ORIGINAL ARTICLE

Sarcopenia, Relative Sarcopenia and Excess Adiposity in Chronic Kidney Disease

Susan L Ziolkowski[1], Jin Long[1], Joshua F Baker, MD[2], Julia F Simard[3], Glenn M Chertow[1], Mary B Leonard[1,4]

1 Department of Medicine, Stanford University School of Medicine, Stanford, CA, **2** Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, **3** Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, **4** Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

Abstract

Aims Conventional definitions of sarcopenia based on lean mass fail to capture low lean mass relative to fat mass, i.e., relative sarcopenia. Unlike percent body fat (%BF) and Quételet's (body mass) index (BMI, kg/m^2), definitions of obesity based on fat mass index (FMI, kg/m^2) are not confounded by lean mass. The objective is to determine the prevalence of sarcopenia, relative sarcopenia, and obesity in CKD, and determine if CKD is associated with relative sarcopenia and obesity, independent of demographics and comorbidities.

Methods and Results DXA-derived appendicular lean mass index (ALMI, kg/m^2) and FMI were assessed in 13,980 NHANES participants. ALMI, FMI, and ALMI relative to FMI (ALMI $_{FMI}$) were expressed as sex- and race/ethnicity-specific standard deviation scores compared with young adults (T-scores) and by age (Z-scores). Sarcopenia was defined as ALMI T-score < -2, relative sarcopenia as ALMI $_{FMI}$ T-score < -2, and low lean mass relative to fat mass for age as ALMI $_{FMI}$ Z-score < -1. Obesity was defined using conventional BMI and %BF cutpoints and as sex- and race/ethnicity-specific FMI cutpoints. Glomerular filtration rate (GFR) was estimated using creatinine- (eGFR$_{Cr}$) and cystatin C- (eGFR$_{Cys}$). The prevalence of relative sarcopenia was higher than the prevalence of sarcopenia, especially in CKD stages 3b and 4 using eGFR$_{Cr}$; these CKD stages were associated with the highest FMI. CKD stage was independently associated with low ALMI $_{FMI}$ for age using eGFR$_{Cys}$. BMI underestimated and %BF overestimated the prevalence of obesity compared with FMI. CKD was not independently associated with obesity by FMI.

Conclusions In CKD, conventional definitions of sarcopenia underestimate muscle deficits and %BF overestimates the prevalence of obesity. CKD is independently associated with relative sarcopenia, but not excess adiposity.

Address for correspondence Susan Ziolkowski, 777 Welch Road, Suite DE, Palo Alto, CA 94304, (650) 725-4738, E-mail: sziolkow@stanford.edu

Keywords: Relative sarcopenia, Sarcopenia, Obesity, Chronic kidney disease, Body mass index, Percent body fat

Received 28 November 2017 **Accepted** 18 December 2017

Introduction

Advanced chronic kidney disease (CKD) is associated with multiple risk factors for low muscle mass, including impaired protein synthesis, accelerated protein catabolism, metabolic acidosis, defects in insulin-like growth factor 1 (IGF-1) signaling, abnormal vitamin D metabolism, and inflammation.[1] Sarcopenia and poor physical function are associated with poorer health-related quality of life and higher morbidity and mortality in persons with end-stage renal disease (ESRD);[2-4] however, the prevalence of sarcopenia in adults with non-dialysis requiring CKD has not been established.

We recently developed a novel approach to adjust lean mass for fat mass (i.e., relative sarcopenia) using dual energy X-ray absorptiometry (DXA)-derived, sex- and race/ethnicity- specific cutpoints in 14,850 National Health and Nutrition Examination Survey (NHANES) recipients.[5] Subsequent studies demonstrated that measures of relative sarcopenia improved prediction of physical performance and incident disability compared with conventional measures of sarcopenia alone.[6, 7]

The prevalence of sarcopenia, relative sarcopenia and excess adiposity using sex- and race/ethnicity-specific cutpoints have not been determined in CKD, and are the focus of this study. We hypothesized that lower eGFR is associated with excess adiposity, sarcopenia, and relative sarcopenia independent of the residual effects of age, sex, and race, as well as comorbidities.

Materials and Methods

Study Population

We used NHANES data from 1999-2006, as these years included DXA body composition measures. NHANES was designed to represent the non-institutionalized, U.S. civilian population using a complex, multistage probability sampling method including oversampling of Non-Hispanic Blacks and Hispanics to produce reliable statistics. This study included 13,980 NHANES participants ≥ 20 years who completed the examination, had body composition data (including results generated by multiple imputation as described below), and had serum creatinine or cystatin C measurements. A total of 1,073 individuals had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 based on the creatinine-based CKD-EPI equation.[8] Cystatin C concentrations were available in a subset of 3,754 (26.9%) participants.

Data Collection

NHANES includes self-reported demographic and socioeconomic data, anthropometric measures, and serum measures of creatinine, cystatin C, albumin, 25-hydroxy vitamin D and bicarbonate concentrations. Methods for standardization and calibration of laboratory assays and DXA results are well-established.[9] Detailed information on physical activity was obtained during the home interview. Each leisure time physical activity was given a Metabolic Equivalent of Task (MET) score according to the Compendium of Physical Activities [10] and participants were categorized as not meeting the minimum goal (< 450 MET/min/week), meeting the minimum goal (450 to < 750 MET/min/week) and exceeding the recommended goal (>750 MET/min/week).

