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Research Article

The Importance of Muscle Versus Fat Mass in Sarcopenic Obesity: A Re-evaluation Using D3-Creatine Muscle Mass Versus DXA Lean Mass Measurements

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Abstract

Background: The combination of sarcopenia and obesity has been associated with physical impairment in older people. However, previous research has relied on assessments of lean mass as a surrogate for muscle mass. We postulate that inaccurate measures of muscle mass may have obscured the role of obesity in sarcopenia and related outcomes. Our aim was to clarify the interactions of muscle and fat with physical performance and adverse outcomes using an accurate measure of muscle mass.

Methods: In a longitudinal study of >1,300 older men (mean age 84 years), we compared a direct measurement of muscle mass (D_3 creatine dilution; D_3Cr) with an approximation of muscle mass (appendicular lean mass [ALM] by dual-energy x-ray absorptiometry [DXA]) and their associations with measures of physical performance (gait speed, chair stand time) and adverse outcomes (incident injurious falls and mobility problems). We measured percent fat mass by DXA.

Results: Low D_3Cr muscle mass was strongly associated with decreased performance and increased risk of adverse outcomes. Increased fat mass had little association after accounting for D_3Cr muscle mass. In contrast, DXA ALM was minimally associated with performance or adverse outcomes, and fatness remained associated with both outcomes after accounting for DXA ALM.

Conclusions: When an accurate assessment of muscle mass (rather than lean mass) is used, reduced muscle mass is highly associated with important outcomes and the negative effects of adiposity are minimal, suggesting that obesity has little relevance for the understanding of important adverse health outcomes of sarcopenia in older men.

Keywords: Sarcopenia, Aging, Disability

The loss of muscle mass (sarcopenia) and the loss of muscle function (dynapenia) result in a major public health problem in the geriatric population (1,2). In fact, muscle mass and strength progressively decline with age while fat mass increases. Each of these trends appears to have adverse health consequences, but the combination (sarcopenic obesity) has been proposed as a particularly strong risk factor for declines in physical performance, increased fall risk, disability and mortality (3), and has been postulated to be a major health problem (4). However, while fat mass can be accurately and precisely measured with dual-energy x-ray absorptiometry (DXA), the measurement of muscle mass has been more challenging. Some methods (total body water, bioelectric impedance, DXA) assess lean mass, which includes not only muscle mass but also soft tissues such as vascular, fibrotic, and connective tissue, as well as organ weight and water (5). DXA appendicular lean mass (ALM), or the lean mass in the arms and legs, has been thought to better approximate muscle mass than total body

lean mass, and is often standardized to height (eg, DXA ALM/ht^2). In studies of lean and fat mass, Baumgartner (6) used DXA ALM/ht^2 measurements to propose a definition of sarcopenic obesity; specifically, when DXA ALM/ht^2 is lower than –2 *SD* of that obtained in a healthy population, and the percent of fat mass (also measured by DXA) is greater than the median of a sex-matched population. That approach has been adapted in many subsequent studies of sarcopenic obesity (4). Because studies measuring lean mass do not accurately quantify muscle (7), it has not been possible to adequately evaluate the independent roles of muscle and fat in sarcopenic obesity as risk factors for adverse health conditions in older people.

Muscle mass can now be directly measured using the D_3-creatine dilution method (8,9) which is conceptually rigorous and well validated in both animal and human studies (7). For instance, in humans, muscle mass determined by the D_3-creatine dilution method is highly correlated to muscle mass measures by MRI (10). To account for body size, total muscle mass is standardized to body weight (D_3Cr muscle mass/weight [wgt]). We have recently confirmed the association of low D_3Cr muscle mass/wgt prospectively with reduced strength, impaired physical performance, increased functional limitations, and increased risk of incident falls and mobility limitation (11). These associations were much stronger than those with DXA lean mass. This work raised the possibility that DXA-based evaluations of the relationships between obesity, sarcopenia, and important clinical outcomes are misleading.

We previously described strong associations between D_3Cr muscle mass measures with physical performance, mobility limitations, and injurious falls in a large, prospective cohort of older men (MrOS) (12). Here, we build on those results to re-examine the issue of sarcopenic obesity. By using an accurate measure of muscle mass (D_3Cr dilution), we aimed to better disentangle the independent and joint associations of muscle mass and fat on physical performance, mobility limitations, and injurious falls, and furthermore to contrast these associations when muscle mass is assessed by D_3Cr dilution versus DXA-derived measures of lean mass.

Methods

MrOS Cohort and Study Sample

In 2000–2002, 5,994 ambulatory community-dwelling men aged ≥65 and older without bilateral hip replacements were enrolled in MrOS, a multicenter cohort study (13,14). The study was approved by the Institutional Review Board at each center and all participants provided informed consent. In 2014–2016, 2,786 survivors were contacted; 1,841 participated in a clinic visit; and 1,641 agreed to the D_3Cr dilution protocol. Of these, 187 were excluded for incorrect completion of the protocol. Six samples were lost and 23 men were excluded because of outlying values for D_3Cr muscle mass/wgt. Further, 49 were missing either outcome or DXA variables. Thus, the main analysis sample was 1,376 men; for the incident mobility problem outcome, the sample was limited to those without prevalent mobility problems (*N* = 1,065).

