, we observed associations of diminished kidney function, estimated by lower 24-hour Clcr, with several characteristics of skeletal muscle function and composition in a

community-based cohort of stroke-free, disability-free, and ambulatory older adults. First, we observed associations of lower Clcr with slower 7-meter and 400-meter gait speeds at baseline. In parallel, we observed associations of lower Clcr with lower calf muscle density and muscle CSA, assessed by pQCT. Also CKD was associated with greater fat CSA compared to no CKD. Finally we observed an association of lower Clcr with a decline in knee-extension strength during long-term follow-up, but no associations with long-term changes in gait speed. The magnitude of these associations was similar to age and support the concept of decreased kidney function as a model of accelerated aging.

To our knowledge this is the first study to comprehensively assess associations of decreased kidney function measured by Clcr with the composition of an important muscle involved in ambulation in a large cohort of older adults. This relationship seemed non-linear with the greatest difference in muscle density and fat CSA observed among those with Clcr <60 ml/min/1.73m². After controlling for physical activity, only the association of Clcr with muscle density remained significant. This may suggest that CKD may be more strongly associated with muscle fat infiltration assessed by muscle density, and is not as precisely measured by using a single cut-point to distinguish muscle from fat on pQCT. We also observed that lower GFR_{cys} but not GFR_{cr-cys} was associated with a similar trend toward lower calf muscle density. Investigation of ambulatory muscle composition by pQCT as opposed to total lean body mass by dual-energy X-ray absorptiometry (DEXA) among older adults is clinically relevant linking reduced kidney function with muscle impairment associated with impaired physical performance and physical functioning. Reduced lower extremity muscle mass and density by pQCT among older adults enrolled in the Health ABC Study and InCHIANTI has been associated with incident mobility limitation²⁸ and all-cause mortality.^{13,14} Furthermore, unlike DEXA, which does not distinguish intermuscular fat from muscle, CT allows for assessment of muscle density as an indicator of intermuscular fat. The relevance of describing muscle density stems from the recently described association of intermuscular fat as a predictor of gait speed decline among older adults¹⁰ and the association of lower calf muscle density with increased mortality.¹² Unlike a prior study demonstrating an association of baseline creatinine with change in total lean body mass using DEXA,¹ we used 24 hour measured Clcr normalized to body surface area and further adjusted for height and weight to avoid potential confounding by body size. Even after finer adjustment for body size, the magnitude of the estimated association of each 10 ml/min/1.73m² lower Clcr with muscle CSA and muscle density was similar to a clinically meaningful difference in age of 1 year. This finer adjustment was also particularly important in investigating the association between kidney function and physical performance.²⁹

Our study confirms the findings from another study demonstrating an association of kidney function on maximal walking speed over 400 meters, but we did not observe a cross-sectional association with knee extension strength.⁴ The magnitude of association of Clcr with gait speed was surprisingly similar for usual 7-meter and fast 400-meter walks. Estimated associations of each 10 ml/min lower Clcr with gait speed were generally similar to those for each 0.6-year of aging. Among those with Clcr <45 ml/min/1.73m² there was a meaningful deficit in usual gait speed with 0.1 m/s decrement considered to be clinically significant.⁹ The magnitude of the association of CKD with decrements in gait speed in our study were similar to that of eGFR<60 ml/min/1.73m² with lower extremity performance in

a study of participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study³⁰ and a recent study investigation from the Framingham study.³¹ Furthermore there was suggestion of additive interaction between CKD and diabetes on usual walking speed. The lack of association between kidney function and knee extension strength at baseline may in part be attributable to differences in the characteristics of the study cohort and measurement technique compared to prior studies.⁴ Compared to the Health ABC Study, which recruited 70- to 79-year-old adults from two cities in the United States, our study population comprised participants residing in rural Tuscany with a broader range of age (65 years and older) and lower proportion of diabetes and excluded individuals with prevalent stroke or transient ischemic attack. The absence of African Americans known to have higher rates of frailty may have also contributed to this difference. Furthermore we used isometric handheld dynamometry compared to isokinetic dynamometry used in the Health ABC Study to arrive at knee strength. Although generally considered to have good reliability with a published interrater intraclass correlation coefficient for knee extension strength between 0.8–0.85,³² use of handheld dynamometry for evaluation of knee strength is effort dependent and prone to subject error. Having multiple measurements over time may reduce subject error and improve precision in estimates of knee extension strength explaining our findings of an association between lower Clcr with lower average knee extension strength over the course of follow-up.

