Cystatin C- and Creatinine-Based Glomerular Filtration Rate Estimation Differences and Muscle Quantity and Functional Status in Older Adults: The Health, Aging, and Body Composition Study

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Rationale & Objective: The difference in the estimated glomerular filtration rate based on cystatin C and that based on creatinine (eGFRDiff) is known to be associated with frailty and mortality. Creatinine is influenced by muscle mass, more so than cystatin C; we aimed to determine whether eGFRDiff is associated with muscle quantity and to what extent muscle quantity explains the relationship between eGFRDiff and poor functional status.

Study Design: A cohort analysis of the health, aging, and body composition study (HABC).

Setting & Participants: Overall, 2,970 HABC participants had their baseline serum creatinine level, cystatin C level, and body composition measured using imaging.

Exposure: Estimated glomerular filtration rates (eGFRs) were calculated using Chronic Kidney Disease Epidemiology Collaboration equations (estimated glomerular filtration rate based on cystatin C [$eGFR_{Cys}$] and estimated glomerular filtration rate based on creatinine [$eGFR_{Cr}$]), and eGFRDiff was calculated as $eGFR_{Cys} - eGFR_{Cr}$.

Outcomes: The total thigh muscle area was evaluated using computed tomography. The health, aging, and body composition study physical performance battery was scored on a continuous scale (standing and walking tasks); poor functional status was characterized by the lowest quartile.

Analytical Approach: We used linear regression to model the cross-sectional association of eGFRDiff and muscle measures. We used logistic regression to evaluate the association of eGFRDiff with poor functional status.

Results: The mean age was 74 ± 3 years; the $eGFR_{Cys}$, $eGFR_{Cr}$, and eGFRDiff was 72 ± 18, 68 ± 15, and 4 ± 14 mL/min/1.73 m², respectively. Compared with participants in the reference group (−10 < eGFRDiff ≤ 10 mL/min/1.73 m²), those in the negative eGFRDiff group (≤−10 mL/min/1.73 m²) were more likely to have comorbidities, a slower gait, and worse functional status. They had an approximately 14-cm² smaller thigh muscle area in a fully adjusted model. Compared with the reference group, those in the negative group had 1.89-fold higher odds of poor functional status (unadjusted). This relationship was minimally attenuated after adjustment for thigh muscle, thigh fat area, appendicular lean mass, and limb fat mass, both individually and in combination.

Limitations: The functional status outcome was specific to HABC. The muscle measures did not capture dynamic turnover.

Conclusions: The difference of $eGFR_{Cys} - eGFR_{Cr}$ provides information on older adults' functional status, which is only partially explained by muscle quantity and quality.

Serum creatinine is an imperfect surrogate for glomerular filtration rate because it is influenced by many factors other than kidney function,[1-3] such as age, sex, muscle mass, and diet. An alternative marker of kidney function, cystatin C, has come into clinical use in the past decade, although it is still not widely used by primary care practitioners. Cystatin C is produced by all nucleated cells; hence, it is less affected by muscle[4] than creatinine and is freely filtered by the glomeruli.[5]

Although differences in associations of serum creatinine and cystatin C with clinical outcomes are fairly well understood, differences within individuals have been less studied. Discrepancies in these markers within individuals may have clinical significance. For example, we have shown that the difference between estimated glomerular filtration rate (eGFR) based on cystatin C and that based on creatinine (eGFRDiff) is associated with prevalent and incident frailty as well as with adverse outcomes and

mortality.[6,7] A potential explanation for this finding is that the differences in the eGFRs reflect the effects of health status and body composition, such as muscle mass and activity, which have important implications for aging and frailty.

Sarcopenia is known to be associated with frailty and adverse outcomes and is potentially responsible for some of the discrepancy between these markers because serum creatinine is more influenced by muscle turnover than cystatin C. At the same time, a number of nonglomerular filtration rate determinants[1,3,4] of both serum creatinine and cystatin C, including body mass index and, more specifically, both fat and muscle mass, may contribute to explaining the difference in eGFRs. Further, the association of creatinine with muscle has not been extensively studied using objective measures of body composition. We set out to examine the association of eGFRDiff with muscle measures and the extent to which the relationship between