D_3Cr Dilution Method to Estimate Muscle Mass

As described previously (15), the method involves ingesting a 30-mg dose of stable isotope labeled creatine (D_3Cr), and providing a fasting, morning urine sample 3–6 days later in which D_3-creatinine, unlabeled creatinine and creatine are measured using HPLC and MS/MS; these measures are then included in an algorithm to determine total body creatine pool size and thus skeletal muscle mass.

Dual-Energy X-Ray Absorptiometry

Total body lean mass, ALM, body fat, and bone mineral content were assessed by whole-body DXA scans (Hologic 4500 scanners, Waltham, MA) (16).

Physical Performance and Incident Falls and Mobility Problems

Gait speed at usual pace was measured over a 6-m course using the average of two trials (m/s) and time to complete five repeated chair stands was assessed (17). During follow-up, MrOS participants answered tri-annual questionnaires about falls and difficulty walking 2–3 blocks or climbing 10 stairs in the preceding 4 months. We used the three questionnaires that followed the participant's Year 10.5 clinic date to define incident falls and mobility problems (11). Injurious falls were classified as a fall injury for which the participant reported visiting a doctor or other health care provider (versus no falls or a fall which did result in medical attention). We defined mobility problems as any new self-reported difficulty walking 2–3 blocks or climbing 10 steps in the year after the visit.

Statistical Approach

We compared characteristics of participants across quartiles of D_3Cr muscle mass/wgt and ALM/Ht^2, using analysis of variance (ANOVA), Wilcoxon tests and chi-square tests as appropriate. Beta coefficients from linear regression models describe the relationship between D_3Cr muscle mass/wgt or ALM/ht^2 (as independent variables in separate models) and physical performance measures (gait speed and chair stands). Models are presented as unadjusted, and adjusted for % fat (as a continuous variable). We also ran unadjusted models that were stratified by quartile of % fat (high: Q4: ≥ 31.86%, low Q1–3: < 31.86%). Interaction *p*-values are presented from separate models that use these variables continuously. Finally, we report the association of percent fat with the performance outcomes (per *SD* increment in percent fat) in unadjusted models; models adjusted for D_3Cr muscle mass/wgt or DXA ALM/ht^2; and unadjusted models stratified by D_3Cr muscle mass/wgt or DXA ALM/ht^2.

Logistic regression was used to estimate the likelihood of incident falls and mobility problems. D_3Cr muscle mass/wgt and ALM/ht^2 by DXA were analyzed as quartiles using the highest quartile as the referent group. We adjusted for age, and then age and % fat. Figure 2 presents a bar chart of mean values in physical performance by quartiles. We used a two-way ANOVA to compare physical performance measures across quartiles of % fat and either D_3Cr muscle mass/wgt or ALM/ht^2. Figure 3 presents odds ratios of mobility limitation and Injurious falls by sarcopenic groups defined using four mutually exclusive combinations of D_3Cr muscle mass/wgt and ALM/ht^2 with percent fat (eg, high fat/low muscle, high fat/high muscle, etc.).

Results

Measurements were available in 1,376 men. The mean age was 84.2 ± 4.1 years, BMI was 26.8 ± 3.6 kg/M^2 (17.5% was ≥ 30), and 90% were Caucasian. DXA ALM/ht^2 was 7.55 ± 0.9 kg/M^2, and D_3Cr muscle mass/wgt was 31 ± 5%. Participant characteristics by categories of D_3-creatine muscle mass (D_3Cr) and adiposity are in Table 1 and by categories of lean mass (DXA) and adiposity are in Supplementary Table 1.

DXA ALM and D_3-Creatine Muscle Mass Are Not Equivalent

The DXA-based body composition measures and D_3Cr muscle mass measurements (as proportions of body weight) are shown graphically

Table 1. Participant Characteristics by: D_3Cr Muscle Mass/wgt and Obesity Status (percent fat)

