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Sarcopenia, Obesity, and Mortality in US Adults With and Without Chronic Kidney Disease

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Introduction: In predialysis chronic kidney disease (CKD), the association of muscle mass with mortality is poorly defined, and no study has examined outcomes related to the co-occurrence of low muscle mass and excess adiposity (sarcopenic obesity).

Methods: We examined abnormalities of muscle and fat mass in adult participants of the National Health and Nutrition Examination Survey 1999–2004. We determined whether associations of body composition with all-cause mortality differed between participants with CKD compared to those without.

Results: CKD modified the association of body composition with mortality ($P = 0.01$ for interaction). In participants without CKD, both sarcopenia and sarcopenic obesity were independently associated with increased mortality compared with normal body composition (hazard ratio [HR] = 1.44, 95% confidence interval [CI] = 1.07–1.93, and HR = 1.64, 95% CI = 1.26–2.13, respectively). These associations were not present among participants with CKD. Conversely, obese persons had the lowest adjusted risk of death, with an increased risk among those with sarcopenia (HR = 1.43, 95% CI = 1.05–1.95) but not sarcopenic-obesity ($P = 0.003$ for interaction by CKD status; HR = 1.21, 95% CI = 0.89–1.65), compared with obesity.

Discussion: Sarcopenia associates with increased mortality regardless of estimated glomerular filtration rate, but excess adiposity modifies this association among persons with CKD. Future studies of prognosis and weight loss and exercise interventions in CKD patients should consider muscle mass and adiposity together rather than in isolation.

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Muscle wasting is common among patients with end-stage renal disease (ESRD) who are receiving dialysis, and associates with increased morbidity and mortality.[1–3] In the earlier stages of chronic kidney disease (CKD), the association of muscle mass with outcomes is less well defined. There are few data on mortality associated with sarcopenia, or low muscle mass, although it is common among individuals with advanced predialysis kidney disease.[4] Studies that have examined urinary creatinine excretion and total lean body mass have yielded inconsistent results.[5–7]

Accurate prognostication may require simultaneously examining the muscle and fat compartments. Body mass index (BMI) levels in the overweight and obese range are associated with the lowest mortality risk in CKD patients.[8] However, persons with CKD who have excess adiposity but are also sarcopenic—a not uncommon finding—are very unlikely to be classified as obese by BMI.[9,10] In hemodialysis patients, this phenotype, called sarcopenic obesity, is associated with greater inflammation and increased mortality.[11] The prognostic significance of sarcopenic obesity in persons with CKD is not known.[12]

We hypothesized that sarcopenia and sarcopenic-obesity are associated with increased all-cause mortality among individuals with CKD who are not on dialysis. Our definition of CKD was restricted to persons with estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 because the pathophysiologic link between CKD and low muscle mass is greatest in this subgroup, and our prior work demonstrated that the prevalence of sarcopenia increased below this threshold.[10] We tested this

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hypothesis using nationally representative data from the National Health and Nutrition Examination Survey (NHANES), including dual-energy x-ray absorptiometry (DEXA)–derived muscle and fat mass to classify participants into 4 mutually exclusive body composition categories: nonsarcopenic nonobese, obese, sarcopenic, and sarcopenic-obese.[10] Our objective was to examine this question among persons with CKD and to determine whether associations differed from those in individuals without CKD in the same nationally representative dataset. We hypothesized that associations of both sarcopenia and sarcopenic obesity with death would be stronger in persons with CKD than in those without, as CKD-induced muscle wasting is likely a poor prognostic factor.

When we initially conducted our analyses, linked mortality data were available with follow-up through December 31, 2006. Subsequently, we repeated our analyses when updated data became available with mortality status ascertained through December 31, 2011. We considered our findings from analyses conducted using the 2011 dataset to be our primary results, given the greater statistical power and longer follow-up time. However, we also compared the results obtained using each of these datasets to examine the impact of the duration of follow-up time on our findings.

MATERIALS AND METHODS

Study Population

NHANES 1999–2004 was a program of studies designed to assess the health and nutritional status of noninstitutionalized civilians in the United States.[13] The NHANES protocol was approved by the National Center for Health Statistics ethics review board, and written informed consent was obtained from all participants. We examined adults ≥20 years old (n = 15,332) with available body composition data (n = 12,732), excluding participants with eGFR <15 ml/min/1.73 m^2 (n = 34) or missing data on covariates of interest (n = 1082). The resultant cohort had 11,616 participants.

Data Collection

Information on race/ethnicity, education, smoking status, and comorbidities was based on self-report. Activity level was calculated as metabolic equivalents (MET-min/wk) based on questions regarding the frequency and duration of activities such as walking, cycling, home or yard work, and moderate or vigorous leisure activity performed within the past 30 days.[14] Participants with diabetes mellitus were defined as those who had a physician diagnosis while not pregnant, were using insulin or oral hypoglycemic medications, or had a glycohemoglobin level of ≥6.5%. Hypertension was defined by systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, history of physician diagnosis, and/or antihypertensive medication use.[15] Cardiovascular disease was defined by self-report of a physician diagnosis of congestive heart failure, coronary heart disease, angina, myocardial infarction, or stroke.

Serum chemistries were measured using the Hitachi 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN) in 1999 to 2001 and the Beckman Synchron LX20 (Beckman Coulter Inc., Brea, CA) in 2002 to 2004. C-reactive protein (CRP) was quantified by latex-enhanced nephelometry. Serum albumin was measured by the bromocresol purple method. A modified kinetic Jaffe reaction was used to measure serum creatinine, and the values from 1999 to 2000 were calibrated to the Cleveland Clinic laboratory standard by multiplying by 1.013 and adding 0.147. Values from 2001 to 2004 did not need correction. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[16] CKD was defined as an eGFR of <60 ml/min/1.73 m^2.

Body Composition Data

Missing and invalid DEXA data were accounted for through multiple imputation by the National Center for Health Statistics.[17] Details of the DEXA quality control, data validation, and multiple imputation procedures are available elsewhere.[17–20] DEXA data for at least 1 body region were imputed in 2472 participants (21.3%). Muscle mass was quantified using the appendicular skeletal muscle mass index (ASMI; total lean mass of the 4 extremities divided by the square of the height).[21] Sarcopenia was defined as ASMI of <5.45 kg/m^2 in women and <7.26 kg/m^2 in men.[21,22] These cutoffs correspond to 2 SDs below the sex-specific means for healthy young adults 18 to 40 years of age and are recommended by the consensus guidelines of the European Working Group on Sarcopenia in Older People.[23,24] We examined ASMI rather total lean mass based on this recommendation, and also because appendicular lean mass is not confounded by changes in visceral lean mass due to chronic disease and is likely more relevant for functional status. Obesity was determined as percentage of total body fat (TBF) greater than 42.1% for women and 29.6% for men, corresponding to the sex-specific 60th percentile for the study sample[22] and to the current World Health Organization guidelines for BMI-defined obesity.[25,26]

Outcome Variables

All-cause mortality was determined primarily through probabilistic record matching with the National Death Index and was available using public-use linked