Diabetes was self-reported by participants who were asked if they were ever told by a doctor that they have “diabetes or borderline diabetes” while not pregnant, the current use of insulin or oral hypoglycemic medications, or a glycohemoglobin >6.5%. Cardiovascular disease was defined by self-report of a physician diagnosis of congestive heart failure, coronary heart disease, angina, myocardial infarction, or stroke. Cancer was defined as self-reported by the question “ever told you had cancer or malignancy.” Smoking status was defined by self-report of smoking >100 cigarettes/ lifetime. Liver disease was defined by an affirmative response to “ Have you ever been told that you had any liver condition?”

eGFR was calculated using the appropriate cystatin C or creatinine age-,sex- and race-specific Chronic Kidney Disease Epidemiology Collaboration calculations.[8, 11] Creatinine values from 1999 to 2000 were calibrated to the Cleveland Clinic laboratory standard by multiplying by 1.013 and then adding 0.147.[9] Albuminuria was defined as urine albumin: creatinine ratio ≥ 25 mg/g for women and ≥ 17 mg/g for men.[12]

CKD stages were defined as follows: Stage 1+ 2 as eGFR ≥ 60 ml/min/1.73m^2 without albuminuria, stage 1A+2A as eGFR ≥ 60 ml/min/1.73m^2 with albuminuria, stage 3a = 45-59 ml/min/1.73m^2, stage 3b = 30-44 ml/min/1.73m^2, stage 4 = 15-29 ml/min/1.73m^2, and stage 5 as <15 ml/min/1.73m^2.

Whole body DXA measures of fat mass and fat free mass have been validated and correlate highly with criterion methods [13, 14] and were acquired using Hologic QDR 4500A fan-beam densitometers (Hologic, Inc, Bedford, MA). DXA exclusion criteria included pregnancy, weight >300 pounds (136 kg, due to the weight limit of the scanner), height >77 inches (195 cm), recent nuclear medicine scan or exposure to radioactive contrast. Whole body quality control phantoms were scanned at least weekly. Each participant and phantom scan was reviewed and analyzed by the NHANES quality control center at University of California San Francisco using standard radiologic techniques and study-specific protocols. DXA scans were not obtained in patients with non-removable objects (prostheses, pacemakers, implants, and casts) and some scans were excluded due to technical errors such as suboptimal participant positioning.

To account for potential biases of non-random missing data, multiple imputation was performed by the National Center for Health Statistics for all participants with invalid or missing data (with the exception of pregnant women) using demographic, socioeconomic, and geographic variables, body measurements, health indicators, dietary and medication use variables, and blood test results.[9, 15] The lean and fat mass for the total body and regions were adjusted using the standard NHANES calibration protocol.[16]

Generation of ALMI, FMI, and ALMI $_{FMI}$ Standard Deviation Scores and Definitions of Outcomes

Sex- and race/ethnicity-specific curves for ALMI and FMI relative to age were previously developed using NHANES data with the LMS method.[17] This method addresses skew, non-linearity, and heteroscedasticity,[18, 19] and is the standard method for expressing body composition results as a standard deviation score. The LMS method normalizes the data using a power transformation; the optimal power to obtain normality is calculated for a series of age groups and the trend is summarized by a smooth line (L). Trends in the mean (M) and coefficient of variation (S) are similarly smoothed. These curves were

used to convert the ALMI and FMI measures to sex- and race/ethnicity-specific Z-scores relative to age, and to T-scores based on LMS values in a 25 year old.

Estimating equations previously developed with NHANES data were applied to adjust the ALMI Z-Scores and T-Scores for FMI Z- and T-scores, respectively, in order to create ALMI $_{FMI}$ Z-Scores and T-Scores.[5] These ALMI $_{FMI}$ Z-Scores scores incorporate the complex and significant interactions among age, sex and race/ethnicity, and conceptually represent the number of standard deviations the ALMI is above or below the mean for a reference group of the same age, sex, race/ethnicity, and FMI Z-Score. The ALMI $_{FMI}$ T-Scores conceptually represent the number of standard deviations the ALMI is above or below the mean for individuals 25 years of age of the same sex, race/ethnicity, and FMI T-score.

Sarcopenia was defined as an ALMI T-score < -2.0 (consistent with convention [20, 21]) and relative sarcopenia as an ALMI $_{FMI}$ T-score < -2.0. Low lean mass relative to fat mass for age (low ALMI $_{FMI}$ for age) was defined as ALMI $_{FMI}$ Z-score of < -1.0. Excess adiposity (obese $_{FMI}$) was defined based on sex- and race/ethnicity-specific FMI cutpoint values developed by Kelly et al. in order to generate a prevalence of obesity that was the same as observed using a BMI cut point of 30 kg/m^2 (obese $_{BMI}$) in 25 year old participants in NHANES.[17] Obese $_{BMI}$ was defined as BMI >30 kg/m^2 and obese $_{\%BF}$ was defined as %BF > 42.1% in women and > 29.6% in men.[22, 23]

Statistics

We performed all the analyses in this study separately with the CKD definitions by both eGFR$_{Cr}$ and eGFR$_{Cys}$. Descriptive statistics were used to characterize the study population, with categorical characteristics summarized as counts/percentages and continuous characteristics summarized as mean with standard error. The overall prevalence of sarcopenia (ALMI T-score <2.0) and relative sarcopenia (ALMI $_{FMI}$ T-score <2.0) was assessed within each eGFR category and tested for linear trends across categories. Univariate logistic regression models were used to examine the association of low ALMI $_{FMI}$ for age (ALMI $_{FMI}$ Z-score <1.0) and ALMI Z-score <-1.0 with pre-specified covariates of interest. Serum albumin was not included in the final models as it may lie on the causal pathway. 25-hydroxy vitamin D was excluded from the final model due as it was only collected from 2001-2006 and available in 10,550 participants. All other variables showing statistically significant associations with the dependent body composition variables were included in multivariable logistic regression models including age, race/ethnicity, smoking, physical activity, diabetes, cancer, cardiovascular disease and liver disease. Sensitivity analyses were done restricting analyses to study participants with both creatinine and cystatin C concentrations.

The prevalence of excess adiposity using sex- and race/ethnicity specific FMI cutpoint values (obese $_{FMI}$) was compared with the prevalence based on a BMI (obese $_{BMI}$) and %BF (obese $_{\%BF}$)[22, 23] and linear trends across eGFR categories were tested. We used multivariable logistic regression models to examine the association of eGFR with obese $_{FMI}$, adjusted for covariates of interest with significant univariate associations, including age, race/ethnicity, smoking, physical activity, diabetes, cancer, cardiovascular disease and liver disease.

