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Low Lean Mass Predicts Incident Fractures Independently From FRAX: a Prospective Cohort Study of Recent Retirees

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ABSTRACT

Whether low muscle mass predisposes to fracture is still poorly understood. In the diagnosis of sarcopenia, different thresholds for low lean mass have been proposed but comparative data for these criteria against hard outcomes such as fractures are lacking. This study aimed to investigate the prevalence of low lean mass according to different thresholds used in operational definitions of sarcopenia and their association with 3-year fracture incidence in a cohort of healthy 63- to 67-year-old community dwellers. In a longitudinal analysis of 913 participants (mean age 65.0 ± 1.4 years) enrolled in the Geneva Retirees Cohort (GERICO) study, lean mass was assessed by dual-energy X-ray absorptiometry (DXA), and low trauma clinical fracture incidence was recorded over a 3-year period. Prevalence of low lean mass ranged from 3.5% to 20.2% according to the threshold applied. During a follow-up of 3.4 ± 0.9 years, 40 (4.4%) participants sustained at least one low trauma fracture. After multivariate adjustment including Fracture Risk Assessment Tool (FRAX) probability with femoral neck bone mineral density (BMD), low lean mass, as defined by Baumgartner thresholds, was associated with higher fracture risk (odds ratio [OR], 2.32; 95% CI, 1.04 to 5.18; $p = 0.040$). It also added significant predictive value beyond FRAX (likelihood ratio test for nested models, 4.28; $p < 0.039$). No significant association was found for other definition thresholds. The coexistence of sarcopenia and a *T*-score <−2.5 at spine or hip was associated with a 3.39-fold (95% CI, 1.54 to 7.46; $p = 0.002$) increase in low trauma fracture risk. In conclusion, low lean mass, as defined by the Baumgartner thresholds, is a predictor of incident fractures in a large cohort of healthy 65-year-old community dwellers, independently of FRAX probability. The increased risk is related to the threshold for low lean mass selected. These findings suggest that identification of sarcopenia should be considered in fracture risk assessment beyond usual risk factors. © 2016 American Society for Bone and Mineral Research.

KEY WORDS: SARCOPENIA; AGING; FRACTURE; MUSCLE MASS; BONE

Introduction

The loss of skeletal muscle mass with advancing age is among the most problematic expression of ageing and a main reason for loss of independence in older adults.[1–7] Major advances have been made in recent years toward a better understanding of the mechanisms for muscle wasting. However, a consensual definition of sarcopenia has still not been reached.[4,6,8–10] Different thresholds for low lean mass—including various derivative indicators of appendicular lean mass (ALM) and cut-off points—have been proposed in the definition of sarcopenia, but their clinical utility to predict relevant endpoints remains to be established.[2,11–14]

Fragility fractures, commonly assigned to osteoporosis, are a major clinical and public health outcome. Although they have been considered as an adverse outcome of sarcopenia, it remains unclear whether low muscle mass predisposes to fractures independently of low bone mass.[6,8,15–20] Most low energy fractures occur upon a fall from standing height, with low muscle mass being a well-established risk factor for falling and hence may predispose to an increased fracture risk.[7] However, the FRAX algorithm—the most widespread fracture prediction tool used worldwide to determine the 10-year probability of absolute risk of osteoporotic fracture and assist with treatment decisions—which integrates several clinical risk factors, does not currently take falls or their determinants into consideration; a main reason is that the recording of falls is of uncertain reliability.[21–24] Whether the objective evaluation of lean mass may contribute to improve fracture prediction remains to be determined. One issue is the threshold of low muscle mass chosen for the diagnosis.[7] To the best to our knowledge, how candidate criteria for low lean mass predict incident fractures independently of usual risk factors has never been studied.

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In the present study, we aimed to investigate the prevalence of low lean mass according to different thresholds used in operational definitions of sarcopenia and their association with 3-year fracture incidence in a large homogeneous cohort of 63- to 67-year-old community dwellers in Switzerland.

Materials and Methods

Study participants

This longitudinal study is based on data from the Geneva Retirees Cohort (GERICO), a prospective ongoing cohort study designed to identify the gene loci and musculoskeletal factors related to fracture risk in recently retired workers from the Geneva area. Between 2008 and 2011, recruited individuals of both genders, ages 63 to 67 years in both rural and urban communities, were enrolled. Participants were recruited through multiple strategies, including targeted mass mailings and advertisements in local newspapers and in local large companies at the time of retirement (ie, age 65 years in Switzerland). They were excluded if they had major comorbidities, particularly those with a history of cancer treated in the past 5 years, chronic renal failure, liver or lung disease, corticosteroid therapy, primary hyperparathyroidism, Paget disease of bone, malabsorption, or any neurological or musculoskeletal condition affecting bone health.

The present analysis was conducted in 913 participants successfully followed up for fracture occurrence over a 3-year period after the baseline examination (ie, 96% of the original cohort). All participants provided written informed consent, and the Geneva University Hospitals Research Ethics Commission approved the study (approval # 11-256).