	Not Low D_3Cr Muscle Mass, Not Obese (*N* = 887)	Low D_3Cr Muscle Mass, Not Obese (*N* = 148)	Not Low D_3Cr Muscle Mass, Obese (*N* = 153)	Low D_3Cr Muscle Mass, Obese (*N* = 188)	Overall (*N* = 1,376)	*p* Value
Age in years, mean (*SD*)	83.8 (4.0)	86.9 (4.2)	83 (3.1)	84.5 (3.9)	84.2 (4.0)	<.001
Age category						<.001
Age <80, *n* (%)	84 (9.5)	3 (2.0)	18 (11.8)	13 (6.9)	118 (8.6)	
Age 80–84, *n* (%)	475 (53.6)	45 (30.4)	91 (59.5)	90 (47.9)	701 (50.9)	
Age 85–89, *n* (%)	240 (27.1)	59 (39.9)	39 (25.5)	64 (34)	402 (29.2)	
Age >90, *n* (%)	88 (9.9)	41 (27.7)	5 (3.3)	21 (11.2)	155 (11.3)	
Race						.122
White, *n* (%)	787 (88.7)	137 (92.6)	138 (90.2)	177 (94.1)	1239 (90.0)	
African American, *n* (%)	23 (2.6)	1 (0.7)	6 (3.9)	3 (1.6)	33 (2.4)	
Asian, *n* (%)	39 (4.4)	5 (3.4)	2 (1.3)	1 (0.5)	47 (3.4)	
Hispanic, *n* (%)	26 (2.9)	3 (2.0)	4 (2.6)	2 (1.1)	35 (2.5)	
Other, *n* (%)	12 (1.4)	2 (1.4)	3 (2.0)	5 (2.7)	22 (1.6)	
BMI, mean (*SD*)	25.5 (2.8)	26.6 (3)	29.5 (3)	30.9 (3.7)	26.8 (3.6)	<.001
BMI ≥30, *n* (%)	57 (6.4)	19 (12.8)	61 (39.9)	101 (53.7)	238 (17.3)	<.001
Walking Speed (m/s)	1.2 (0.2)	1 (0.3)	1.1 (0.2)	1 (0.3)	1.1 (0.3)	<.001
Walking Speed ≤0.8 m/s, *n* (%)	49 (5.6)	33 (22.8)	9 (6.0)	45 (24.2)	136 (10.0)	<.001
Incident Fall Injury, *N* (%)	80 (9.0)	26 (17.6)	10 (6.5)	28 (14.9)	144 (10.5)	<.001
ALM (kg), mean (*SD*)	22.3 (3.0)	22.2 (3.1)	22.4 (3.0)	23 (3.6)	22.4 (3.1)	.042
D_3Cr muscle mass (kg), mean (*SD*)	24.9 (3.8)	19.8 (2.9)	26.2 (3.5)	22.3 (3.7)	24.1 (4.1)	<.001
D_3Cr Muscle Mass/wgt, mean (*SD*)	0.33 (0.04)	0.25 (0.02)	0.30 (0.02)	0.24 (0.02)	0.31 (0.05)	<.001
ALM/ht² (kg/m²), mean (*SD*)	7.5 (0.8)	7.4 (0.9)	7.6 (0.9)	7.7 (1.0)	7.6 (0.9)	.037

Notes: Low muscle mass defined using lowest quartile of D3Cr muscle mass/wgt: Q1 < 0.27. Obesity defined using highest quartile of percent body fat, Q4 ≥ 31.86%. ALM = appendicular lean mass; BMI = appendicular lean mass; wgt = weight.

in Figure 1. D_3Cr muscle mass in the 1,376 men is ranked from highest (left) to lowest (right), with each individual's corresponding DXA measures of bone mineral mass, fat mass, total lean mass, and ALM. Several patterns are apparent. First, DXA bone mineral mass is a minor component of body composition. Second, the proportion of weight that is DXA total lean mass is, as expected, considerably larger than the proportion that is D_3Cr muscle mass. Although the proportions of lean mass and D_3Cr muscle mass are correlated, there is considerable variation between them (r^2 = .46). Third, ALM is not equivalent to D_3Cr muscle mass.

D_3Cr Muscle Mass/wgt and DXA ALM/ht² Have Different Relationships to %Fat.

As reported (11), men with higher fat mass tended to have higher D_3Cr muscle mass (r = 0.24, p < .001) and also tended to have higher ALM (r = .40, p < .001). However, the muscle mass proportion by D_3Cr (D_3Cr muscle mass/wgt) was negatively correlated with % fat (r = –.59, p < .001) while DXA ALM/ht² and % fat were not related (r = .02, p = .38).

Associations of Physical Performance with Fat Mass and D_3Cr Muscle Mass or DXA Lean Mass

There were strong associations between low D_3Cr muscle mass and poor physical performance that were essentially independent of adiposity, while DXA ALM/ht² was weakly if at all associated with physical performance and in those models adiposity retained a significant effect. Figure 2 illustrates these associations when body composition measures are in quartiles. Lower D_3Cr muscle mass/wgt was independently associated with lower walking speed and shorter chair stand time, but there was no independent effect of fat (walking speed) or the effect was weak (chair stand time). Lower DXA ALM/

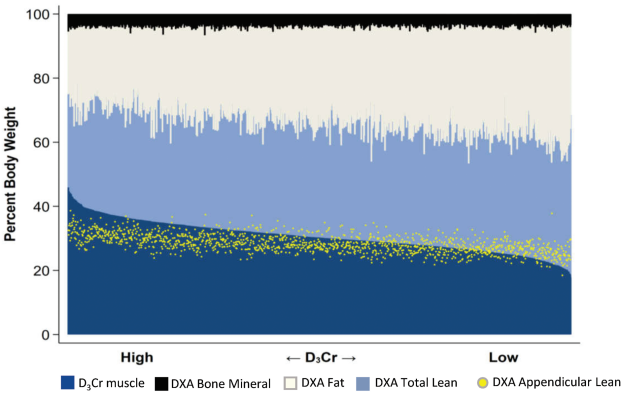

Figure 1. Comparison of components of body composition, each as a percent of body weight, in 1,376 older men. In combination, the three-compartment DXA measures of bone mineral, fat and total lean equal 100%. Superimposed are the measures of D_3Cr muscle and DXA ALM. The men are ranked with those with highest D_3Cr on the left and lowest on the right. ALM = appendicular lean mass; DXA = dual-energy x-ray absorptiometry. Full color version is available within the online issue.