We considered 2-tailed p-values <0.05 statistically significant. We did not adjust for multiple comparisons given the multiple body composition outcomes are highly correlated. We performed all analyses using survey procedures with SAS version 9.4 for Unix (SAS Institute, Cary, North Carolina) to account for the complex sampling design of NHANES and appropriately weighted participants in statistical models.

Results

Participant characteristics

The NHANES participant characteristics are summarized in Table 1, according to eGFR$_{Cr}$ category. Participants with eGFR <60 ml/min/1.73m^2 were more likely to be older, report lower physical activity, have diabetes, cancer, cardiovascular disease and liver disease. Serum albumin was lower, and serum CRP higher with more advanced CKD stage. A higher percentage of participants with eGFR <30 ml/min/1.73m^2 were Non-Hispanic Black race/ethnicity and smokers.

Prevalence of Sarcopenia and Relative Sarcopenia

The prevalence of sarcopenia and relative sarcopenia according to eGFR$_{Cr}$ category is shown in Table 2 and Figure 1. The prevalence of sarcopenia by the conventional ALMI T-score < -2.0 definition was higher with lower eGFR$_{Cr}$ (p for trend <0.01), while the prevalence of relative sarcopenia was progressively higher with CKD stage with the exception of stage 5 (p for trend <0.01). Mean FMI T-scores were higher with more advanced CKD stages through stage 4 (p for trend <0.01), accounting for the progressively higher prevalence of relative sarcopenia, compared with sarcopenia. For example, the mean FMI T-score was 0.90 among those with stage 4 CKD and the prevalence of relative sarcopenia was 6-fold greater than the prevalence of sarcopenia. In contrast, the FMI T-score

was lowest in stage 5 CKD and this resulted in comparable prevalence of sarcopenia and relative sarcopenia.

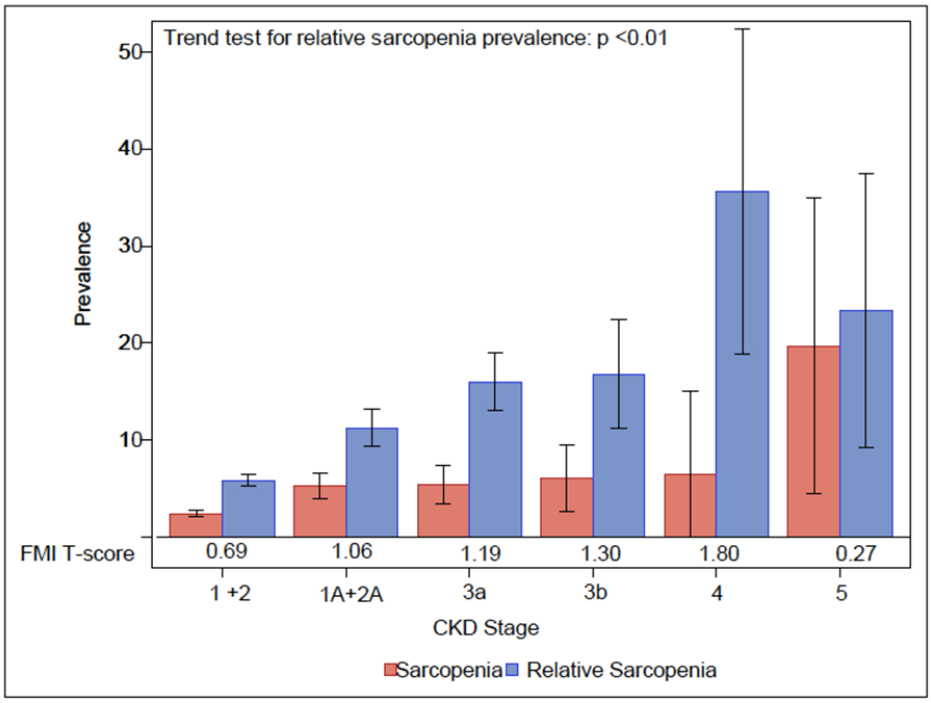
Table 1 Participant characteristics by Creatinine eGFR in 13,980 participants of the National Health and Nutrition Examination Survey 1999–2006