Muscle and bone mass measurements

Participants underwent whole-body scan and local bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR Discovery instrument (Hologic, Inc., Waltham, MA, USA). All DXA scans, which were completed with the same device, were performed by a trained technician following a strict protocol. Quality control and phantom calibration procedures were performed daily prior to each scanning session. Total lean mass and ALM, fat mass, bone mineral content (BMC), and BMD were determined. ALM calculation was based on the sum of lean mass in the arms and legs.

Osteoporosis and osteopenia (also further referred to as low BMD) were defined as a lumbar spine or femoral neck or total hip BMD *T*-score ≤ -2.5 and ≤ -1, respectively, with *T*-scores derived from the Third National Health and Nutrition Examination Survey (NHANES III) reference database for femoral neck.[25]

Participants' body weight was measured to the nearest 0.1 kg using a certified scale and standing height to the nearest 0.1 cm using a stadiometer (Holtain Ltd., Crymych, UK). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The following derivative values were calculated: ALM/height^2 and ALM/BMI.

Fracture ascertainment

Follow-up fractures were identified by self-report during scheduled interviews. Information was obtained once by structured in-person ($n = 755$ participants; 83%), telephone ($n = 125$ participants; 14%), or mail ($n = 33$ participants; 4%) interview. Participants were asked to report fractures that had occurred since the baseline examination and further information regarding fracture was gathered through a structured interview, which included in-depth questions regarding the fracture site and the circumstances surrounding each fracture event. Written confirmation (eg, discharge summary, radiologist report) was requested. For the purpose of the present study, low trauma clinical fractures (ie, due to falls from a standing height or less) were analyzed.[26] Fractures of fingers, toes, and skull were excluded from the analysis. All low trauma fractures were confirmed by X-ray or medical/surgical report, except in four cases in which a medical interview confirmed the presence of fracture.

Covariates

Covariates were assessed at baseline examination. Participants completed questionnaires and face-to-face interviews collecting information on demographic characteristics, medical history, physical activity, lifestyle and behavioral factors.[27,28] Dietary calcium and protein intakes were estimated using a validated food frequency questionnaire.[29,30]

The 10-year probabilities of major osteoporotic fracture and of hip fracture were calculated with the FRAX tool (www.shef.ac.uk/FRAX/), using country-specific data, with inclusion of femoral neck BMD.[24] The FRAX probabilities are based on the following clinical risk factors: age, gender, BMI, previous history of fracture, parental history of hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, other types of secondary osteoporosis, and alcohol, in addition to femoral neck BMD if available. We used the FRAX estimate of major osteoporotic fracture in all analyses.

Blood samples were collected after an overnight fast, and serum was prepared and stored at −70°C until analyses. All determinations were performed batchwise. Serum amino-terminal propeptide of type 1 procollagen (P1NP) and β-carboxy-terminal cross-linked telopeptide of type 1 collagen (CTx) were measured on a Cobas-6000 instrument using Elecsys reagents (Roche Diagnostics, Rotkreuz, Switzerland). Total 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) were determined on the same analyzer with reagents obtained from the same manufacturer. Insulin-like growth factor 1 (IGF-1) was measured with an automated chemiluminescence-based immunoassay using two monoclonal antibodies (Immunodiagnostic System, Herler, Denmark).

Operational definitions of sarcopenia

For this study, the term "sarcopenia" was used in its original context to describe the loss of lean mass (ie, as defined by Rosenberg in 1989, derived from the Greek "sarcos" referring to flesh and "penia," a lack of).[1] The two terms are here considered synonymous and used interchangeably. It should be noted that it has been proposed recently to introduce the term dynapenia in addition to sarcopenia to refer specifically to the loss of muscle function.[10,31]

The various thresholds for low lean mass proposed by: (1) Baumgartner et al.,[2] (2) Delmonico et al.,[32] (3) the European Working Group on Sarcopenia in Older People (EWGSOP),[11] (4) the International Working Group (IWG) on sarcopenia,[12] (5) the Society on Sarcopenia, Cachexia, and Wasting Disorders (SCWD),[33] and (6) the Foundation of the National Institutes of Health (FNIH) sarcopenia project were applied.[13] Each definition—based on lean mass assessment by DXA alone[2,32]

or in conjunction with muscle function testing[11–13,33]—uses different derivative indicators of ALM and cut-off points for its respective criteria of low lean mass.

Baumgartner definition

The gender-specific thresholds were defined as a value of ALM adjusted by height^2 two standard deviations below the mean of a younger reference population, based on data from the New Mexico Elder Health study (ie, 5.45 kg/m^2 in women and 7.26 kg/m^2 in men).[2]

Delmonico definitions (Delmonico 1 and Delmonico 2)

In a first definition (further referred to as Delmonico 1), the gender-specific thresholds were defined as a value of ALM adjusted by height^2 below the 20th percentile of gender-specific distribution of a reference population, based on data from the Health, Aging, and Body Composition (Health ABC) study (ie, 5.67 kg/m^2 in women and 7.25 kg/m^2 in men).[32] In a second definition (further referred to as Delmonico 2), the gender-specific thresholds were defined based on residuals from linear regression models predicting ALM from height and fat mass, with the same Health ABC study population as a reference. For each participant of our original cohort a residual was calculated as a difference between observed and predicted ALM. The following gender-specific linear models regressing ALM by height and total body fat mass were fit: ALM $= -13.21 + 14.76 \times$ height $+ 0.23 \times$ total fat mass, for women; ALM $= -22.59 +$ 24.21 $\times$ height $+ 0.21 \times$ total fat mass, for men. The gender-specific thresholds were defined as a value of residual value below the 20th percentile of the gender-specific distribution of residuals.