ht² was associated with lower chair stand time but not with walking speed, and percent fat was associated with an independent, deleterious effect on physical performance. The interactions between percent fat and DXA ALM/ht² were not significant, but the slowest chair stand time was in men with highest percent fat and lowest D_3Cr muscle mass/wgt. The relationships were not different when analyses were done using ALM/BMI rather than ALM/ht².

Adjustment for adiposity, or stratification by % fat (quartiles 1–3 vs quartile 4), in analyses of physical performance revealed the same patterns (Table 2). Each 1 *SD* decrement in D_3Cr muscle mass/wgt was associated with both slower walking speed (–0.11 m/s) and slower chair stands (0.34/10 seconds). Adjustment for percent fat had little impact. Also, when stratified by percent fat, the association between D_3Cr muscle mass/wgt and chair stands was minimally but significantly stronger for those in the higher fat group (interaction p = –.033). In contrast, there was no association between ALM/ht² and walking speed. After adjustment for fat, ALM/ht² was minimally associated with walking speed. Stratification by percent fat showed no significant association between ALM/ht² and walking speed in either the high fat or low fat group. Lower ALM/ht² was associated with worse chair stand time, remained significant after adjustment for fat, and stratification by percent fat did not significantly alter the association. These results were similar when D_3Cr muscle mass/ht² was substituted for D_3Cr muscle mass/wgt, when ALM/wgt was substituted for ALM/ht², or when ALM and D_3Cr muscle mass were used without body size adjustment.

Moreover, adiposity had little effect on measures of physical performance after adjustment for D_3Cr muscle mass/wgt but remained important in models using ALM/ht². Higher percent fat was associated with slower walking speed and chair stands in unadjusted models (Supplementary Table 2) but these associations were no longer significant with adjustment for D_3Cr muscle mass/wgt. In contrast, associations between percent fat and slower walking speed and chair stands were essentially unchanged and remained significant after adjustment for ALM/ht². In stratified models, there was a slight association between percent fat and slower walking speed in those with low D_3Cr muscle mass/wgt but the interaction was not significant. The association between percent fat and chair stand time was slightly stronger in those with high (vs low) D_3Cr muscle mass (interaction p value = .030). In models stratified by ALM/ht², however, higher percent fat was associated with slower walking speed and chair stands in both strata of lean mass in a similar direction (p for interaction > .05).

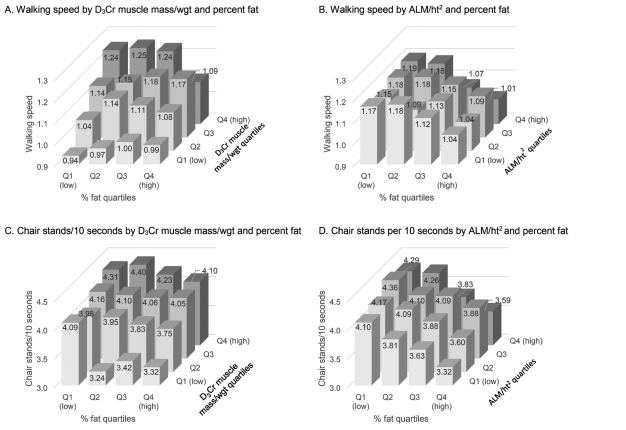

Figure 2. The associations between physical performance measures and D_3Cr muscle mass or ALM. All models are adjusted for age. ALM = appendicular lean mass. (**A**) Mean walking speed by quartiles of D_3Cr muscle mass/wgt and %fat. Interaction p-value derived from a model with continuous fat, D_3Cr muscle mass/wgt and an interaction term. Fat quartile cut points: Q1<23.84, Q2 23.84–<27.82, Q3 27.82–<31.86, Q4≥ 31.86. D_3Cr muscle mass/wgt Quartile Cut points: Q1<0.27, Q2 0.27–<0.30, Q3 0.30–<0.34, Q4≥0.34. (**B**) Mean walking speed by quartiles of ALM/ht² and %fat. Interaction p-value derived from a model with continuous fat, ALM/ht², and an interaction term. Fat quartile cut points: Q1<23.84, Q2 23.84–<27.82, Q3 27.82–<31.86, Q4≥31.86. ALM/ht² Quartile cut points: Q1<6.93, Q2 6.93–<7.49, Q3 7.49–<8.11, Q4≥8.11. (**C**) Mean number of chair stands per 10 s by quartiles of D_3Cr muscle mass/wgt and %fat. Interaction p-value derived from a model with continuous fat, D_3Cr muscle mass/wgt and an interaction term. Fat quartile cut points: Q1<23.84, Q2 23.84–<27.82, Q3 27.82–<31.86, Q4≥ 31.86. D_3Cr muscle mass/wgt quartile cut points: Q1<0.27, Q2 0.27–<0.30, Q3 0.30–<0.34, Q4≥0.34. (**D**) Mean number of chair stands per 10 seconds by quartiles of ALM/ht² and %fat. Interaction p-value derived from a model with continuous fat, ALM/ht² and an interaction term. Fat quartile cut points: Q1<23.84, Q2 23.84–<27.82, Q3 27.82–<31.86, Q4≥31.86. ALM/ht² quartile cut points: Q1<6.93, Q2 6.93–<7.49, Q3 7.49–<8.11, Q4≥8.11. ALM = appendicular lean mass; wgt = weight.