PLAIN-LANGUAGE SUMMARY

Kidney function is typically estimated based on the serum creatinine level, although this may be less reliable at the extremes of muscle mass. The difference between the estimated glomerular filtration rate based on cystatin C (eGFR$_{Cys}$) and that based on creatinine (eGFR$_{Cr}$) has been shown to provide information on functional status, frailty, and the risk of death in older adults. The aim of this study is to determine whether muscle mass explains the association of this difference (eGFRDiff = eGFR$_{Cys}$ − eGFR$_{Cr}$) with functional status. We found that muscle quantity only partially attenuated this relationship. This might be related to the measures of muscle evaluated, which did not capture data regarding the dynamic muscle activity leading to creatinine generation. Future studies are needed to better understand the determinants of eGFRDiff.

eGFRDiff and functional status is explained by surrogates of muscle mass in a community-living cohort of well-functioning older adults. The health, aging, and body composition (HABC) study cohort was an ideal setting for this study question because it included older adults who were at the risk of functional decline but were independent to perform activities of daily living at baseline. Various measures of both muscle area, determined using imaging, and muscle strength, determined using functional testing, are available. Given that creatinine and cystatin C are known to be affected by body composition, we hypothesized that a positive eGFRDiff (ie, estimated glomerular filtration rate based on cystatin C [eGFR$_{Cys}$] > estimated glomerular filtration rate based on creatinine [eGFR$_{Cr}$]) would be associated with a greater muscle area and strength and that markers of muscle mass and strength would attenuate the association between eGFRDiff and functional status.

METHODS

Study Population

The HABC cohort comprised 3,075 well-functioning older adults aged 70-79 years who were independent to perform activities of daily living and free of walking or stair-climbing difficulties. The participants were recruited from a random sample of White Medicare beneficiaries and all age-eligible Black community residents at 2 sites, in Pittsburgh, Pennsylvania, and in Memphis, Tennessee, between 1997 and 1998. The participants provided informed consent for study participation, and each institutional review board approved the protocol. The present analysis used deidentified data and, thus, was exempted from ethics committee approval. This analysis excluded 95 participants who did not have data regarding cystatin C or creatinine levels or imaging for muscle mass at the baseline available. Given that creatinine-based glomerular filtration rate remains the standard evaluation method for kidney function in clinical practice, our analysis also excluded those with a baseline creatinine-based eGFR of <15 mL/min/1.73 m^2, resulting in 2,970 (96.6% of the HABC cohort) eligible patients for the current study.

Exposure

Data regarding markers of kidney function were collected at the baseline. The serum creatinine level was measured using a colorimetric technique on the Johnson & Johnson VITROS 950 Chemistry Analyzer using the enzymatic method. The baseline serum creatinine measurements were not calibrated. The cystatin C level was measured at the HABC core laboratory, at the University of Vermont, Burlington, Vermont, using the Behring nephelometer II analyzer (Dade Behring Inc), which used a particle-enhanced immunonepholometric assay (N Latex Cystatin C).[8]

The eGFRs were calculated using cystatin C-based (eGFR$_{Cys}$) and creatinine-based (eGFR$_{Cr}$) Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[9] The cystatin C-based CKD-EPI equation includes the baseline cystatin C level, sex, and age. The creatinine-based CKD-EPI equation includes the baseline creatinine level, sex, age, and race. The variable of interest, eGFRDiff, was calculated as eGFR$_{Cys}$ − eGFR$_{Cr}$. We performed sensitivity analyses using the newly published 2021 CKD-EPI eGFR$_{Cr}$ equations without the race factor.[10]

Clinical Outcomes

Functional status was rated using the health ABC, aging, and body composition physical performance battery (HABCPPB), which grades 4 tasks (usual walk time, narrow walk time, chair stand, and standing balance). Each task is graded as the ratio of the performance of the participant to the best possible performance,[11] thus providing a score between 0 and 1. The total maximum score for the HABCPPB is 4 points, with higher scores indicating better performance. Poor functional status was defined as an HABCPPB score in the lowest quartile.