	Estimated GFR (ml/min/1.73m^2) by CKD-EPI					
	≥60	≥60 + albuminuria	45 – 59	30 – 44	15 – 29	< 15
CKD Stage	1+2	1A+2A	3a	3b	4	5
N (creatinine)	11017	1779	741	225	63	44
Demographics and Socioeconomics						
Age, median (IQR)	44.6 (32.5,58.6)	56.4 (40.8,67.9)	73.8 (65.8, 80.3)	75.0 (67.6, 80.6)	73.3 (65.8, 79.9)	62.2 (51.1, 69.4)
Women	5446 (50.1%)	817 (47.4%)	399 (58.9%)	112 (62.1%)	29 (44.9%)	20 (52.1%)
Race/ethnicity						
Non-Hispanic White	5849 (80.1%)	787 (73.6%)	531 (89.6%)	158 (88.9%)	31 (74.1%)	12 (56.7%)
Non-Hispanic Black	2386 (11.4%)	447 (15.6%)	133 (8.5%)	42 (9.5%)	19 (20.4%)	24 (38.9%)
Mexican American	2782 (8.6%)	545 (10.8%)	77 (1.9%)	25 (1.6%)	13 (5.5%)	8 (4.4%)
Lifestyle Factors						
Physical Activity						
<450 MET/min/week	7634 (66.0%)	1385 (74.2%)	564 (73.4%)	191 (85.4%)	55 (92.2%)	35 (85.6%)
450 - 750 MET/min/week	1378 (14.5%)	145 (10.4%)	71 (10.3%)	17 (8.7%)	4 (4.1%)	6 (9.4%)
>750 MET/min/week	1960 (19.5%)	243 (15.5%)	104 (16.2%)	16 (5.9%)	4 (3.7%)	3 (5.0%)
Smoker	5350 (50.2%)	983 (57.2%)	388 (48.8%)	117 (50.4%)	39 (70.5%)	25 (71.3%)
Comorbidities						
Diabetes	902 (5.8%)	553 (24.2%)	198 (22.2%)	73 (27.9%)	42 (61.0%)	18 (29.6%)
Cancer	711 (6.7%)	151 (9.0%)	151 (20.5%)	52 (23.9%)	9 (22.7%)	5 (11.8%)
Cardiovascular disease	722 (5.4%)	289 (13.1%)	234 (28.0%)	104 (46.8%)	37 (66.1%)	23 (54.1%)
Liver condition	191 (1.3%)	86 (4.0%)	80 (9.4%)	36 (15.2%)	10 (18.5%)	7 (13.6%)
Laboratory Studies						
Serum Albumin (g/dL)	4.3 ± 0.01	4.3 ± 0.01	4.2 ± 0.02	4.1 ± 0.04	4.0 ± 0.06	3.9 ± 0.10
Serum CRP (mg/dL)	0.4 ± 0.01	0.6 ± 0.04	0.5 ± 0.03	0.8 ± 0.10	0.8 ± 0.20	1.3 ± 0.25
Bicarbonate (mEq/L)	24.3 ± 0.09	24.2 ± 0.12	24.5 ± 0.15	24.1 ± 0.27	22.7 ± 0.72	22.9 ± 1.15
Vitamin D (nmol/L, n = 10,550)	63.5 ± 0.82	57.7 ± 1.06	63.9 ± 1.43	59.4 ± 1.99	54.6 ± 2.45	48.7 ± 4.76
Vitamin D deficiency	5802 (44.3%)	1113 (53.9%)	365 (42.8%)	119 (49.6%)	40 (49.3%)	36 (76.3%)
Data are presented as n (%) or mean ± SD unless otherwise specified.						

Table 2 Participant body composition characteristics by Creatinine eGFR in 13,980 participants of the National Health and Nutrition Examination Survey 1999–2006

	Estimated GFR (ml/min/1.73m^2) by CKD-EPI					
	≥60	≥60 + albuminuria	45 – 59	30 – 44	15 – 29	< 15
CKD Stage	1+2	1A+2A	3a	3b	4	5
Measures of Obesity						
BMI, kg/m^2						
Male	27.91±0.10	30.28±0.33	28.70±0.41	29.49±0.60	29.16±0.97	27.93±1.62
Female	28.30±0.16	29.18±0.46	29.38±0.46	29.33±0.77	31.79±2.01	25.62±1.39
FMI, kg/m^2						
Male	8.04±0.06	9.51±0.08	8.98±0.21	9.50±0.33	9.86±0.52	8.68±0.91
Female	11.71±0.11	12.25±0.30	12.76±0.29	12.90±0.49	14.37±1.14	9.61±0.90
FMI T-score	0.34 ± 0.02	0.53 ± 0.04	0.63 ± 0.03	0.69 ± 0.06	0.87 ± 0.10	0.17 ± 0.19
FMI Z-score	-0.02 ± 0.02	0.14 ± 0.04	0.08 ± 0.04	0.22 ± 0.09	0.47 ± 0.16	-0.35 ± 0.22
%Body Fat						
Male	27.90±0.11	30.17±0.29	30.70±0.34	31.38±0.57	33.19±0.87	30.27±1.71
Female	40.00±0.16	40.16±0.41	42.48±0.33	42.91±0.68	44.38±0.99	36.25±1.58
Prevalence of Obesity						
Obese $_{BMI}$	3574 (31.1%)	751 (42.5%)	258 (35.6%)	86 (40.5%)	30 (42.7%)	9 (20.5%)
Obese $_{FMI}$	4014 (34.1%)	839 (44.8%)	326 (43.4%)	112 (49.7%)	36 (55.2%)	13 (33.8%)
Obese $_{\%BF}$	4624 (40.1%)	907 (48.9%)	429 (57.3%)	133 (59.7%)	45 (71.7%)	12 (35.9%)
Measures of Lean Mass						
ALMI, kg/m^2						
Male	8.62± 0.02	8.83±0.08	8.27±0.11	8.36±0.14	7.99±0.30	7.75±0.36
Female	6.78±0.03	6.88±0.08	6.64±0.09	6.57±0.16	6.81±0.39	6.36±0.25
ALMI T-score	-0.03 ± 0.02	-0.02 ± 0.05	-0.20 ± 0.05	-0.21 ± 0.09	-0.42 ± 0.22	-0.84 ± 0.19
ALMI Z-Score	-0.01 ± 0.02	0.10 ± 0.05	0.15 ± 0.05	0.23 ± 0.09	0.02 ± 0.22	-0.65 ± 0.16
ALMI$_{FMI}$ T-score	-0.30 ±0.02	-0.52 ±0.04	-0.86 ±0.05	-0.98 ± 0.10	-1.45 ± 0.21	-1.21 ± 0.22
ALMI$_{FMI}$ Z-score	0.01 ± 0.02	-0.03 ± 0.04	0.15 ± 0.05	0.10 ± 0.08	-0.43 ± 0.19	-0.51 ± 0.18
Prevalences of Sarcopenia, Relative Sarcopenia and Low Lean Mass Relative to Fat Mass for Age						
Sarcopenia	306 (2.4%)	102 (5.3%)	41 (5.4%)	19 (6.0%)	3 (6.4%)	7 (19.7%)
Relative Sacropenia	757 (5.8%)	225 (11.2%)	133 (16.0%)	47 (16.8%)	18 (35.6%)	10 (23.3%)
Low Lean for Age	1538 (13.6%)	285 (16.9%)	50 (13.9%)	13 (7.1%)	7 (23.5%)	7 (28.6%)
Data are presented as n (%) or mean ± SD.						