Associations of Mobility Limitation and Injurious Falls with Fat Mass and D_3Cr Muscle Mass or DXA ALM/ht²

In models adjusted for age, men in the lowest quartile of D_3Cr muscle mass/wgt were 2.7-fold more likely to experience an incident injurious fall, 9.8-fold more likely to have a prevalent mobility limitation, and 2.7-fold more likely to experience incident mobility limitation (Table 3). Adjustment for percent fat did not substantially change these associations. In contrast, in models adjusted for age, ALM/ht² was not associated with incident injurious falls or mobility limitation, and further adjustment for percent fat had little effect on

Table 2. Association (beta coefficient) for D_3Cr Muscle Mass/wgt, DXA ALM/ht² and Physical Performance, with Adjustment or Stratification by Percent Fat

	D_3Cr muscle mass/wgt		ALM/ht²	
	Walking speed	Chair stands/10 s	Walking speed	Chair stands/10 s
Unadjusted	–0.10 (–0.11, –0.09)	–0.34 (–0.39, –0.28)	–0.001 (–0.015, 0.012)	–0.11 (–0.16, –0.05)
Adjusted for % fat	–0.11 (–0.12, –0.09)	–0.32 (–0.39, –0.25)	–0.003 (–0.016, 0.010)	–0.11 (–0.17, –0.06)
Stratified models				
High % fat (quartile 4: ≥ 31.86)	–0.08 (–0.11, –0.06)	–0.30 (–0.44, –0.17)	–0.001 (–0.027, 0.025)	–0.12 (–.26, 0.01)
Low % fat (quartiles 1–3: <31.86)	–0.09 (–0.10, –0.07)	–0.28 (–0.34, –0.22)	–0.005 (–0.020, 0.010)	–0.12 (–0.18, –0.06)
p-interaction	.151	.033	.848	.709

Note: Reported per *SD* increment: D_3Cr muscle mass/wgt: –0.05, percent body fat: 5.9%, ALM/ht²: –0.87. ALM = appendicular lean mass; wgt = weight.

Table 3. Association (odds ratio) for D_3Cr Muscle Mass/wgt or DXA ALM/ht^2 with Prevalent and Incident Mobility Limitations or Incident Injurious Falls, with Adjustment by Percent Fat

	D_3Cr Muscle Mass/wgt					
	Incident Injurious fall		Prevalent Mobility Limitation		Incident Mobility Limitation*	
	Age-adjusted	+ % fat	Age-adjusted	+ % fat	Age-adjusted	+ % fat
Quartile 1 D_3Cr muscle mass/wgt (low)	2.7 (1.5, 4.7)	4.1 (2.1, 7.9)	9.8 (6.1, 15.7)	7.8 (4.5, 13.5)	2.7 (1.8, 4.0)	2.0 (1.2, 3.1)
Quartile 2 D_3Cr muscle mass/wgt	1.4 (0.8, 2.6)	1.9 (1.0, 3.7)	3.3 (2.0, 5.4)	2.9 (1.7, 4.8)	1.9 (1.3, 2.8)	1.6 (1.0, 2.4)
Quartile 3 D_3Cr muscle mass/wgt	2.0 (1.1, 3.5)	2.3 (1. 35, 4.1)	2.0 (1.2, 3.3)	1.8 (1.0, 3.0)	1.3 (0.9, 1.9)	1.1 (0. 85, 1.7)
Quartile 4 D_3Cr muscle mass/wgt (high)	1.00 referent	1.00 referent	1.00 referent	1.00 referent	1.00 referent	1.00 referent
p trend	.003	<.001	<.001	<.001	<.001	<.001
	ALM/ht^2					
	Incident Injurious fall		Prevalent Mobility limitation		Incident Mobility Limitation	
	Age-adjusted	+ % fat	Age-adjusted	+ % fat	Age-adjusted	+ % fat
Quartile 1 ALM/ht^2 (low)	1.0 (0.6, 1.8)	1.0 (0.6, 1.8)	0.5 (0.4, 0.7)	0.5 (0.3, 0.7)	0.8 (0.5, 1.1)	0.7 (0.5, 1.1)
Quartile 2 ALM/ht^2	1.2 (0.7, 2.0)	1.2 (0.7, 2.0)	0.6 (0.4, 0.9)	0.6 (0.4, 0.8)	0.8 (0.5, 1.1)	0.8 (0.5, 1.1)
Quartile 3 ALM/ht^2	1.4 (0.8, 2.2)	1.4 (0.8, 2.2)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	0.9 (0.6, 1.3)	0.9 (0.6, 1.2)
Quartile 4 ALM/ht^2 (high)	1.00 referent	1.00 referent	1.00 referent	1.00 referent	1.00 referent	1.00 referent
p trend	.926	.926	<.001	<.001	.125	.093

Note: ALM = appendicular lean mass; wgt = weight.