Muscle quantity was estimated based on the area of the thigh muscles (in cm^2), determined using computed tomography (CT) with 9,800 Advantage (General Electric) at the Pittsburgh site and either Somatom Plus 4 (Siemens) or PQ 2000 S (Marconi Medical Systems) at the Memphis site. Axial CT scans were obtained for each participant at the baseline study visit. The femoral height was measured, and the CT scanner was placed at half the distance between the medial edge of the greater trochanter and the intercondylar fossa to obtain midthigh images. The slice thickness was set at 10 mm. Muscle, bone, and adipose tissue were distinguished based on their measured density (in Hounsfield units). Their respective areas were determined by multiplying the number of pixels at a given Hounsfield

unit area by the pixel area. The total thigh muscle area was calculated as the total muscle area within the fascial lines minus bone (Hounsfield unit > 150 units) and adipose tissue. The total abdominal muscle area was calculated as the total muscle area of the right and left psoas, lateral abdominal muscles, and rectus abdominal muscles. Body composition was also measured using dual-energy x-ray absorptiometry (DXA; QDR 4500 A, Hologic, Inc). The lean mass was calculated as the total mass minus bone mineral content and fat mass. The appendicular lean mass was calculated as the sum of the arm and leg lean mass. The fat-free mass was calculated as the sum of the lean mass and bone mineral content of the trunk and limbs.

Other Study Measurements

Sociodemographic data (including age, ethnicity and race, sex, and level of education) as well as data on smoking habits, past medical history (including hypertension and diabetes mellitus), and medication use were collected at the baseline via questionnaires. The participants were asked how many times they had fallen within the past 12 months via a questionnaire. The standing height (in mm) was measured at the baseline using a wall-mounted Harpenden stadiometer and weight (in kg) using a standard balance beam scale. The baseline body mass index was calculated as weight / height^2 (in kg/m^2). The serum albumin and C-reactive protein levels were measured at the baseline.

An isometric dynamometer (Jaymar; JLW Instruments) was used to assess grip strength (in kg). Two measurements were made on each side, and the average of the 4 readings was used for analysis. Gait speed was evaluated over a 6-m walk (in m/s).

Statistical Analysis

We examined eGFRDiff continuously (per standard deviation [SD] = 14 mL/min/1.73 m^2), and the study population was divided into 3 groups based on their baseline eGFRDiff as follows: (1) negative eGFRDiff group, ≤−10 mL/min/1.73 m^2; (2) reference group, −10 mL/min/1.73 m^2 < eGFRDiff ≤ 10 mL/min/1.73 m^2; and (3) positive eGFRDiff group, >10 mL/min/1.73 m^2. We opted for a cutoff of 10 mL/min/1.73 m^2 so that at least 15% of the population would be included in each extreme group. We evaluated the participants' baseline characteristics across the groups using mean (SD) for continuous and n (%) for categorical variables.

We first examined the associations between eGFRDiff and muscle area determined using CT to establish this association and its potential confounders. We used linear regressions to test the association of eGFRDiff with the total thigh muscle area, quadriceps muscle area, and abdominal muscle area (determined using CT) as well as with the appendicular lean mass indexed to squared height, fat-free mass, and limb fat mass (determined using DXA). We used the total thigh muscle area, determined

using CT, as the best potential indicator of muscle quantity for further analyses. The models were first unadjusted and then adjusted for age, sex, race, education, body mass index, serum albumin and C-reactive protein, smoking status, diabetes, hypertension, study site, and CKD category based on eGFR$_{Cr}$. The proportion of participants with missing covariates was minimal, and no computed data were used in adjusted regression models.

For our second objective, we examined whether measures of muscle quantity explained the association between eGFRDiff and functional status. We used logistic regression to examine the association between eGFRDiff and poor functional status, which was defined as being in the lowest quartile of the HABCPPB score. Multivariate adjustments used the same adjusted model sequences as those mentioned above. We then further adjusted for individual measures of body composition: thigh muscle area, thigh fat area, appendicular lean mass, limb fat mass, and fat-free mass. In the sensitivity analyses, we arbitrarily modified the cutoff to define poor functional status as being the lowest decile and the lowest 30% of the HABCPPB score.

Given that body composition has been shown in other studies[12-14] to differ based on sex and race, we specifically assessed the effect of interactions among these variables on the association between eGFRDiff and thigh muscle area in the sensitivity analyses. Additionally, we re-examined our main results using the new 2021 CKD-EPI creatinine-based equation, which did not include the race coefficient.[10] The total number of participants in this sensitivity analysis dropped from 2,970 to 2,968 because of "new" eGFR$_{Cr}$ crossing the 15 mL/min/1.73 m^2 cutoff for inclusion.

Statistical analyses were performed using SAS, version 9.4, and SAS Enterprise, version 7.1, with P values <0.05 considered statistically significant for all analyses, including interaction terms.