IWGS definition

The IWGS proposed thresholds similar to those identified by Newman et al.,[14] based on data from the Health ABC population. The gender-specific cut-off points were defined as a value of ALM adjusted by height^2 below the lowest 20% distribution of the predictive population (ie, 5.67 kg/m^2 for women and 7.23 kg/m^2 for men).[14,32]

EWGSOP definition

The EWGSOP proposed two options in their report:[11,34,35] the first includes the thresholds proposed by Baumgartner et al.[2] and the second, the thresholds proposed by Newman et al.,[14] as detailed above for the IWGS definition. Thus these thresholds are further referred to as EWGSOP 1 and EWGSOP 2, respectively.

SCWD definition

The SCWD proposed thresholds similar to those identified by Kelly et al.[36] The gender-specific thresholds were defined as a value of ALM adjusted by height^2 two standard deviations below the mean of a younger reference population, based on data from the NHANES IV (ie, 5.18 kg/m^2 in women and 6.81 kg/m^2 in men).[33,36]

FNIH definition

The FNIH thresholds were based on a pooled data set of nine large studies and derived from classification and regression analyses. The gender-specific cut-off points were defined as a value of ALM adjusted for BMI below which older adults had a higher likelihood of significant muscle weakness and/or slow gait speed (ie, 0.512 for women and 0.789 for men).[13,37]

Statistical analysis

The prevalence of low lean mass in the study population was assessed for all thresholds applied in the operational definitions of sarcopenia. Baseline characteristics of study participants, including by lean mass status and gender, were summarized using mean and standard deviation (SD) for continuous variables or counts and percentages for categorical variables. Means and proportions were compared using a χ^2 test for categorical variables, and Student's *t* test or Wilcoxon rank sum test for continuous variables. The characteristics of participants with and without incident fractures were also compared. Normal distributions were tested using the Shapiro–Francia W test and Skewness/Kurtosis tests.

The associations between low lean mass and low trauma fractures were assessed using univariate (model 0) and multivariate logistic regression models, also stratified by gender. Multivariate models included the following: adjustment for gender, age, length of follow-up and FRAX probability with femoral neck BMD (model 1); model 1 with further adjustment for other potential confounders including physical activity, protein and calcium intakes, and PTH (ie, variables found to be significant in univariate analysis) (model 2); and backward stepwise linear regression models starting with all variables included in model 2 (model 3) ($p < 0.20$ retained in model). We also developed all the above models (ie, models 0 to 3) but with inclusion of low BMD (ie, a lumbar spine or femoral neck or total hip *T*-score $\leq$–1) and femoral neck *T*-score instead of FRAX probability. Finally, in a secondary analysis, we aimed to fully address whether low lean mass is associated with incident low trauma fractures independent of FRAX clinical risk factors. Thus all regression analyses were rerun using FRAX clinical risk factors as separate covariates instead of FRAX probability.

The overall ability of each threshold to discriminate between participants with or without incident fractures was assessed by calculating the sensitivity and specificity, the area under the receiver operating characteristic curve (AUC) (ie, higher values of this analysis indicate a better discrimination of the model), and the Akaike information criterion (AIC), which assesses the goodness-of-fit and informativeness of the models (ie, smaller values of this analysis indicate a better model fit). We also assessed the added predictive value of the combination of low lean mass and FRAX using a likelihood ratio (LR) test for nested models. The LR statistic provides a global measure of model fit, and the difference between χ^2 two values is used to test the improvement in model fit. In addition, the "event" and "nonevent" two-category Net Reclassification Improvement (NRI) indices, which correspond to the changes in the true-positive and false-positive rates, were determined using the "incrisk" command with bootstrap 95% CIs computed using 1000 repeats.[38,39]

Finally, to investigate the effect of the coexistence of sarcopenia and densitometric osteoporosis (ie, "sarco-osteoporosis") on the risk of incident fractures, we classified participants into four subgroups, according to their sarcopenia (ie, normal lean mass versus low lean mass) and osteoporotic (ie, normal BMD versus *T*-score $\leq$–2.5) status, and applied regression models.

Tests were two-sided, and p values < 0.05 were considered significant. Stata version 12.1 (Stata Corporation, Inc., College Station, TX, USA) was used for all analyses.

Results

Nine hundred and thirteen participants (729 [80%] women) followed up for an average of 3.4 ± 0.9 years were included in this analysis. Participants were community-dwelling older individuals with a mean age of 65 ± 1.4 years (Table 1). Values of dietary intakes, anthropometric variables, physical activity evaluation, calcitropic hormones, and biochemical markers of bone turnover indicate a particular healthy population. The prevalence of low lean mass according to the different thresholds ranged from 3.5% ($n = 32$) (FNIH definition) to 20.2% ($n = 184$) (Delmonico 2 definition) (Table 2). Only 8 participants (0.9%) were identified as having low lean mass according to all definitions.