*Because the number of men with follow-up for incident mobility limitation (N = 1,065) is different than for prevalent mobility limitation (N = 1,376) the quartile limits are slightly different. D_3Cr muscle mass/wgt Prevalent Quartile cut points: Q1<0.27, Q2 0.27-<0.30, Q3 0.30-<0.34, Q4 ≥ 0.34. D_3Cr muscle mass/wgt Incident Quartile cut points: Q1<0.28, Q2 0.28-<0.31, Q3 0.31-<0.35, Q4 ≥ 0.35 ALM/ht^2 Prevalent Quartile cut points: Q1<6.93, Q2 6.93-<7.49, Q3 7.49-<8.11, Q4 ≥ 8.11. ALM/ht^2 Incident Quartile cut points: <6.93, Q2 6.93-<7.47, Q3 7.47-<8.04., Q4 ≥ 8.04.

this null association. Moreover, men in the lower quartile of ALM/ht^2 were significantly *less* likely to have prevalent mobility limitation, and adjustment for percent fat did not change this association.

Those with both lower D_3Cr muscle mass/wgt and higher percent fat were more likely to have prevalent mobility limitation and to experience mobility limitation during follow-up, but there was not a significant interaction in the effects of muscle mass and adiposity (Figure 3). In contrast, the associations between ALM/ht^2 with prevalent or subsequent mobility limitation were small, and higher %fat was highly significant. The likelihood of injurious fall was also higher in men with lower D_3Cr muscle mass/wgt while there was little difference by fat category. However, those with higher and lower DXA ALM/ht^2 had a comparable likelihood of injurious falls, there was little difference in categories of percent fat. In age-adjusted models, percent fat was not significantly associated with incident injurious falls (Supplementary Table 4). Further adjustment for D_3Cr muscle mass/wgt or ALM/ht^2 resulted in a *lower* likelihood of injurious falls for those with higher fat. Men in the highest quartile of percent fat had a higher likelihood of prevalent and incident mobility limitation. After further adjustment for D_3Cr muscle mass/wgt, the association between percent fat and prevalent mobility limitation was no longer significant, while the association with incident mobility limitation remained significant but was attenuated. After adjustment for age and ALM/ht^2, the associations of high percent fat with increased likelihood of prevalent and incident mobility limitation remained unchanged. These results were similar when ALM/BMI was considered in place of ALM/ht^2.

Discussion

Our major finding is that muscle mass measured by D_3Cr dilution is strongly and independently associated with physical performance and risk of injurious falls or mobility limitation, and that the degree of body fatness has little influence on these outcomes once D_3Cr muscle mass is considered. Thus, in older men, the clinical importance of "sarcopenic obesity"—the combined effect of muscle and fat on adverse physical outcomes—is minimal when muscle mass is accurately measured with D_3Cr dilution. On the other hand, an approximation of muscle mass, DXA ALM/ht^2, had little independent effect on measures of physical function or incident adverse events, and fatness remained an important contributor after accounting for DXA ALM.

We previously reported that muscle mass measured by D_3Cr dilution is robustly associated with physical performance and incident mobility limitation and injurious falls. We reasoned that those novel results could be very relevant for the evaluation of the relative contributions of muscle mass and fatness to those outcomes, and hence, for the understanding of sarcopenic obesity. On the basis of other estimates of muscle mass, it has been previously postulated that lower muscle mass and increased fatness both contributed substantially to adverse outcomes in older adults. In fact, we found that when muscle mass is assessed with D_3Cr dilution the influence of overall fatness on physical performance and incident outcomes is very small while muscle mass retains strong associations. These results provide a new framework for considering sarcopenic obesity in which reduced muscle mass plays a dominant role in determining the degree of physical impairment and the risk of related adverse outcomes such as injurious falls and mobility limitation. The contribution of obesity to other health consequences that have been attributed to sarcopenic obesity, such as cardiometabolic syndromes (18), may be greater, and the influence of specific fat compartments, such as muscle fat infiltration (19), might be important in addition to the mass of muscle itself.