RESULTS

General Characteristics

A total of 2,970 participants were included in this study (96.6% of the entire HABC study sample). Men represented 48% of the sample, 41% were Black, and the average age was 74 ± 3 (SD) years (Table 1). The average eGFR$_{Cys}$, eGFR$_{Cr}$, and eGFRDiff was 72 ± 18, 68 ± 15, and 4 ± 14 mL/min/1.73 m^2, respectively. Compared with those with minimal differences in eGFRDiff, those in the ≤−10 mL/min/1.73 m^2 group (ie, with eGFR$_{Cr}$ being >10 mL/min/1.73 m^2 higher than eGFR$_{Cys}$) were more likely to have hypertension or diabetes mellitus but were less likely to have ever smoked. They also had higher C-reactive protein concentrations, had worse functional status, and were more likely to have fallen in the previous year. Furthermore, they had a larger adipose and smaller muscle area, as determined using the CT scan, and were more likely to have a slower gait and weaker grip. The HABC physical performance battery score was missing in

Table 1. Baseline Characteristics by eGFRDiff (eGFR$_{Cys}$ − eGFR$_{Cr}$) Groups in Well-Functioning Community-Living Older Adults

Baseline Characteristics	Negative eGFRDiff ≤ −10 mL/min/ 1.73 m^2	Reference −10 < eGFRDiff ≤ 10 mL/min/ 1.73 m^2	Positive eGFRDiff > 10 mL/min/ 1.73 m^2	Total
Participants	446	1,565	959	2,970
Mean eGFRDiff (SD), mL/min/1.73 m^2	−17 (7)	0.6 (5)	20 (8)	4 (14)
Range eGFRDiff, mL/min/1.73 m^2	−47 to −10	−10 to 10	10 to 77	−47 to 77
Mean cystatin C (SD), mg/dL	1.2 (0.3)	1.1 (0.3)	0.9 (0.1)	1.0 (0.3)
Mean eGFR$_{Cys}$ (SD), mL/min/1.73 m^2	58 (13)	68(17)	87 (14)	72 (18)
Mean creatinine (SD) mg/dL	1.0 (0.2)	1.1 (0.3)	1.0 (0.2)	1.0 (0.3)
Mean eGFR$_{Cr}$ (SD), mL/min/1.73 m^2	75 (14)	67 (16)	67 (12)	68 (15)
Mean age (SD), y	74 (3)	74 (3)	73 (3)	74 (3)
Men, n (%)	226 (51)	787 (50)	425 (44)	1,438 (48)
White, n (%)	258 (58)	931 (59)	555 (58)	1,744 (59)
Never smoker, n (%)	174 (39)	683 (44)	447 (47)	1,304 (44)
Hypertension, n (%)	241 (55)	820 (53)	448 (47)	1,509 (51)
Diabetes mellitus, n (%)	85 (19)	244 (16)	108 (11)	437 (15)
Mean body mass index (SD), kg/m^2	28 (5)	28 (5)	27 (4)	27 (5)
Median C-reactive protein (IQR), mg/dL	1.98 (1.15 to 3.64)	1.79 (1.03 to 3.31)	1.45 (0.90 to 2.62)	1.67 (0.99 to 3.13)
Frailty measures				
Poor functional status, n (%)	163 (38)	373 (25)	175 (19)	711 (25)
HABCPPB score, mean (SD)	2.0 (0.6)	2.2 (0.5)	2.3 (0.5)	2.2 (0.5)
Fallers in past 12 mo, n (%)	108 (24)	328 (21)	181 (19)	617 (21)
Average grip strength (SD), kg	27.9 (10.0)	30.0 (10.0)	30.7 (10.3)	29.9 (10.1)
6-m gait speed (SD), m/s	1.12 (0.24)	1.17 (0.23)	1.22 (0.23)	1.18 (0.24)
CT scan				
Abdominal muscle area (SD), cm^2	69 (20)	71 (19)	70 (19)	70 (19)
Total thigh muscle area (SD), cm^2	214 (52)	224 (55)	225 (57)	223 (56)
Quadriceps muscle area (SD), cm^2	99 (26)	103 (26)	104 (27)	103 (26)
Thigh fat area (SD), cm^2	194 (113)	177 (99)	169 (86)	177 (98)
Total body fat mass (SD), kg	28.9 (10.1)	27.0 (8.6)	25.3 (7.6)	26.7 (8.6)
Limb fat mass (SD), kg	13.7 (5.3)	12.8 (4.5)	12.2 (4.0)	12.7 (4.5)
DXA scan				
Total fat-free mass (SD), kg	48.9 (10.2)	49.2 (10.3)	48.4 (10.5)	48.9 (10.4)
Appendicular lean mass/height^2 (SD), kg/m^2	7.19 (1.24)	7.23 (1.28)	7.16 (1.32)	7.20 (1.29)