Figure 1 Prevalence of sarcopenia (ALMI T-score < -2.0), relative sarcopenia (ALMI $_{FMI}$ T-score < -2.0) and mean FMI T-score by CKD stage in 13,980 participants of the National Health and Nutrition Examination Survey 1999–2006



Association of CKD with Low ALMI and Low ALMI $_{FMI}$, Independent of Age

The association of low ALMI $_{FMI}$ for age with CKD is shown in Table 3**,** comparing results based on $eGFR_{Cr}$ and $eGFR_{Cys}$. The $eGFR_{Cys}$-based models showed a progressively higher odds of low ALMI $_{FMI}$ for age with more advanced CKD stage (p for trend = 0.02). $eGFR_{Cr}$ models demonstrated higher odds of low ALMI $_{FMI}$ for age in persons with stage 4 and 5 CKD; although the trend was not statistically significant. Smoking (OR 1.14, 95% CI 1.01, 1.29, p=0.04) and physical inactivity defined as < 450 MET/min/week (OR 1.95, 95% CI 1.60, 2.39, p < 0.001 compared with >750 MET/min/week) remained significantly associated with low ALMI $_{FMI}$ for age in the multivariable model. The association between ALMI Z-score <-1.0 with CKD using either $eGFR_{Cys}$ or $eGFR_{Cr}$ was not statistically significant.

Among the subset of participants with 25-hydroxy vitamin D concentrations, adjustment for vitamin D deficiency did not alter the associations of CKD with low ALMI $_{FMI}$ for age (data not shown).

Prevalence of Obesity and Comparison of Definitions

Table 2 and Figure 2 show the prevalence of obesity by $eGFR_{Cr}$ category defined by FMI (obese $_{FMI}$), %BF (obese $_{\%BF}$) and BMI (obese $_{BMI}$). A higher prevalence of obesity using all three definitions was evident in all CKD stages except stage 5, compared with normal or near normal kidney function (eGFR ≥60 ml/min/1.73m^2 without albuminuria). A higher prevalence of obesity was observed for definitions using DXA measures of fat mass, compared with obese $_{BMI}$. The highest prevalence of obesity was observed for obese $_{\%BF}$. Participants with stage 5 CKD had the lowest prevalence of obesity by all three measures.

Association of CKD with Obese $_{FMI}$

Table 4 summarizes the multivariable logistic regression models for the association of CKD with obese $_{FMI.}$ Lower eGFR was not associated with higher odds of obese $_{FMI}$ independent of covariates in $eGFR_{Cr}$ models (p for trend = 0.18) or $eGFR_{Cys}$ models (p for trend= 0.06).

Figure 2 Prevalence of obesity defined by BMI, %BF, and FMI by CKD stage in 13,980 participants of the National Health and Nutrition Examination Survey 1999–2006

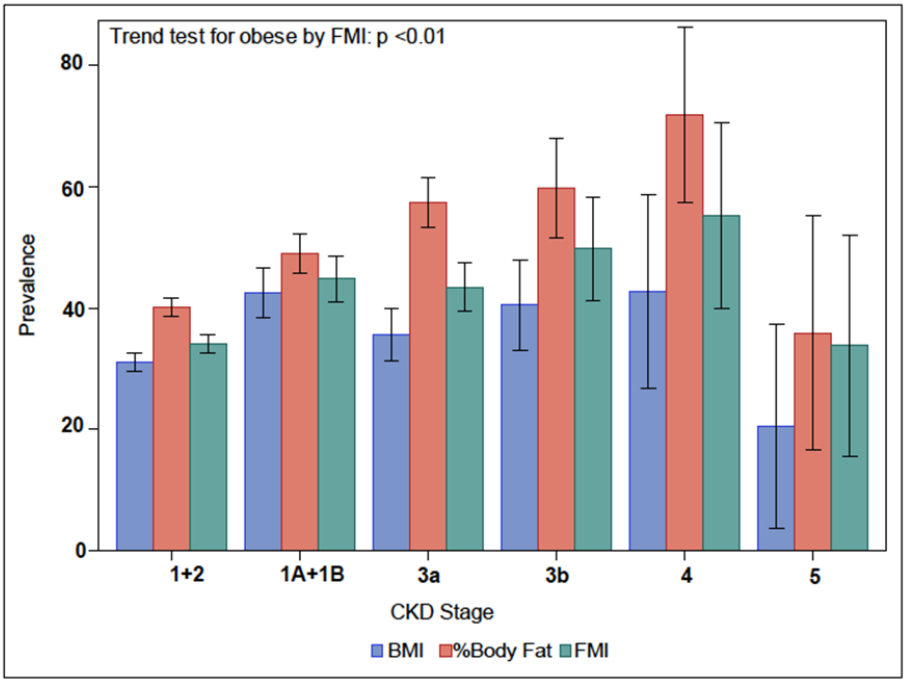


Table 3 Odds ratios for low lean mass relative to fat mass for age ($ALMI_{FMI}$ Z-score < - 1.0) by CKD stage compared to CKD stage 1+2 from multivariate logistic regression adjusted for smoking status, physical activity and cardiovascular disease

CKD Stage	eGFR Creatinine	eGFR Cystatin C
	OR (95% CI) p-value	OR (95% CI) p-value
1A+2A	1.21 (0.99-1.48) P =0.62	1.39 (1.03-1.89) P=0.60
3a	0.94 (0.71-1.24) P = 0.08	1.30 (0.92-1.85) P=0.26
3b	0.79 (0.49-1.28) P = 0.02*	1.53(0.88-2.64) P=0.94
4	2.12 (0.97-4.64) P=0.13	2.06 (0.72-5.89) P=0.52
5	2.42 (1.02-5.71) P=0.08	2.46 (0.81-7.48) P=0.30
	P for trend= 0.26	**P for trend= 0.02**

Table 4 Odds ratios for obesity defined by FMI sex and race specific cutpoints by CKD stage compared to CKD stage 1+2 from multivariate logistic regression adjusted for race, age, diabetes, liver disease, physical activity and cardiovascular disease