Table 3 presents the clinical characteristics of participants by lean mass status, according to the Baumgartner et al. definition and gender. Participants with low lean mass had lower BMI, physical activity level, calcium and protein intakes, PTH levels, and femoral neck areal bone mineral density (*T*-score), compared with nonsarcopenic participants ($p < 0.05$ for all comparisons).

Of the 913 original participants, 68 (7.5%) sustained at least one incident fracture ($n = 71$ fractures) and 40 sustained (4.4%) at least one incident low trauma fracture ($n = 43$ fractures) during follow-up. Most frequent low trauma fractures occurred at wrist ($n = 11$), ankle ($n = 9$), and proximal humerus ($n = 6$). Among study population, FRAX probability with femoral neck BMD was associated with incident low trauma fractures (crude OR, 1.09; 95% CI, 1.05 to 1.13; $p < 0.001$). There was no significant interaction between sarcopenia status, as defined using Baumgartner thresholds, and FRAX with low trauma fracture incidence (p for interaction, $p = 0.542$).

As shown in Table 4, baseline ALM and total lean mass were lower in participants with incident fractures compared with those without incident fractures ($p < 0.02$, for ALM; $p < 0.04$, for total lean mass), also when ALM was expressed as ALM/height^2 or ALM/BMI ($p < 0.05$ for both comparisons). Fractured participants were also more likely to be female and to present lower femoral neck *T*-score and higher FRAX probabilities ($p < 0.05$ for all comparisons).

In regression analyses, ALM ($p = 0.048$) and ALM/BMI ($p = 0.016$) taken as continuous variables were found to be significantly associated with incident fractures. However, these

Table 1. Characteristics of the Study Population

Age (years)	65.0 ± 1.4
Gender (female)	729 (79.9)
BMI (kg/m^2)	
<18.5	12 (1.3)
18.5 to <25	472 (51.7)
25 to <30	309 (33.8)
≥30	120 (13.1)
Physical activity (kcal/day)	575 ± 330
Protein intake (g/day)	74.5 ± 23.2
Calcium intake (mg/day)	1175 ± 423
Current estrogen use	165 (18.1)
Serum parameters[a]	
25OHD [75–250 nmol/L]	67.2 ± 26.9
PTH [1.1–6.8 pmol/L]	4.5 ± 1.8
P1NP [19–83 μg/L]	44.5 ± 20.0
CTx [104–782 ng/L]	376 ± 191
IGF-1 [38–192 ng/mL]	117 ± 32
T-score femoral neck	−1.24 ± 0.96
FRAX (%)	
Major osteoporotic fracture	11.3 ± 5.8
Hip fracture	1.7 ± 2.0
Follow-up duration (years)	3.4 ± 0.9

Results are reported as mean ± standard deviation or *n* (%), ($n = 913$).

BMI = body mass index; 25OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone; P1NP = amino-terminal propeptide of type 1 procollagen; CTx = β-carboxy-terminal cross-linking telopeptide of type 1 collagen; IGF-1= insulin-like growth factor 1; FRAX = Fracture Risk Assessment Tool.

[a]Reference values between square brackets.

Table 2. Prevalence of Low Lean Mass According to Operational Definitions of Sarcopenia

Definition	Reference	Cut-off points	Prevalence *n* (%)
Baumgartner (EWGSOP 1)[a]	Baumgartner et al. 1998[2]	ALM/height^2 ♂ ≤7.26 kg/m^2 ♀ ≤5.45 kg/m^2	102 (11.2)
Delmonico 1	Delmonico et al. 2007[32]	ALM/height^2 ♂ ≤7.25 kg/m^2 ♀ ≤5.67 kg/m^2	157 (17.2)
Delmonico 2	Delmonico et al. 2007[32]	Under 20th percentile of the gender-specific distribution of residuals of linear regression of ALM with height and fat mass	184 (20.2)
IWGS (EWGSOP 2)[a]	Fielding et al. 2011[12]	ALM/height^2 ♂ ≤7.23 kg/m^2 ♀ ≤5.67 kg/m^2	156 (17.1)
SCWD	Morley et al. 2011[33]	ALM/height^2 ♂ ≤6.81 kg/m^2 ♀ ≤5.18 kg /m^2	42 (4.6)
FNIH	Studenski et al. 2014[13]	ALM/BMI ♂ <0.789 ♀ <0.512	32 (3.5)

$n = 913$.

ALM/height^2 = appendicular lean mass (sum of lean mass in the arms and legs) adjusted for height squared; EWGSOP = European Working Group on Sarcopenia in Older People; IWGS = the International Working Group (IWG) on sarcopenia; SCWD = Society on Sarcopenia, Cachexia, and Wasting Disorders; ALM/BMI = appendicular lean mass adjusted for body mass index; FNIH = Foundation of the National Institutes of Health sarcopenia project.