Our findings (Figure 1) demonstrate that measurement of muscle mass with D_3Cr dilution and its relationship to adiposity are fundamentally different from muscle mass approximated by DXA ALM. As we have previously reported (11) total lean mass is only moderately

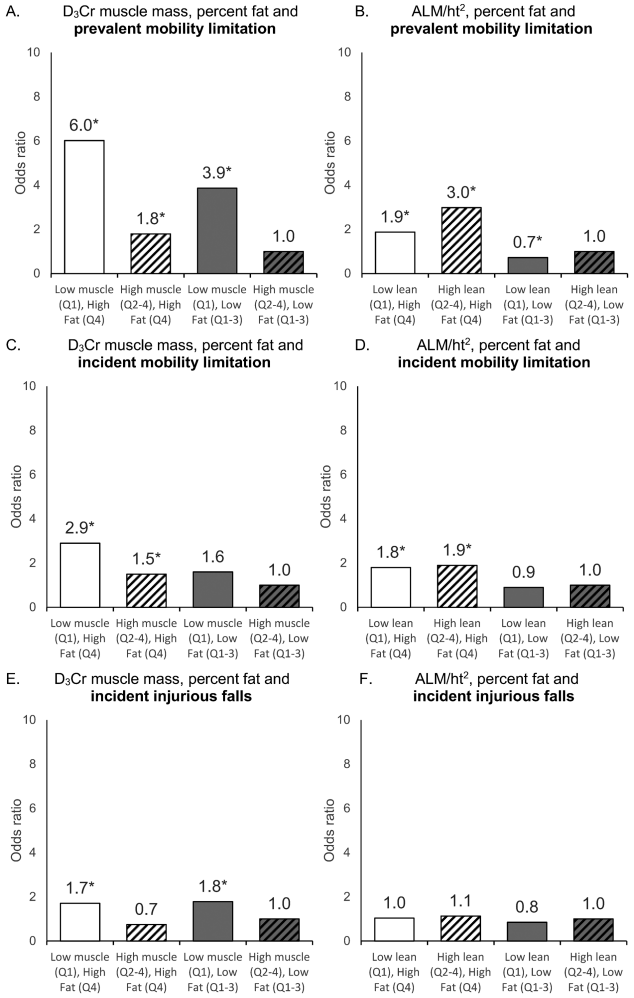

Figure 3. The likelihood of mobility limitation and injurious falls by fat categories and D_3Cr muscle mass or ALM. Men are stratified into higher and lower percent fat (Quartile 4 vs Quartiles 1–3) and either higher or lower D_3Cr muscle mass/wgt or high or low ALM/ht^2 (Quartile 1 vs Quartiles 2–4). * Significant at $p <$ .05 against reference group. (**A**) Likelihood of prevalent mobility limitation by muscle and fat groups using quartiles of D_3Cr muscle mass/wgt and %fat. Interaction *p*-value derived from a model with continuous fat, D_3Cr muscle mass/wgt and an interaction term. Fat quartile cut points: High Q4≥ 31.86, Low Q1–3 <31.86. D_3Cr muscle mass/wgt quartile cut points: High Q2–4≥0.27, Low Q1<0.27. (**B**) Likelihood of prevalent mobility limitation by lean and fat groups using quartiles of ALM/ht^2 and %fat. Interaction *p*-value derived from a model with continuous fat, ALM/ht^2 and an interaction term. Fat quartile cut points: High Q4≥ 31.86, Low Q1–3 <31.86. ALM/ht^2 quartile cut points: High Q2–4≥6.93, Low Q1<6.93. (**C**) Likelihood of incident mobility limitation by muscle and fat groups using quartiles of D_3Cr muscle mass/wgt and %fat. Interaction *p*-value derived from a model with continuous fat, D_3Cr muscle mass/wgt and an interaction term. Fat quartile cut points: High Q4≥31.00, Low Q1–3<31.00. D_3Cr muscle mass/wgt quartile cut points: High Q2–4≥0.28, Low Q1<0.28. (**D**) Likelihood of incident mobility limitation by lean and fat groups using quartiles of ALM/ht^2 and %fat. Interaction *p*-value derived from a model with continuous fat, ALM/ht^2 and an interaction term. Fat quartile cut points: High Q4≥31.00, Low Q1–3<31.00. ALM/ht^2 quartile cut points: High Q2–4 ≥6.93, Low Q1<6.93. (**E**) Likelihood of incident injurious falls by muscle and fat groups using quartiles of D_3Cr/wgt and %fat. Interaction *p*-value derived from a model with continuous fat, D_3Cr muscle mass/wgt and an interaction term. Fat quartile cut points: High Q4≥ 31.86, Low Q1–3 <31.86. D_3Cr muscle mass/wgt quartile cut points: High Q2–4≥0.27, Low Q1<0.27. (**F**) Likelihood of incident injurious falls by lean and fat groups using quartiles of ALM/ht^2 and %fat. Interaction *p*-value derived from a model with continuous fat, ALM/ht^2 and an interaction term. Fat quartile cut points: High Q4≥ 31.86, Low Q1–3 <31.86. ALM/ht^2 quartile cut points: High Q2–4≥6.93, Low Q1<6.93. ALM = appendicular lean mass; wgt = weight.

correlated (r = .66, p < .001) with muscle mass by D_3Cr. This is not a surprising finding since lean mass includes organ weights, tissues, and water that are not muscle. Similarly, ALM, commonly used in sarcopenia research as a surrogate measure of skeletal muscle, is only modestly correlated with D_3Cr muscle mass, there is considerable individual variation in the correlation and the relationship is inconsistent across the range of muscle mass by D_3Cr. Moreover, ALM/ht^2 is unrelated to D_3Cr muscle mass/wgt. Thus, ALM and ALM/ht^2 are inadequate substitutes for directly measured muscle mass by D_3Cr dilution.

