AJKD
Original Investigation

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

Baback Roshanravan, MD, MS,[1] Kushang V. Patel, PhD, MPH,[2] Cassianne Robinson-Cohen, PhD,[1] Ian H. de Boer, MD, MS,[1] Ann M. O'Hare, MD,[3] Luigi Ferrucci, MD, PhD,[4] Jonathan Himmelfarb, MD,[1] and Bryan Kestenbaum, MD, MS[1]

Background: Chronic kidney disease 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.

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

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

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

Results: Mean age of participants was 74 ± 7 (SD) years, with 183 having Clcr < 60 mL/min/1.73 m^2. After adjustment, each 10–mL/min/1.73 m^2 decrement in Clcr was associated with 0.01 (95% CI, 0.004-0.017) m/s slower 7-m usual walking speed and 0.008 (95% CI, 0.002-0.014) m/s slower 400-m walking speed. Each 10–mL/min/1.73 m^2 decrement in Clcr was associated with 28 (95% CI, 0.8-55) mm^2 lower muscle area and 0.15 (95% CI, 0.04-0.26) mg/cm^3 lower muscle density. After adjustment, lower Clcr was associated with slower mean 7-m ($P = 0.005$) and 400-m ($P = 0.02$) walk and knee extension strength ($P = 0.001$) during the course of follow-up. During a mean follow-up of 7.1 ± 2.5 years, each 10–mL/min/1.73 m^2 lower baseline Clcr was associated with 0.024 (95% CI, 0.01-0.037) kg/y greater decline in knee strength.

Limitations: Single baseline measurement of Clcr and 3-year interval between follow-up visits may lead to nondifferential 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.

Am J Kidney Dis. 65(5):737-747.

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 physiologic 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 and in particular slower gait speed.[7] Among patients with CKD and community-dwelling older adults, lower physical performance is potently associated with all-cause mortality.[7,9]

Previous studies of community-dwelling older adults investigating the association of kidney function and skeletal muscle impairment generally are 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 level among more than

From the [1]Division of Nephrology, Department of Medicine, University of Washington Kidney Research Institute; [2]Department of Anesthesiology and Pain Medicine and [3]Veterans Affairs Puget Sound Healthcare System, University of Washington, Seattle, WA; and [4]Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD.

Received May 19, 2014. Accepted in revised form October 6, 2014. Originally published online December 23, 2014.

Address correspondence to Baback Roshanravan, MD, MS, Kidney Research Institute, University of Washington Nephrology Division; Box 359606, 325 9th Ave, Seattle, WA 98104. E-mail: broshanr@u.washington.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2014.10.016

3,000 older adults from the Health ABC (Health, Aging, and Body Composition) 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 computed tomography (CT) with gait speed decline,[10] incident mobility limitation,[11] and mortality among older adults,[12-14] no study has 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 CT (pQCT), and physical performance, assessed by standardized testing, among community-dwelling older Northern Italian adults 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 2 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 published previously.[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 at baseline and who completed an adequate 24-hour urine collection (Fig 1). For longitudinal analyses, we studied those who had one or more follow-up assessment.

Exposure Measurement

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

Serum creatinine was measured on a Roche/Hitachi analyzer (Roche Diagnostics, GmbH) and urine creatinine was measured on an ADVIA Centaur Immunoassay system (Bayer Diagnostics).

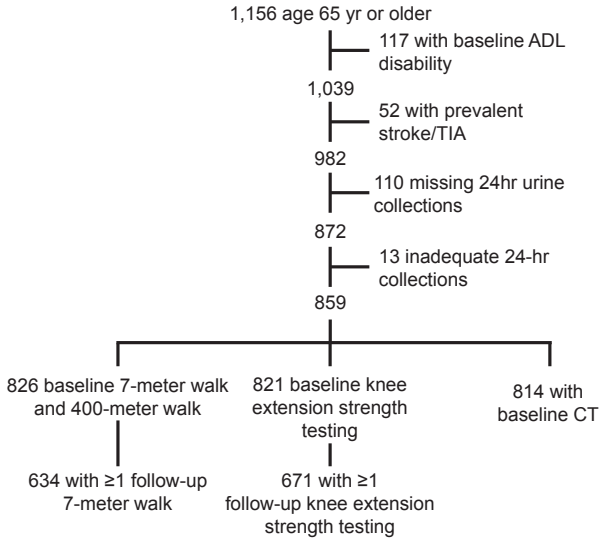

Figure 1. Flow diagram of the Invecchiare in Chianti (InCHIANTI) Study sample. Inadequate 24-hour urine collection was defined as 24-hour creatinine excretion < 10 mg/kg of lean body mass daily in men and <8 mg/kg of lean body mass daily in women. Abbreviations: ADL, activity of daily living; CT, peripheral quantitative computed tomography; TIA, transient ischemic attack.

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 of 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, with the Dade Behring Nephelometer II System and using a particle-enhanced immunonephelometric assay (N Latex Cystatin C kit; Dade Behring Inc).

Physical Performance Outcome Measures

Gait speed and knee extension strength were assessed at each follow-up. For the 7-m 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 2 photocells connected to a recording chronometer. The faster of 2 trials was used in the analysis. For the 400-m walk, participants were asked to walk as fast as they could throughout the test; only 1 timed 400-m 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 2 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) 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] Muscle density (in milligrams per cubic centimeter), muscle cross-sectional area (CSA; in millimeters squared), and fat CSA (in millimeters squared) were ascertained using BonAlyse software, version 3.1 (BonAlyse Ltd). Density thresholds of 15 and 180 mg/mm^3 were