[a]The EWGSOP recommended two different options for low lean mass threshold (Cruz-Jentoft et al. 2010).[11]

Table 3. Characteristics of Study Participants According to Lean Mass Status[a] and Gender

	Female ($n = 729$)		Male ($n = 184$)		All ($n = 913$)	
	No sarcopenia ($n = 647$)	Sarcopenia ($n = 82$)	No sarcopenia ($n = 164$)	Sarcopenia ($n = 20$)	No sarcopenia ($n = 811$)	Sarcopenia ($n = 102$)
Age (years)	65.0 ± 1.4	64.9 ± 1.4	65.2 ± 1.4	65.1 ± 1.4	65.0 ± 1.4	65.0 ± 1.4
BMI (kg/m^2)						
<18.5	8 (1.2)	4 (4.9)	0 (0)	0 (0)	8 (1.0)	4 (3.9)
18.5 to <25	318 (49.1)	76 (92.7)	60 (36.6)	18 (90.0)	378 (46.6)	94 (92.2)
25 to <30	224 (34.6)	2 (2.4)	81 (49.4)	2 (10.0)	305 (37.6)	4 (3.9)
≥30	97 (15.0)	0 (0)*	23 (14.0)	0 (0)*	120 (14.8)	0 (0)*
Physical activity (kcal/day)	561 ± 303	361 ± 183*	755 ± 407	437 ± 196*	600 ± 336	376 ± 187*
Protein intake (g/day)	73.1 ± 22.7	62.8 ± 16.6*	84.7 ± 24.1	81.9 ± 22.9	75.5 ± 23.4	66.5 ± 19.4*
Calcium intake (mg/day)	1178 ± 421	1033 ± 360*	1241 ± 444	1120 ± 447	1190 ± 426	1050 ± 378*
Serum parameters[b]						
25OHD [75–250 nmol/L]	66.8 ± 27.7	72.6 ± 28.6	66.9 ± 23.0	60.1 ± 18.4	66.8 ± 26.8	70.2 ± 27.3
PTH [1.1–6.8 pmol/L]	4.6 ± 1.8	4.2 ± 1.3*	4.5 ± 1.7	4.0 ± 1.6	4.6 ± 1.8	4.2 ± 1.3*
P1NP [19–83 μg/L]	46.5 ± 20.6	48.0 ± 21.4	35.7 ± 13.6	38.4 ± 19.2	44.3 ± 19.8	46.2 ± 21.2
CTx [104–782 ng/L]	388 ± 194	422 ± 218	311 ± 149	333 ± 150	373 ± 188	405 ± 209.7
IGF-1 [38–192 ng/mL]	115 ± 31	109 ± 31	126 ± 31	130 ± 37	117 ± 32	113 ± 33
T-score femoral neck	−1.2 ± 1.0	−1.6 ± 0.9*	−1.0 ± 0.9	−1.7 ± 0.5*	−1.2 ± 1.0	−1.6 ± 0.9*
FRAX (%)						
Major osteoporotic fracture	12.1 ± 5.7	12.4 ± 7.1	7.7 ± 4.0	8.9 ± 4.0	11.2 ± 5.7	11.7 ± 6.7
Hip fracture	1.7 ± 2.0	2.3 ± 2.7	1.4 ± 1.6	1.9 ± 0.9*	1.7 ± 1.9	2.2 ± 2.4*
Follow-up duration (years)	3.4 ± 0.9	3.5 ± 1.0	3.3 ± 0.8	3.9 ± 1.2	3.4 ± 0.9	3.6 ± 1.1

Results are reported as mean ± standard deviation, or *n* (%).

BMI = body mass index; 25OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone; P1NP = amino-terminal propeptide of type 1 procollagen; CTx = β-carboxy-terminal cross-linking telopeptide of type 1 collagen; IGF-1 = insulin-like growth factor 1; FRAX = Fracture Risk Assessment Tool.

[a]Baumgartner thresholds for sarcopenia.

[b]Reference values between square brackets.

*Significant difference between sarcopenic and nonsarcopenic participants at $p < 0.05$.

associations were lost after adjustment for gender and length of follow-up (data not shown).

Participants with low lean mass, as defined with Baumgartner et al. or SCWD thresholds, had a higher incidence of low trauma fractures compared with those with a lean mass above the definition threshold (9/102 [8.8%] versus 31/811 [3.8%], $p = 0.029$ for Baumgartner et al. thresholds; 5/42 [11.9%] versus 35/871 [4.0%], $p = 0.015$ for SCWD thresholds, respectively). In contrast, no significant differences in incident fractures were found when low lean mass was based on other thresholds. No participant with FNIH low lean mass criteria experienced any low trauma fracture, so the regression models could not be run.