Note: Conversion factor for units: serum creatinine in mg/dL to μmol/L, ×88.4. Abbreviations: CT, computed tomography; DXA, dual-energy x-ray absorptiometry; eGFR$_{Cr}$, creatinine-based estimated glomerular filtration rate; eGFR$_{Cys}$, cystatin C-based estimated glomerular filtration rate; eGFRDiff, difference between eGFR$_{Cys}$ and eGFR$_{Cr}$; HABCPPB, health, aging, and body composition study physical performance battery; IQR, interquartile range; SD, standard deviation.

22 (5%), 65 (4%), and 25 (3%) participants in the eGFRDiff negative, reference, and positive groups, respectively. The missing covariates were as follows: education in 6 participants in the reference group and 2 participants in the positive group, smoking status in 4 participants in the reference group and 1 participant in the positive group, and C-reactive protein level in 4 participants in the reference group and 3 participants in the positive group.

Association Between eGFRDiff and Muscle Quantity

The average thigh muscle area, as determined using the CT scan, for the entire study population was 223 ± 56 cm^2. For each higher SD increment in eGFRDiff, the thigh muscle area was 7.3 (95% confidence interval: [6.3; 8.3]) cm^2 larger after adjusting for demographics, inflammation markers, cardiovascular risk factors, kidney disease stage, and study site (Table 2). Those in the negative eGFRDiff group had an approximately 14-cm^2 smaller thigh muscle area than those in the reference group in the fully adjusted model.

Association Between eGFRDiff and Functional Status

Compared with the reference group, those in the negative eGFRDiff group had 1.89-fold higher odds of having poor functional status in the unadjusted model. This relationship was only minimally attenuated and remained highly statistically significant in the fully adjusted model after adjustment for thigh muscle, thigh fat area, appendicular lean mass, and limb fat mass, both individually and in combination (Table 3). When eGFRDiff was considered as a continuous variable, each 1 SD increment in eGFRDiff

Table 2. Association Between eGFRDiff (eGFR$_{Cys}$ − eGFR$_{Cr}$) and Thigh Muscle Area (cm^2) Determined Using Computed Tomography Scan

	Model 1		Model 2	
Exposure	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**
eGFRDiff (per SD = 14 increments)	4.5 (3.2 to 5.7)	<0.001	7.3 (6.3 to 8.3)	<0.001
Negative eGFRDiff group (≤−10 mL/min/1.73 m^2)	−10.2 (−14.0 to −6.4)	<0.001	−13.9 (−16.9 to −11.0)	<0.001
Reference eGFRDiff group (−10 < eGFRDiff ≤ 10 mL/min/1.73 m^2)	0 (ref)		0 (ref)	
Positive eGFRDiff group (>10 mL/min/1.73 m^2)	4.5 (1.6 to 7.4)	<0.01	8.3 (6.0 to 10.6)	<0.001

Note: Model 1 = adjusted for age, sex, and race. Model 2 = model 1 + education, body mass index, serum albumin, C-reactive protein, smoking, hypertension, diabetes, chronic kidney disease category by eGFR$_{Cr}$, and study site. Abbreviations: CI, confidence interval; eGFR$_{Cr}$, creatinine-based estimated glomerular filtration rate; eGFR$_{Cys}$, cystatin C-based estimated glomerular filtration rate; eGFRDiff, difference between eGFR$_{Cys}$ and eGFR$_{Cr}$; ref, reference; SD, standard deviation.

was associated with 23% lower odds of having poor functional status in the fully adjusted model (Table 4). Once again, the results remained similar when each body composition measure was individually accounted for. Furthermore, the results were similar when poor functional status was defined alternatively as the lowest 10th or 30th rather than the lowest 25th percentile of the HABCPPB score.

Stratification by Race

We found a significant association between eGFRDiff and thigh muscle area based on race (P < 0.01) but not based on sex (P = 0.05) in the fully adjusted models. Therefore, in secondary analyses, we stratified the population by race to examine this further (Table 5). We found directionally similar associations in both the race strata, although eGFRDiff was associated with larger-magnitude differences in the thigh muscle area among the Black participants compared with the observed associations among the White participants.