To our knowledge this is the first study to evaluate associations of kidney function by Clcr with long-term changes in objectively measured physical performance measures over time. Although we did not detect associations with changes in gait speed throughout follow-up, we did observe associations of lower baseline Clcr and faster annual decline in knee extension strength. This finding may suggest that the declines in knee extension strength precede declines in mobility, as has been suggested by prior studies of older adult populations.^{11,17} No studies have assessed the impact of changes in knee strength on mobility decline, particularly among persons who have kidney disease. Compared to Clcr, GFR_{cys} did not demonstrate any meaningful association with longitudinal change in either physical performance or knee extension strength.

Multiple metabolic complications associated with CKD may accentuate processes associated with aging and further contribute to muscle atrophy and diminished physical performance leading to adverse health-related outcomes. Complications of CKD such as metabolic acidosis and inflammation may result in insulin resistance and protein degradation leading to muscle atrophy.^{33–36} Muscle atrophy has important implications in persons with reduced kidney function and may lead to increased morbidity and mortality. Sarcopenia (loss of muscle mass) and dynopenia (loss of muscle strength or power) is the final common pathway for mechanisms underlying frailty characterized by slow walking speed, diminished strength, physical inactivity, weight loss, and exhaustion.³⁷ Lower kidney function has been associated with increased risk of frailty,³⁸ a clinical syndrome associated with increased risk of premature death or dialysis among persons with CKD.⁶ Importantly, atrophy in ambulatory muscles among persons with CKD may lead to declines in walking speed recently shown to be strongly associated with premature death among persons with CKD.⁷

Strengths of the study include 24-hour urine collection for calculation of Clcr, pQCT measurements of muscle composition, standardized measurements of potential confounding variables, repeated longitudinal measurements of physical performance, and the representative community-based population. Our study also has several limitations. First, we were limited in our longitudinal analysis by low numbers of participants with severely decreased kidney function. Second, measurements of physical performance were performed every three years, which may have limited our ability to detect an association over time, particularly among those with more severe reductions in kidney function. Third, the measurement of Clcr at only one time-point with variable collection times may have resulted in non-differential misclassification attenuating and have also contributed to lack of association between baseline Clcr and slope of decline in gait speed. Finally, the purposeful selection of relatively high-functioning older adults who were ADL disability-free and stroke-free may have also attenuated our estimates of association.

In summary we demonstrate that among community dwelling older adults, diminished Clcr is associated with lower density and CSA of an important ambulatory muscles coinciding with diminished walking speed and longitudinal declines in knee extension strength. These findings warrant more research into understanding the determinants of lower extremity muscle atrophy among persons with diminished kidney function. Elucidation of these determinants will help facilitate targeted intervention trials focused on reducing muscle atrophy and assessing improvement in physical performance, morbidity as well as mortality in this high-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

CONSORT Diagram of InCHIANTI sample. Inadequate 24hr urine collection was defined as a 24hr creatinine excretion of $<10\text{mg/kg}$ lean body mass daily in men and $<8\text{mg/kg}$ lean body mass daily in women. Abbreviation: CT – peripheral quantitative computed tomography.

Figure 2.

Predicted adjusted mean of 7-meter usual walking speed and 400-meter walk by creatinine clearance. Black line is the lowess curve for the linear trend. Adjusted for age, sex, height, and weight, site, education, smoking, diabetes, and coronary artery disease. Plots exclude top 1% of gait speeds. Creatinine clearance not normalized to body surface area.

Figure 3.

Predicted adjusted mean of knee extension strength and usual walking speed by longitudinal exam age among different categories of creatinine clearance. Adjusted for sex, height, and weight. Plots exclude greatest 2.5% age and physical performance in each sample. Shaded areas indicate the interquartile range for exam age. Creatinine clearance values are not standardized to body surface area

Table 1

Baseline characteristics of study sample.

	Missing	Cler <45 (n=45)	Cler 45-59 (n=138)	Cler 60-89 (n=428)	Cler 90 (n=214)
Mean no. of visits		1.8 ±1.1	2.4 ±1.2	2.8 ±1.1	3 ±1.2
Demographics					
Age (y)	0	79 ±8	77 ±7	73 ±6	72 ±5
Female sex	0	30(67)	95(69)	236(55)	99(46)
Education	8				
None		18(40)	46(33)	111(26)	43(20)
Elementary		19(42)	70(51)	238(56)	128(60)
Secondary		4(9)	9(7)	29(7)	16(7)
High school		3(7)	10(7)	49(11)	24(11)
Lifestyle factors					
Smoking	0	7(16)	17(12)	56(13)	33(15)
Physical Activity	4				
Sedentary		17(38)	29(21)	50(12)	12(6)
Light-Moderate		26(58)	104(76)	349(82)	184(86)
Moderate-High		2(4)	4(3)	27(6)	17(8)
Animal protein consumption (g/d)	3	44(13)	47(15)	47(15)	51(15)
Examination results					
BMI	1	27.4 ±4.8	27 ±4	27.7 ±4.1	27.4 ±3.8
Systolic BP	11	155 ±20	154 ±22	150 ±20	153 ±20
Comorbidities					
Diabetes	0	4(9)	9(7)	59(14)	30(14)
CAD	0	5(11)	19(14)	50(12)	15(7)
COPD	0	8(18)	9(7)	45(11)	21(10)
Medications					
ACE inhibitor/ARB	0	12(27)	38(28)	89(21)	56(26)
β-blocker	0	3(7)	5(4)	13(3)	10(5)
Any antihypertensive	0	22(49)	62(45)	146(34)	94(44)