CKD Stage	eGFR Creatinine	eGFR Cystatin C
	OR (95% CI) p-value	OR (95% CI) p-value
1A+2A	1.12 (0.96-1.31) P=0.01*	1.02 (0.74-1.39) P=0.84
3a	0.85 (0.70-1.05) P=0.60	1.46 (1.10-1.94) P=0.09
3b	0.89 (0.61-1.29) P=0.54	1.41 (0.90-2.19) P=0.23
4	0.70 (0.36-1.36) P=0.67	1.49 (0.72-3.09) P=0.26
5	0.44(0.16-1.20) P=0.17	0.45(0.09-2.38) P=0.22
	P for trend= 0.18	**P for trend=0.06**

Discussion

In this cross-sectional study, estimates of the prevalence of excess adiposity and sarcopenia in CKD varied by the definitions used to assess the constructs. Notably, this study demonstrated that the prevalence of low muscle mass was lower using traditional definitions of sarcopenia compared to measures that account for adiposity, i.e., relative sarcopenia. The clinical significance of this distinction lies in the recent HEALTH ABC study demonstrating that relative sarcopenia better discriminated those with poor physical functioning and a greater risk of incident disability, compared with conventional measures of sarcopenia.[7] This study also demonstrated the substantial degree to which prevalence of obesity with %BF was over-estimated and the prevalence of obesity with BMI was under-estimated in individuals with CKD, when considering FMI as the criterion standard.

Obesity defined by BMI and computed tomography (CT) measures of adiposity are associated with incident CKD and development of ESRD.[24-26] BMI as a traditional measure of obesity does not distinguish between lean and fat mass and may fail to identify excess adiposity in the setting of sarcopenia. Similarly, DXA derived percent body fat (%BF= fat mass/ total mass) is a limited index of obesity in individuals with sarcopenia: in two individuals with the same fat mass, a lower lean mass will result in a higher %BF. Obesity cutpoints derived by fat mass alone (FMI, kg/m^2) overcome these limitations.

Muscle mass, adiposity and their relations are known to differ substantially by racial/ethnic groups and age.[17, 27] Therefore, methodological challenges in defining sarcopenia and obesity limit the generalizability of previous studies given the lack of race/ethnicity cutpoints. As the burden of advanced CKD is disproportionately higher for blacks and Hispanics in the United States, failure to account for these differences is of particular concern.[28, 29]

There is a strong direct relation between FMI and ALMI in the general population with correlation coefficients exceeding 0.50 independent of age, sex and race/ethnicity.[5] Therefore, conventional definitions of sarcopenia based on lean mass alone may fail to capture low lean mass relative to fat mass among persons with higher fat mass, i.e., relative sarcopenia.[30]

Previous studies on the prevalence of sarcopenia in persons with non-dialysis requiring CKD yielded conflicting results. In two US NHANES studies [one based on bioimpedance analysis (BIA) measures of the skeletal muscle index[31] and one based on DXA ALMI[22]], sarcopenia was defined based on values more than two standard deviations below the sex-specific mean value in young adults. CKD was not associated with sarcopenia in either study, independent of age and comorbid conditions. These studies were limited by lack of adjustment for higher fat mass in CKD, and by the confounding effects of race/ethnicity given that criteria for sarcopenia were not race/ethnicity-specific. ALMI is markedly higher in black persons, compared with persons of other race/ethnicities.[5, 17] For example, in the entire NHANES dataset for our study, the odds of sarcopenia (using the cut points employed by Sharma, et al.[22]) in black compared with white participants were 0.30 (95% CI 0.25, 0.36), independent of age and sex. In the Korean NHANES study, sarcopenia was defined based on values of DXA-derived appendicular lean mass as a percentage of body weight (ALM/weight) more than two SDs below the sex-specific mean in young adults.[32] Adjusted analyses showed CKD was associated with higher odds of sarcopenia in men, but not women. While the ALM/body weight ratio does incorporate body weight, it does not capture the complex interactions between lean and fat mass that vary by age, sex, and race/ethnicity.

To our knowledge, this is the first study to use a fat-adjusted equation to define sarcopenia in CKD and one of few studies to use our novel approach that incorporates the complex interactions among fat and lean mass with age, sex and race/ethnicity. Recent evidence suggests the importance of adjusting for fat when studying lean mass due to the expected increase in lean mass with fat mass.[6, 7] That increase in lean mass with higher fat mass is age-, sex-, and race/ethnicity-dependent; to what degree it is accounted for by differences in physical activity is unknown.[5, 23, 33] Failure to account for adiposity in sarcopenia definitions may lead to misclassification of patients with a relative deficit in lean for their amount of adiposity. Our analysis suggests that this misclassification may be particularly relevant in CKD as only low $ALMI_{FMI}$ for age was significantly associated with CKD while low ALMI for age was not.

After adjustment for confounders, our results also showed disparate odds of low $ALMI_{FMI}$ for age and obesity $_{FMI}$ using $eGFR_{Cr}$ and $eGFR_{Cys}$. The known effects of muscle mass/creatinine generation on the serum creatinine concentration and the known effects of fat mass on the serum cystatin C concentration (more fat mass is associated with higher cystatin C concentrations) likely results in an underestimation of the prevalence of sarcopenia when $eGFR_{Cr}$ is used and an overestimation of the prevalence of obesity when $eGFR_{Cys}$ is used.[34] This finding highlights the complexity of studying sarcopenia and obesity in the CKD population and either the application of other marker solutes (e.g., beta trace protein) when studying the association between CKD and body composition, or at a minimum, the recognition that conventional GFR-estimating equations can be biased by alterations from the typical muscle or fat mass.

A recent study addressed misclassification of obesity based on BMI measures by reporting DXA-derived body composition results in NHANES participants with and without CKD.[22] The study defined obesity based on percent body fat (%BF) and reported that BMI markedly underestimated the prevalence of obesity in CKD.[22] %BF is a flawed index of obesity in individuals with sarcopenia and indeed, the diagnosis of obesity based on high %BF was most common among persons with sarcopenia reflecting a likely over-estimate of the excess adiposity in CKD.