The results were not materially different when the new 2021 CKD-EPI eGFR$_{Cr}$ calculations were used[10] (Tables S1

and S2), and in the sensitivity analyses, in which poor functional status was defined by the lowest decile or lowest 30% rather than the lowest quartile, used in primary analyses.

DISCUSSION

Among a large cohort of well-functioning community-living Black and White older adults, we demonstrated that those with a negative eGFRDiff (ie, a higher eGFR$_{Cr}$ than eGFR$_{Cys}$) had a nearly 2-fold higher risk of poor functional status. On average, they also had close to a 14-cm^2 smaller thigh muscle area, as determined using the CT scan, in the fully adjusted models. However, accounting for lower muscle mass, determined using CT, did not meaningfully affect the association between eGFRDiff and poor functional status. This measure only partially attenuated the association. Furthermore, our findings remained similar regardless of which measure of muscle or fat we accounted for. We did not identify a body composition measure that could substantially explain the relationship between eGFRDiff and functional status in these well-functioning community-living older adults.

Table 3. Association of eGFRDiff (eGFR$_{Cys}$ − eGFR$_{Cr}$) Group and Poor Functional Status (Lowest Quartile HABCPPB Score, ie, Score < 1.89)

	Negative eGFRDiff Group (≤−10 mL/min/1.73 m^2)		Reference Group	Positive eGFRDiff Group (>10 mL/min/1.73 m^2)	
Logistic Regression Models	**OR (95% CI)**	**P value**	**OR**	**OR (95% CI)**	**P value**
Cases/n	**163/446**		**373/1,565**	**175/959**	
Model 1	1.99 (1.54-2.56)	<0.001	1	0.72 (0.58-0.90)	<0.001
+ Thigh muscle area on CT	1.78 (1.37-2.31)	<0.001	1	0.79 (0.63-0.99)	<0.001
+ Thigh fat area on CT	1.97 (1.53-2.55)	<0.001	1	0.73 (0.59-0.91)	<0.001
+ Appendicular lean mass on DXA scan	1.97 (1.53-2.55)	<0.001	1	0.73 (0.58-0.90)	<0.001
+ Limb fat mass on CT	1.94 (1.50-2.51)	<0.001	1	0.74 (0.59-0.92)	<0.001
+ Fat free mass on DXA scan	1.96 (1.51-2.55)	<0.001	1	0.71 (0.57-0.89)	<0.001
+ Abdominal muscle area on CT	2.05 (1.58-2.66)	<0.001	1	0.72 (0.58-0.91)	<0.001
+ Total thigh muscle area + thigh fat area + appendicular lean mass + limb fat mass	1.68 (1.29-2.19)	<0.001	1	0.80 (0.64-1.00)	<0.001

Note: Model 1 = adjusted for age, sex, race, education, body mass index, serum albumin, C-reactive protein, smoking, hypertension, diabetes, chronic kidney disease category by eGFR$_{Cr}$, and study site. Abbreviations: CI, confidence interval; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; eGFR$_{Cr}$, creatinine-based estimated glomerular filtration rate; eGFR$_{Cys}$, cystatin C-based estimated glomerular filtration rate; eGFRDiff, difference between eGFR$_{Cys}$ and eGFR$_{Cr}$; HABCPPB, health, aging, and body composition study physical performance battery; OR, odds ratio.

Table 4. Association of eGFRDiff (eGFR$_{Cys}$ − eGFR$_{Cr}$) and Poor Functional Status (Lowest Quartile of HABCPPB Score, ie, Score ≤ 1.89)

	eGFRDiff (Per SD = 14 increment)	
Logistic Regression Models	**OR (95% CI)**	**P value**
Cases/N: 711/2,970		
Model 1	0.70 (0.63-0.77)	<0.001
+ Thigh muscle area on CT	0.75 (0.67-0.83)	<0.001
+ Thigh fat area on CT	0.70 (0.63-0.77)	<0.001
+ Appendicular lean mass on DXA scan	0.70 (0.63-0.78)	<0.001
+ Limb fat mass on CT	0.71 (0.64-0.78)	<0.001
+ Fat-free mass on DXA scan	0.69 (0.62-0.77)	<0.001
+ Abdominal muscle area on CT	0.69 (0.62-0.76)	<0.001
+ Total thigh muscle area + thigh fat area + appendicular lean mass + limb fat mass	0.77 (0.69-0.85)	<0.001

Note: Model 1 = adjusted for age, sex, race, education, body mass index, serum albumin, C-reactive protein, smoking, hypertension, diabetes, chronic kidney disease category by eGFR$_{Cr}$, and study site. Abbreviations: CI, confidence interval; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; eGFR$_{Cr}$, creatinine-based estimated glomerular filtration rate; eGFR$_{Cys}$, cystatin C-based estimated glomerular filtration rate; eGFRDiff, difference between eGFR$_{Cys}$ and eGFR$_{Cr}$; HABCPPB, health, aging, and body composition study physical performance battery; OR, odds ratio; SD, standard deviation.