Results from logistic regression models are reported in Fig. 1. Univariate analysis (model 0) showed significant associations between low lean mass, as defined with Baumgartner et al. and SCWD thresholds, and incident fractures (crude OR, 2.43; 95% CI, 1.12 to 5.27; $p = 0.024$; and OR, 3.23; 95% CI, 1.20 to 8.71; $p = 0.021$, respectively). After adjustment for gender, age, length of follow-up and FRAX probability (model 1), low lean mass, as defined with the Baumgartner et al. thresholds, remained independently associated with incident fractures (adjusted OR, 2.32; 95% CI, 1.04 to 5.18; $p = 0.040$). Odds for low trauma fractures were not significant in these analyses for low lean mass defined using other thresholds, neither in gender-stratified analyses. The association found for the Baumgartner et al. definition persisted even after adjustment for other potential confounders (model 2), including physical activity, protein and calcium intakes, and PTH (OR, 2.72; 95% CI, 1.11 to 6.62; $p = 0.028$), as well as in stepwise backward analysis (model 3) (OR, 2.26; 95% CI, 1.01 to 5.03; $p < 0.046$). Moreover, these associations remained significant when low BMD (ie, a lumbar spine or femoral neck or total hip *T*-score ≤−1) or femoral neck *T*-score was entered in the models instead of FRAX probability, as well as with additional adjustment for estrogen use (data not shown). Finally, all observed associations persisted when FRAX clinical risk factors were considered as separate covariates instead of FRAX probability (OR for the model including length of follow-up and FRAX risk factors, 2.70; 95% CI, 1.09 to 6.72; $p = 0.032$).

Table 5 shows the discriminative performances of the different thresholds for the incident fractures outcome. All thresholds had low sensitivity to identify sarcopenic participants with incident fractures (ranging from 12.50% to 27.50%), whereas specificity was high (83.05% to 96.76%) for identifying nonsarcopenic participants without incident fractures. AUC values were >0.50 for all models, but between 0.60 and 0.70, indicating moderate discriminatory ability. The Baumgartner et al. model yielded the best model fit measures for both AIC (ie, the lowest value) and AUC (ie, the highest value). Overall, when compared with a reference model with age and gender alone, differences in the AUCs tended to be small in absolute magnitude, with the greatest difference found in the AUC of 0.038 (for the Baumgartner et al. thresholds). In terms of added predictive value, the addition of low lean mass, according to

Table 4. Characteristics of Study Participants With and Without Incident Low Trauma Fracture

	No incident fracture ($n = 873$)	Incident fracture ($n = 40$)
Age (years)	65.0 ± 1.4	65.3 ± 1.5
Gender (female)	691 (79.2)	38 (95.0)*
BMI (kg/m^2)		
<18.5	11 (1.3)	1 (2.5)
18.5 to <25	454 (52.0)	18 (45.0)
25 to <30	294 (32.7)	15 (37.5)
≥30	114 (13.1)	6 (15.0)
Physical activity (kcal/day)	577 ± 332	543 ± 279
Protein intake (g/day)	74.5 ± 23.2	75.1 ± 23.1
Calcium intake (mg/day)	1172 ± 420	1250 ± 491
Serum parameters[a]		
25OHD [75–250 nmol/L]	67.4 ± 27.0	64.2 ± 23.9
PTH [1.1–6.8 pmol/L]	4.5 ± 1.7	5.1 ± 2.8
P1NP [19–83 μg/L]	44.4 ± 19.8	46.2 ± 22.9
CTx [104–782 ng/L]	376.2 ± 189.7	373.5 ± 209.8
IGF-1 [38–192 ng/mL]	116.6 ± 31.6	116.1 ± 37.9
Body composition parameters		
Total fat mass (g)	23,119 ± 7951	24,637 ± 8442
Total BMC (g)	2086 ± 406	1853 ± 337*
Femoral neck BMD (g/cm^2)	0.72 ± 0.1	0.68 ± 0.1*
Total lean mass (g)	43,740 ± 8769	41,248 ± 7005*
ALM	18.6 ± 4.3	17.2 ± 3.3*
ALM/height^2 (kg/m^2)	6.8 ± 1.1	6.4 ± 1.0*
ALM/BMI	0.74 ± 0.2	0.68 ± 0.1*
FRAX (%)		
Major osteoporotic fracture	11.1 ± 5.7	15.2 ± 6.8*
Hip fracture	1.7 ± 1.8	3.2 ± 4.1*
Follow-up duration (years)	3.4 ± 0.9	3.7 ± 1.1

Results are reported as mean ± standard deviation or *n* (%), $n = 913$.

BMI = body mass index; 25OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone; P1NP = amino-terminal propeptide of type 1 procollagen; CTx = β-carboxy-terminal cross-linking telopeptide of type 1 collagen; IGF-1 = insulin-like growth factor 1; BMC = bone mineral content; BMD = bone mineral density; ALM = appendicular lean mass; ALM/height^2 = appendicular lean mass adjusted for height squared; ALM/BMI = appendicular lean mass adjusted for body mass index; FRAX = Fracture Risk Assessment Tool.

[a]Reference values between square brackets.

*Significant difference between participants with incident fracture and without incident fracture at $p < 0.05$.

Baumgartner et al. thresholds, to FRAX model improved the AUC from 0.70 (95% CI, 0.63 to 0.78) to 0.72 (95% CI, 0.65 to 0.79), with an improved overall incident fractures prediction (LR test for nested models, 3.85; $p = 0.0496$). The improvement in model fit remained significant even after adjustment for potential confounding factors (LR test for nested models, 4.28; $p < 0.039$). The event NRI (–0.55, 95% CI; –0.75 to 0.34) and nonevent NRI (0.79; 95% CI, –0.48 to 0.83) for addition of low lean mass to FRAX, at an optimal risk threshold set at 4%, were not significant.