Our results reinforce the evidence that BMI underestimates the incidence of obesity in CKD.[22] We showed a higher prevalence of obesity with lower eGFR when using FMI as compared to BMI. As expected, due to relative reductions in muscle mass in CKD, the prevalence of obesity by %BF was magnified. Given the growing use of %BF to define excess adiposity, it is important to recognize the degree to which this definition is confounded by sarcopenia in persons with and without CKD.

There are several limitations to the study including its cross-sectional design; as such, we cannot infer a causal relation between CKD and altered body composition. In addition to the biases raised above related to metrics of adiposity, the determination of lean mass by DXA can confounded by an excess of extracellular fluid (often, but not always large enough to result in overt edema) resulting in an over-estimate of lean (body cell) mass in some persons with CKD in whom magnetic resonance imaging would be more accurate. While DXA is quite accurate at the assessment of fat mass,[13, 14] it is not as simple to apply broadly across the population as is body weight or waist circumference, and is more costly. Kidney Disease Improving Global Outcomes (KDIGO) guidelines now recommend the use of DXA in CKD to assess bone mineral density, so it is possible full body DXA could also be performed in the future including T and Z scores of ALMI adjusted for FMI on clinical reports.[35] Dependent on how these measures relate to clinical outcomes in future studies, this information could aid clinicians in identifying those patients at highest risk for frailty, fracture, disability and death.

In conclusion, sarcopenia and relative sarcopenia are more prevalent in persons with CKD. Excess adiposity is common in CKD and confounds the assessment of sarcopenia. Sarcopenia associated with aging, frailty, malignancy and/or chronic inflammatory disease, and morbid obesity – all increasing in prevalence – confound the relation between actual and estimated GFR, which in turn challenges our ability to accurately assess the true relations between CKD and body composition.

Acknowledgement

This research was supported by National Institutes of Health grants F32 DK111083 (SZ) and K24 DK076808 (MBL).

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports (von Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports. J Cachexia Sarcopenia Muscle Clinical Reports 2016; 1;e28:1-2.)

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

CKD	chronic kidney disease
ESRD	end stage renal disease
NHANES	National Health and Nutrition Examination Survey
DXA	Dual Energy X-Ray Absorptiometry
eGFR	estimated glomerular filtration rate
$eGFR_{Cys}$	estimated glomerular filtration rate using cystatin C equation
$eGFR_{Cr}$	estimated glomerular filtration rate using creatinine equation
ALMI	appendicular lean mass index (kg/m^2)
FMI	fat mass index (kg/m^2)
$ALMI_{FMI}$	ALMI relative to FMI
BMI	body mass index (kg/m^2)
%BF	percent body fat
$Obese_{FMI}$	obesity defined by FMI
$Obese_{\%BF}$	obesity defined by %BF
$Obese_{BMI}$	obesity defined by BMI

References

1. [1] X.H. Wang, W.E. Mitch. Mechanisms of muscle wasting in chronic kidney disease. Nature Reviews Nephrology 2014;10:504-16.
2. [2] N. Noori, J.D. Kopple, C.P. Kovesdy, U. Feroze, J.J. Sim, S.B. Murali, A. Luna, M. Gomez, C. Luna, R. Bross, A.R. Nisenson, K. Kalantar-Zadeh. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. Clinical journal of the American Society of Nephrology 2010; 12: 2258-68.
3. [3] Y. Bao, L. Dalrymple, G.M. Chertow, G.A. Kaysen, K.L. Johansen. Frailty, dialysis initiation, and mortality in end-stage renal disease. Archives of internal medicine 2012; 14: 1071-7.
4. [4] K.L. Johansen, G.A. Kaysen, L.S. Dalrymple, B.A. Grimes, D.V. Glidden, S. Anand, G.M. Chertow. Association of physical activity with survival among ambulatory patients on dialysis: the Comprehensive Dialysis Study. Clinical journal of the American Society of Nephrology 2013; 2: 248-53.
5. D. Weber, J. Long, M.B. Leonard, B. Zemel, J.F. Baker. Development of Novel Methods to Define Deficits in Appendicular Lean Mass Relative to Fat Mass. PLoS One 2016; 11.
6. J.F. Baker, J.T. Giles, D. Weber, M.B. Leonard, B.S. Zemel, J. Long, S. Ibrahim, P.P. Katz. Assessment of muscle mass relative to fat mass and associations with physical functioning in rheumatoid arthritis. Rheumatology 2017; 6: 981-988.
7. J.F. Baker, J. Long, M.B. Leonard, T. Harris, M.J. Delmonico, A. Santanasto, S. Satterfield, B. Zemel, D.R. Weber. Estimation of Skeletal Muscle Mass Relative to Adiposity Improves Prediction of Physical Performance and Incident Disability. The journals of gerontology. Series A, Biological sciences and medical sciences 2017.
8. A.S. Levey, L.A. Stevens, C.H. Schmid, Y. Zhang, A.F. Castro, H.I. Feldman, J.W. Kusek, P. Eggers, F. Van Lente, T. Greene, J. Coresh. A New Equation to Estimate Glomerular Filtration Rate. Annals of internal medicine 2009; 9: 604-612.
9. National Health and Nutrition Examination Survey. Available from:
10. http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm.B.E. Ainsworth, W.L. Haskell, M.C. Whitt, M.L. Irwin, A.M. Swartz, S.J. Strath, W.L. O'Brien, D.R. Bassett, K.H. Schmitz, P.O. Emplaincourt, D.R. Jacobs, A.S. Leon. Compendium of physical activities: an update of activity codes and MET intensities. Medicine and science in sports and exercise 2000; 9: S498-504.
11. L.A. Stevens, J. Coresh, C.H. Schmid, H.I. Feldman, M. Froissart, J. Kusek, J. Rossert, F Van Lente, R.D. Bruce, Y.L. Zhang, T. Greene, A.S. Levey. 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 2008; 3: 395-406.
12. I.H. de Boer, B.C. Astor, H. Kramer, W. Palmas, K. Rudser, S.L. Seliger, M.G. Shilpak, D.S. Siscovick, M.Y. Tsai, B. Kestenbaum. Mild elevations of urine albumin excretion are associated with atherogenic lipoprotein abnormalities in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2008; 1: 407-14.
13. J. LaForgia, J. Dollman, M.J. Dale, R.T. Withers, A.M. Hill. Validation of DXA body composition estimates in obese men and women. Obesity 2009; 4: 821-6.
14. M.I. Goran, M.J. Toth, E.T. Poehlman. Assessment of research-based body composition techniques in healthy elderly men and women using the 4-compartment model as a criterion method. International journal of obesity and related metabolic disorders 1998; 2: 135-42.
15. N. Schenker, L.G. Borrud, V.L. Burt, L.R. Curtin, K.M. Flegal, J. Hughes, C.L. Johnson, A.C. Looker, L. Mirel. Multiple imputation of missing dual-energy X-ray absorptiometry data in the National Health and Nutrition Examination Survey. Statistics in medicine 2011; 3: 260-76.
16. D.A. Schoeller, F.A. Tylavsky, D.J. Baer, W.C. Chumlea, C.P. Earthman, T. Fuerst, T.B. Harris, S.B. Heymsfield, M. Horlick, T.G. Lohman, H.C. Lukaski, J. Shepherd, R.M. Siervogel. QDR 4500A dual-energy X-ray absorptiometer underestimates fat