	Missing	Clcr <45 (n=45)	Clcr 45–59 (n=138)	Clcr 60–89 (n=428)	Clcr 90 (n=214)
Laboratory data					
Serum Creatinine (mg/dL)	0	1.1 ±0.4	1.0 ±0.2	0.9 ±0.2	0.8 ±0.2
Serum Cystatin C (mg/L)	87	1.3 ±0.6	1.1 ±0.2	1 ±0.2	0.9 ±0.2
Clcr (ml/min/1.73 m ²)	0	38 ±6	54 ±4	75 ±8	108 ±14
eGFR _{cr} (ml/min/1.73 m ²)*	0	59 ±14	65 ±11	72 ±11	80 ±11
eGFR _{cys} (ml/min/1.73 m ²)*	87	59 ±20	68 ±19	76 ±17	82 ±16
eGFR _{cr-cys} (ml/min/1.73 m ²)*	87	59 ±19	63 ±14	75 ±13	85 ±15
Hemoglobin (g/dL)	5	13.3 ±1.2	13.4 ±1.2	13.9 ±1.3	14 ±1.2
25-hydroxyvitamin D (nmol/L)	25	42 ±31	51 ±46	52 ±34	57 ±32
Albumin (g/dL)	2	4.2 ±0.3	4.2 ±0.3	4.2 ±0.3	4.3 ±0.2
Interleukin 6 (pg/mL)	1	4.9 ±13.2	2.2 ±2.3	1.8 ±1.9	1.6 ±1.7
Follow-up					
Baseline visit only		21(47)	50(36)	88(21)	32(15)
First visit		12(27)	28(20)	83(19)	37(18)
Second visit		4(9)	20(28)	93(22)	39(18)
Third visit		8(18)	32(23)	164(38)	106(50)

Note: Clcr expressed in mL/min/1.73 m². Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation. Conversion factor for serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; Clcr, creatinine clearance; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate

* Calculated with Chronic Kidney Disease Epidemiology Collaboration equation.

Table 2

Cross-sectional associations of Clcr and age with physical performance measures.

	7-m usual walk (m/s)				400-m walk (m/s)				Knee extension (kg)		
	No.	Mean $\pm$ SD	AMD (95% CI)	No.	Mean $\pm$ SD	AMD (95% CI)	No.	Mean $\pm$ SD	AMD (95% CI)	No.	Mean $\pm$ SD
Clcr 90 ml/min/1.73m ²	214	1.25 $\pm$ 0.24	Reference ^a	201	1.29 $\pm$ 0.21	Reference ^b	212	17 $\pm$ 5.8	Reference ^c	212	17 $\pm$ 5.8
Clcr 60–89 ml/min/1.73m ²	428	1.19 $\pm$ 0.25	–0.004 (–0.037, 0.030) ^a	389	1.24 $\pm$ 0.23	–0.002 (–0.041, 0.020) ^b	423	16.9 $\pm$ 6	0.37 (–0.32, 1.07) ^c	423	16.9 $\pm$ 6
Clcr 45–59 ml/min/1.73m ²	138	1.06 $\pm$ 0.28	–0.044 (–0.091, 0.004) ^a	113	1.14 $\pm$ 0.24	–0.040 (–0.084, 0.004) ^b	140	15.6 $\pm$ 6	0.50 (–0.40, 1.39) ^c	140	15.6 $\pm$ 6
Clcr <45 ml/min/1.73m ²	45	0.93 $\pm$ 0.28	–0.112 (–0.177, –0.047) ^a	32	1.05 $\pm$ 0.25	–0.101 (–0.169, –0.034) ^b	43	13 $\pm$ 5	–0.93 (–2.27, 0.41) ^c	43	13 $\pm$ 5
Per 10- ml/min/1.73m ² lower Clcr			–0.010 (–0.017, –0.004)			–0.008 (–0.014, –0.002)			–0.015 (–0.14, 0.11)		
Per 1-SD lower Clcr*			–0.023 (–0.038, –0.008)			–0.018 (–0.032, –0.005)			–0.033 (–0.31, 0.25)		
Per 1-y older age			–0.017 (–0.02, –0.015)			–0.017 (–0.02, –0.015)			–0.19 (–0.24, –0.14)		
Per 1-SD older age*			–0.112 (–0.129, –0.095)			–0.111 (–0.127, –0.09)			–1.25 (–1.57, –0.93)		

Note: Model adjusted for age, sex, height, weight, site, smoking, education, Diabetes, coronary artery disease, total daily animal protein consumption

^aP for trend =0.008^bP for trend = 0.007^cP for trend = 0.8* SDs of Clcr and age are 22 ml/min/1.73 m² and 6.5 years, respectively.