Using Baumgartner et al. thresholds, the prevalences of low lean mass alone, osteoporosis alone, and low lean mass–osteoporosis were 7.7% ($n = 70$), 8.4% ($n = 77$), and 9.3% ($n = 85$), respectively. Low lean mass prevalence was significantly higher in osteoporotic (19.8%) and osteopenic (11.5%) participants than in participants with normal BMD (4.4%; $p = 0.001$). Participants with low lean mass were more likely to have osteoporosis than other participants (OR, 2.39; 95% CI, 1.51 to 3.79; $p < 0.001$). After adjustment for age, gender, and length of follow-up, the OR for incident fractures in sarco-osteoporotic participants, compared with participants with normal BMD and lean mass, was 3.39 (95% CI, 1.54 to 7.46; $p = 0.002$).

Discussion

This prospective longitudinal study conducted in a large homogeneous cohort of 65-year-old community dwellers shows that low lean mass, as defined with Baumgartner et al. thresholds, is a predictor of incident fractures over a 3-year period, independently of FRAX probability. No association was found when low lean mass was defined using other proposed thresholds. To the best of our knowledge, this is the first study examining the predictive value of low lean mass, as defined by several thresholds used in various operational definitions of sarcopenia, against fractures in older adults.

The present prospective longitudinal findings add to the few previous studies suggesting an association between low lean mass and incident hip fractures, including a recent case-control study showing in the Health ABC cohort that decreased ALM/height^2—defined as the lowest two quartiles of the population studied—increased the likelihood of hip fracture risk in men.[20] In a cross-sectional study conducted among an older Chinese population, Hong et al[19] found that lower ALM/height^2—defined as less than two SDs below the mean of a younger reference population—was associated with an increased risk of hip fracture both in men and women. Further studies are required to determine the mechanisms by which low lean mass influences fracture. In our study, the association found between incident fractures and low ALM was independent of FRAX probability with BMD or low BMD, suggesting extraskeletal or skeletal factors not captured by FRAX or BMD. For instance, low lean mass may act on fracture through falls' risk. Especially, low lean mass may lead to reduced muscle strength and physical impairments and in turn increase the risk of falls. Interestingly, in a recent retrospective longitudinal study, falls' risk was also selectively predicted by the Baumgartner et al. thresholds.[7] In this study comparing several operational definitions of sarcopenia as predictor of prospective incidence of falls, the Baumgartner et al. definition had the highest validity for predicting the rate of falls, whereas the EWGSOP definition, with the combination of low lean mass and low muscle function, slightly but not significantly increased the risk prediction estimates.[7] Also, bone quality may play an important role beyond bone mass in resistance to fracture. Several studies have reported strong positive association between muscle mass and poorer quality of bones.[40–42] This is further supported by a recent study showing independent relationships between ALM/height^2 and bone microarchitecture including cortical area and thickness in older men and women.[43] There is growing interest in the cross-talk between muscle and bone.[44–49] Especially, beyond the well-studied mechanical coupling of these two tissues, the field has yet to clarify the molecular, genetic, and biochemical linkages between muscle and bone. We carried out additional analysis to address the concomitant effects of osteoporosis and sarcopenia on fractures' risk and showed that in sarco-osteoporotic participants the risk was about threefold higher that in participants with normal BMD and lean mass. Chalhoub and colleagues recently highlighted a potential strong role of sarcopenia and low BMD in fracture risk