mass in comparison with criterion methods in adults. The American journal of clinical nutrition 2005; 5: 1018-25.
17. T.L. Kelly, K.E. Wilson, S.B. Heymsfield. Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One 2009; 9.
18. K.M. Flegal, T.J. Cole. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. National health statistics reports 2013; 63: 1-3.
19. T.J. Cole. The LMS method for constructing normalized growth standards. European journal of clinical nutrition 1990; 1: 45-60.
20. C.L. Cheung, K.S. Lam, B.M. Cheung. Evaluation of Cutpoints for Low Lean Mass and Slow Gait Speed in Predicting Death in the National Health and Nutrition Examination Survey 1999-2004. The journals of gerontology. Series A, Biological sciences and medical sciences 2016; 1: 90-5.
21. R.R. McLean, D.P. Kiel. Developing consensus criteria for sarcopenia: an update. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2015; 4: 588-92.
22. D. Sharma, M. Hawkins, M.K. Abramowitz. Association of sarcopenia with eGFR and misclassification of obesity in adults with CKD in the United States. Clinical journal of the American Society of Nephrology 2014; 12: 2079-88.
23. R.N. Baumgartner, S.J. Wayne, D.L. Waters, I. Janssen, D. Gallagher, J.E. Morley. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obesity research 2004; 12: 1995-2004.
24. C.Y. Hsu, C.E. McCulloch, C. Iribarren, J. Darbinian, A.S. Go. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006; 1: 21-8.
25. A. Vivante, E. Golan, D. Tzur, A. Leiba, A. Tirosh, K. Skorecki, R. Calderon-Margalit. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Archives of internal medicine 2012; 21: 1644-50.
26. M. Madero, R. Katz, R. Murphy, A. Newman, K. Patel, J. Ix, C. Peralta, S. Satterfield, L. Fried, M. Shilpak, M. Sarnak. Comparison between Different Measures of Body Fat with Kidney Function Decline and Incident CKD. Clinical journal of the American Society of Nephrology 2017; 6: 893-903.
27. A.M. Silva, W. Shen, M. Heo, D. Gallagher, Z. Wang, L.B. Sardinha, S.B. Heymsfield. Ethnicity-Related Skeletal Muscle Differences Across the Lifespan. American journal of human biology : the official journal of the Human Biology Council 2010; 1: 76-82.
28. USRDS: Renal Data System (USRDS) Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2008.
29. C.A. Peralta, R. Katz, I. DeBoer, J. Ix, M. Sarnak, H. Kramer, D. Siscovick, S. Shea, M. Szklo, M. Shilpak. Racial and Ethnic Differences in Kidney Function Decline among Persons without Chronic Kidney Disease. Journal of the American Society of Nephrology 2011; 7: 1327-1334.
30. A.B. Newman, V. Kupelian, M. Visser, E. Simonsick, B. Goodpaster, M. Nevitt, S.B. Kritchevsky, F.A Tylavsky, S.M. Rubin, T.B. Harris. Sarcopenia: alternative definitions and associations with lower extremity function. Journal of the American Geriatrics Society 2003; 11: 1602-9.
31. R.N. Foley, C. Wang, A. Ishani, A.J. Collins, A.M. Murray. Kidney function and sarcopenia in the United States general population: NHANES III. American journal of nephrology 2007; 3: 279-86.
32. S.J. Moon, T.H. Kim, S.Y. Yoon, J.H. Chung, H.-J. Hwang. Relationship between Stage of Chronic Kidney Disease and Sarcopenia in Korean Aged 40 Years and Older Using the Korea National Health and Nutrition Examination Surveys (KNHANES IV-2, 3, and V-1, 2), 2008–2011. PLoS ONE 2015; 6.
33. J.P. Loenneke, P.D. Loprinzi, T. Abe. The prevalence of sarcopenia before and after correction for DXA-derived fat-free adipose tissue. European journal of clinical nutrition 2016; 12: 1458-1460.
34. J.S. Chew-Harris, C.M. Florkowski, P.M. George, J.L. Elmslie, Z.H. Endre. The relative effects of fat versus muscle mass on cystatin C and estimates of renal function in healthy young men. Annals of clinical biochemistry 2013; 1: 39-46.
35. M. Ketteler, G.A. Block, P. Evenepoel, M. Fukagawa, C.A. Herzog, L. McCann. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney international 2017; 1: 26-36.