Our findings also indicate that ALM/ht^2 and D_3Cr muscle mass are quite different in their associations with body fat. While the proportion of body fat was not correlated with ALM/ht^2, a consistent finding in previous studies, percent body fat was lower in men with higher D_3Cr muscle mass. This discrepancy may be due to fundamental differences in the measurements. In support of the inverse relationship of D_3Cr muscle mass and percent body fat, muscle mass is important in energy metabolism and adiposity might be predicted to be inversely related to muscle mass. We previously reported (11) that D_3Cr muscle mass was significantly associated with physical activity. Other research suggests that an estimate of muscle mass is closely associated with basal metabolic rate (BMR) (20). Thus, differences in BMR and physical activity, the two major components of total daily energy expenditure, may explain the relationship between D_3Cr muscle mass and body fatness.

In view of our findings, the interpretation of the condition sarcopenic obesity is highly dependent on the method used to measure muscle mass. First, the associations between low D_3Cr muscle mass/wgt and poor physical performance were strong and independent of adiposity. Also, while higher percent fat was associated with slower walking speed and worse chair stands performance, adjustment for D_3Cr muscle mass/wgt largely attenuated these associations. In contrast, the associations between ALM/ht^2 and physical performance were weaker or nonsignificant, adjustment for % fat strengthened those relationships, and the negative associations between percent fat and physical performance remained significant after adjustment for ALM/ht^2. Moreover, in stratified models of D_3Cr muscle mass/wgt and percent fat there was minimal effect of adiposity on physical performance. Although there was a suggestion that adiposity was more associated with chair stand time in the highest quartile of fatness, the effect was very small. But, in similar models using ALM/ht^2 there was a prominent negative association of percent fat. These comparisons suggest that fat has little independent association with physical performance when muscle mass is measured by D_3Cr dilution, but has important adverse effects when measured by ALM/ht^2. Similarly, there were strong associations between low D_3Cr muscle mass/wgt and prevalent and incident mobility limitation and incident injurious falls regardless of adjustment for percent fat. Conversely, there was no association between ALM/ht^2 and incident injurious falls or mobility limitation, and the likelihood of prevalent mobility limitation was actually *lower* in men with higher ALM/ht^2. These associations were largely unchanged by adjustment for percent fat.

Why higher %fat was more often associated with poor physical performance and adverse outcomes in models with DXA ALM/ht^2 is uncertain, but may reflect that DXA ALM/ht^2 is a less accurate measurement of muscle and has little or no independent relationship with adverse outcomes. We have shown here that higher fat mass is associated with lower D_3Cr muscle mass/wgt, and thus, in analyses that include DXA ALM/ht^2 and %fat, higher fat mass may be a reflection of proportionately lower muscle mass.

This study has major strengths. It is a unique comparison of a direct measurement of muscle mass using D_3Cr with assessment of ALM in the evaluation of the sarcopenic obesity. We examined a large cohort of community dwelling, older men, a group at risk of

impaired physical performance and adverse health outcomes, in a longitudinal, observational study design. The cohort included a wide range of muscle and fat mass, allowing adequately testing of the hypotheses proposed. Study sites were experienced and assessment methods were standardized. The major limitation of our work is that that the participants were older men who were primarily Caucasian; our findings may not pertain to other groups. We purposefully did not address the complex issue of defining sarcopenia in general, but rather concentrated on the more focused issue of sarcopenic obesity.

In sum, these results suggest that the independent and joint associations of adiposity and muscle mass vary substantially by the method used to approximate muscle mass. In contrast to previous studies that were based on measures of DXA ALM, our results using the D_3Cr dilution method suggest that muscle mass is a primary determinate of physical performance and adverse outcomes, and that the effects of higher body fatness are less important. While there may be a small adverse effect of adiposity combined with low muscle mass in older men, the importance of sarcopenic obesity appears to be minor when muscle mass is measured accurately, and the term "sarcopenic obesity" has few implications for physical function, injurious falls and mobility limitation. Overall, these findings have implications for further examination of the interactions of muscle and fat, and how these contribute to adverse health outcomes.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Author Contributions

Study concept and design: E.S.O. and P.M.C. Acquisition of subjects and/or data: E.S.O. and P.M.C. Analysis and interpretation of data: All the authors. Preparation of initial manuscript: E.S.O., P.M.C., and K.E.P.

Conflict of Interest

None of the authors have relationships or activities that could appear to have influenced the submitted work. W.J.E. and M.H. are listed as coinventors on the granted patents for the D_3-Cr dilution method. However, they do not derive any income or royalties or own the intellectual property for the method.

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