There are several potential explanations for this unexpected finding. First, there might have been issues with the measurement of muscle quantity and quality that were not fully captured by our muscle mass and strength measurements, rendering the analyses subject to residual confounding. Muscle mass can be quantified using a variety of measures, whether it is volume or area that is being assessed using imaging or muscle function and strength assessed based on a clinical evaluation. Prior studies have examined the skeletal muscle index adjusted for height[15] or weight,[16] the measure of muscle mass, determined using DXA,[17] or bioimpedance.[18] It is unclear which measure best reflects muscle mass. We chose to present here the measure of muscle quantity, which had the strongest association with eGFRDiff and functional status, because it would, therefore, be most likely to capture mediating effects. This measure was the thigh muscle area, determined using the CT scan, which is relevant to the functional status outcome assessed based on the HABCPPB score. Nonetheless, all these imaging modalities provide static views of muscle mass or volume, and they do not capture the dynamic muscle activity that leads to creatinine generation. One potential explanation for our findings is that creatinine production (and thus excretion) may be related to muscle function or daily activity rather than to muscle quantity; this might not be well captured by CT or DXA measures.

Second, it might be that there were other determinants of eGFRDiff because of other intrinsic differences between the markers in the older adults that came into play. Indeed, cystatin C has been described as a biomarker of aging because it reliably reflects kidney function, which is a critical determinant of health outcomes in older adults.[19] Higher cystatin C levels have been associated with worse physical disabilities and comorbidities among the elderly population,[20] even within a range of relatively normal kidney function. In our study, the participants in the negative-eGFRDiff group (ie, with higher cystatin C levels) tended to be older and perform more poorly on the HABCPPB.

Table 5. Association Between eGFRDiff (eGFR$_{Cys}$ − eGFR$_{Cr}$) With Thigh Muscle Area (cm^2) on Computed Tomography Scan, Stratified by Race

	White Participants (N = 1,744)		Black Participants (N = 1,226)	
Exposure	**β (95% CI)[a]**	**P value**	**β (95% CI)[a]**	**P value**
eGFRDiff (per SD = 14 increments)	6.0 (4.7 to 7.2)	<0.001	9.2 (7.4 to 11.0)	<0.001
Negative eGFRDiff group (≤−10 mL/min/1.73 m^2)	−10.1 (−13.6 to −6.6) n = 258	<0.001	−19.3 (−24.5 to −14.2) n = 188	<0.001
Reference eGFRDiff group (−10 < eGFRDiff ≤ 10 mL/min/1.73 m^2)	0 (ref) n = 931		0 (ref) n = 634	
Positive eGFRDiff group (>10 mL/min/1.73 m^2)	7.4 (4.7 to 10.1) n = 555	<0.001	9.7 (5.7 to 13.7) n = 404	0.001
	Mean thigh muscle area		Mean thigh muscle area	
	214.3 ± 53.9		234.9 ± 55.7	

Abbreviations: CI, confidence interval; eGFR$_{Cr}$, creatinine-based estimated glomerular filtration rate; eGFR$_{Cys}$, cystatin C-based estimated glomerular filtration rate; eGFRDiff, difference between eGFR$_{Cys}$ and eGFR$_{Cr}$; ref, reference.
[a]Adjusted for age, sex, education, body mass index, serum albumin, C-reactive protein, smoking, hypertension, diabetes, chronic kidney disease category by eGFR$_{Cr}$, and study site.

Close to half of the study population (1,405/2,970; 47.3%) had a discrepancy between eGFR$_{Cys}$ and eGFR$_{Cr}$ of ≥10 mL/min/1.73 m^2 in either direction. This is consistent with the findings of our previous work in other cohorts.[6,7] The present study aimed at understanding the determinants of this difference. We hypothesized that muscle quantity would account for the association between eGFRDiff and poor functional status, and we were surprised to find that this was not the case. The HABC study comprises well-functioning older adults. It is possible that our results would have been different in athletes or young healthy adults, who may have higher muscle function,[21] or in malnourished patients with cancer or critically ill hospitalized patients, who may have muscle wasting[22] and decreased function. Future studies are needed to better understand the determinants of this difference in various populations with different muscle quantity and function. Nonetheless, we confirmed that eGFRDiff is clinically relevant and provides information in terms of functional status.