AMD, adjusted mean difference; CI, confidence interval; Clcr, creatinine clearance; SD, standard deviation

Table 3

Cross-sectional associations of Clcr with pQCT imaging measurements of calf muscle.

	Muscle CSA (mm ²)			Muscle Density (mg/cm ³)		Fat CSA (mm ²)	
	No.	Mean ±SD	AMD (95% CI)	Mean ±SD	AMD (95% CI)	Mean ±SD	AMD (95% CI)
Clcr 90 ml/min/1.73m ²	207	6478 ±1213	Reference ^a	71.7 ±3.3	Reference ^b	1731 ±997	Reference ^c
Clcr 60–89 ml/min/1.73m ²	410	6223 ±1255	-119 (-265, 27) ^a	71.3 ±3.4	-0.10 (-0.62, 0.42) ^b	1922 ±1178	90 (-27, 207) ^c
Clcr <60 ml/min/1.73m ²	179	5804 ±1048	-84 (-260, 93) ^a	70 ±3.5	-0.97 (-1.66, -0.28) ^b	2080 ±1242	177 (19, 335) ^c
Per 10-ml/min/1.73m ² lower Clcr			-28 (-55, -0.8)		-0.15 (-0.26, -0.04)		18(-4, 41)
Per 1-SD lower Clcr [*]			-64 (-126, -1.8)		-0.35 (-0.60, -0.10)		52 (-0.4, 104)
Per 1-y older age			-30 (-41, -20)		-0.15(-0.19, -0.11)		-4(-15, 5)
Per 1-SD older age [*]			-196 (-264, -129)		-0.98 (-1.25, -0.70)		-30 (-96, 35)

Note: Model adjusted for age, sex, height, weight, site, smoking, education, Diabetes, coronary artery disease, and total daily animal protein consumption.

AMD, adjusted mean difference; CI, confidence interval; Clcr, creatinine clearance; CSA, cross-sectional area; pQCT, peripheral quantitative computed tomography; SD, standard deviation

^{*} SDs of Clcr and age are 20 ml/min/1.73 m² and 6.5 years, respectively.

^a P=0.04. 18 individuals missing height measurements at baseline.

^b P=0.006. 18 individuals missing height measurements at baseline

^c P=0.1. 18 individuals missing height measurements at baseline.

Table 4

Adjusted difference in mean annual change in physical performance by category of Clcr.

	7-m usual walk (m/s per y)			400-m walk (m/s per y)			Knee Strength (kg per y)		
	No.	Unadjusted mean annual change (95% CI)	Adjusted difference in mean annual change (95% CI)	No.	Unadjusted mean annual change	Adjusted difference in mean annual change (95% CI)	No.	Unadjusted mean annual change	Adjusted differences in mean annual change (95% CI)
Clcr 90 ml/min/1.73 m ²	182	-0.013(-0.017, - 0.008)	Reference ^a	154	-0.017(-0.020, - 0.014)	Reference ^b	183	-0.073(-0.140, - 0.005)	Reference ^c
Clcr 60–89 ml/min/1.73 m ²	340	-0.014(-0.017, - 0.012)	-0.046(-0.117, 0.024) ^a	283	-0.017(-0.019 - 0.014)	-0.045(-0.106, 0.017) ^b	356	-0.119(-0.206, - 0.032)	-0.115(-0.191, - 0.039) ^c
Clcr <60 ml/min/1.73 m ²	112	-0.014(-0.024, - 0.005)	-0.003(-0.095, 0.088) ^a	88	-0.015(-0.023, - 0.007)	-0.019(-0.098, 0.061) ^b	132	-0.185(-0.291, - 0.078)	-0.154 (-0.248, - 0.061) ^c
Per 10-ml/min/1.73 m ² lower Clcr			-0.006(-0.020, 0.007)			-0.001(-0.013, 0.010)			-0.024 (-0.037, - 0.010)
Per 1-y older			-0.014(-0.016, - 0.012)			-0.016(-0.018, - 0.014)			-0.119(-0.151, - 0.088)

Note: Model adjusted for age, sex, height, weight, site, smoking, education, Diabetes, coronary artery disease, and total daily animal protein consumption

CI, confidence interval; Clcr, creatinine clearance

^aP = 0.4^bP = 0.8^cP = 0.001