This study has several strengths. This HABC study included a large sample of elderly participants who were independent and well-functioning at the baseline and were able to walk without difficulty. This age group reflects a population at high risk of functional decline and sarcopenia. The HABC cohort provided various objective measures of muscle quantity, including quantification using imaging (CT and DXA scans), as well as clinical evaluations of muscle strength, which allowed for a relatively comprehensive assessment of our research question. We recognize that body composition is influenced by sex and race, and we found that the association between eGFRDiff and thigh muscle area was not consistent across these groups. However, when we stratified the population by race, we found similar directions of results in either race, and the associations appeared stronger in the Black participants than in the White participants.

One limitation of this study is that the functional status outcome evaluated here is specific to the HABC dataset and has not been widely used in other studies. It assessed muscle function of the lower extremities exclusively. However, our results were similar whether we defined "poor functional status" as the lowest decile, lowest quartile, or lowest 30% of the HABCPPB score. The HABCPPB score was missing for <4% of the population across the eGFRDiff groups, and similar results were found when participants with missing HABCPPB scores were excluded from the analyses. Second, muscle area, determined using imaging, is a static measure that does not capture dynamic muscle turnover. Third, we did not have timed collections of urine creatinine, which would have been a more direct proxy of creatinine production, and we did not have the measured glomerular filtration rate to compare these estimates with; we adjusted our models for chronic kidney disease category using eGFR$_{Cr}$, which remains the marker of choice of kidney function in clinical practice.

In conclusion, this study confirmed previous findings that the difference between eGFR based on cystatin C and that based on creatinine is clinically relevant and strongly associated with poor functional performance in well-functioning community-living older adults. We demonstrated here that lower eGFRDiff is also strongly associated with lower muscle quantity and muscle strength. Despite eGFRDiff being associated with lower muscle area, low muscle mass did not meaningfully attenuate the relationship of eGFRDiff with functional status. Future studies are needed to better understand the determinants of this difference to understand the mechanisms responsible for its strong and consistent relationship with frailty, mortality, and other clinical outcomes.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Table S1: Using the new 2021 creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation, the association between eGFRDiff$_{New2021}$ (A) and eGFRDiff$_{New2021}$ groups (B) with thigh muscle area, determined using CT scan, stratified by race, was determined.

Table S2: Using the new 2021 creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation, the association between eGFRDiff$_{New2021}$ with poor functional status, stratified by race (the lowest quartile of the health, aging, and body composition study physical performance battery score is ≤1.66 for Black participants and ≤2.05 for White participants), was determined.

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Is eGFRDiff associated with muscle quantity and functional status in older adults?

Kidney Medicine

Health, Ageing, Body & Composition study (HABC)

n = 2970

Calculated eGFRDiff
(eGFR$_{Cys}$ – eGFR$_{Cr}$)

Outcomes

Total thigh muscle area using CT

Physical performance battery scored *(HABCPPB)*

Results

Mean

Age
74 (±3) years

eGFR$_{Cys}$ **72 (±18)** mL/min/1.73m^2

eGFR$_{Cr}$ **68 (±15)** mL/min/1.73m^2

eGFRDiff **4 (±14)** mL/min/1.73m^2

	Negative eGFRDiff ≤ -10 n = 446	Reference -10 < eGFRDiff ≤ +10 n = 1565	Positive eGFRDiff > 10 n = 959
Diabetes	19%	16%	11%
Hypertension	55%	53%	47%
6 meter gait speed (SD) m/s	1.12 (0.24)	1.17 (0.23)	1.22 (0.23)
Thigh muscle area (SD) cm^2	214 (52)	224 (55)	225 (57)
Poor functional status	38%	25%	19%

Conclusion: The difference eGFR$_{Cys}$ - eGFR$_{Cr}$ provides information on older adults' functional status, which is only partially explained by muscle quantity and quality.

Reference: Potok A, Ix JH, Shlipak MG et al. Cystatin C and creatinine-based glomerular filtration rate estimation differences and muscle quantity and functional status in older adults - the HABC study. *Kidney Medicine*, 2022

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