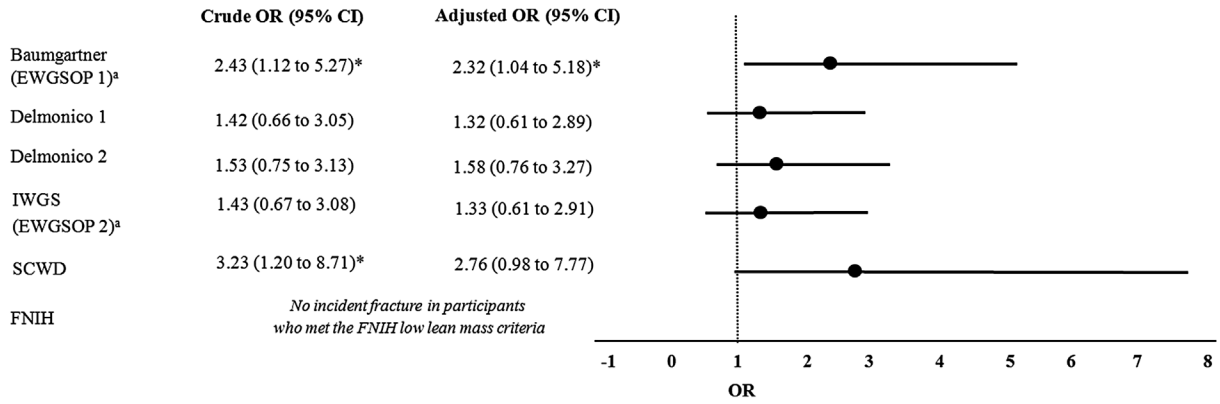

Fig. 1. Crude and adjusted odds ratio (OR) for the association between low lean mass thresholds, as proposed in different operational definitions of sarcopenia, and incidence of low trauma fracture over a 3-year follow-up ($n = 913$). Adjustment was made for gender, age, length of follow-up and FRAX probability with femoral neck BMD. OR = odds ratio; CI = confidence interval; EWGSOP = European Working Group on Sarcopenia in Older People; IWGS = the International Working Group (IWG) on sarcopenia; SCWD = Society on Sarcopenia, Cachexia, and Wasting Disorders; FNIH = Foundation of the National Institutes of Health sarcopenia project. [a]The EWGSOP recommended two different options for low lean mass threshold. *Significant at $p < 0.05$.

incidence in older men, but defining sarcopenia as a combination of low lean mass and strength.[17] The in-depth exploration of the relationships between sarcopenia and osteoporosis in fracture risk should be considered as a high priority, given their clinical relevance and the tremendous burden both cause at individual and societal levels.[48]

In contrast, other studies failed to find any association between low lean mass and fracture incidence; among these was a recent investigation based on data from the Osteoporotic Fractures in Men cohort study, which explored different sarcopenia definitions against hip fractures, including Baumgartner et al. thresholds.[18] Yu and colleagues, applying the Asian Working Group for Sarcopenia thresholds in an older Chinese population, also failed to find any significant association with all incident fractures.[15] The discrepancies between our findings and those of these other studies may be related to differences in populations (eg, older and less homogeneous samples, race/ethnicity) or definition applied (eg, Asian Working Group for Sarcopenia thresholds).

Our study suggests that the relationship between decreasing lean mass and increasing risk of fracture was threshold-based rather than continuous, and that the increased risk of incident fractures was clearly related to the threshold for low lean mass selected. Similar results have been recently reported in relation to falls.[7] Comparative data for candidate criteria for sarcopenia against hard outcomes are still sparse. To establish the clinical relevance of the proposed thresholds and validate them in different populations remains a pivotal basis for operationalization of the condition and widespread adoption in clinical and research settings. Further studies in the field should help elucidate whether interventions effective at attenuate, prevent, or ultimately reverse skeletal lean mass loss, may prevent hard outcomes in older people such as major mobility disability or fractures. A recent phase 2 trial of a 6-month myostatin-targeted treatment showed for the first time that an increase in lean mass translated into improvement of several measures of physical performance in older adults.[50]

Findings suggest that identification of sarcopenia—which can be assessed simultaneously with the BMD measurement—should be considered in fracture risk assessment beyond usual risk factors, and that clinicians should recognize the potential role of muscle wasting in determining fracture risk.[8,51] The lack of associations for the other thresholds does not imply that low lean mass assessment may not be useful for a given set of

Table 5. Diagnostic Performances of the Thresholds of Low Lean Mass for Incident Fractures' Outcome

	Sensitivity (%)	Specificity (%)	AIC[a]	AUC[a]
Baumgartner (EWGSOP 1)[b]	22.50	89.35	322.00	0.668
Delmonico 1	22.50	83.05	326.07	0.635
Delmonico 2	27.50	80.18	325.18	0.641
IWGS (EWGSOP 2)[b]	22.50	83.16	326.06	0.635
SCWD	12.50	95.76	322.86	0.652
FNIH	*No incident fracture in participants who met the FNIH low lean mass criteria*			

$n = 913$.

AIC = Akaike information criterion; AUC = area under the receiving operating characteristic curve; EWGSOP = European Working Group on Sarcopenia in Older People; IWGS = the International Working Group (IWG) on sarcopenia; SCWD = Society on Sarcopenia, Cachexia, and Wasting Disorders; FNIH = Foundation of the National Institutes of Health sarcopenia project.

[a]AIC and AUC for models adjusted for gender and age. AUC for model with gender and age was 0.630.

[b]The EWGSOP recommended two different options for low lean mass threshold.

patients and should not contradict the importance of muscle mass in the pathogenesis of osteoporotic fractures. Discriminative performances, including low sensitivity and marginal improvements in AUC beyond simple model, do suggest that low lean mass may have limited value solely in classifying risk for future low trauma fractures in a healthy, relatively young older population. Its use alone may not be optimal but lean mass may be a potential clinical risk factor to be considered, especially in refinements of FRAX and other fracture prediction models. Regarding the nonsignificant NRI analysis, the categorization may have led to a loss of predictive information and less statistical power than a test considering the full range of probabilities. Moreover, the analysis may have been restricted by the relatively small number of events and the fact that the FRAX was designed to predict the risk of fracture at 10 years and the current follow-up is limited to 3 years.

The most prominent strengths of the present study were the large homogeneous sample of 65-year-old individuals, the longitudinal analysis of incident fractures—a clinically important aging outcome—over 3 years, the application of several proposed thresholds for low lean mass criteria in one study population, and a limited loss to follow-up. However, several limitations need to be acknowledged. First, the older adults who volunteered to participate in this study were relatively healthy, community-dwelling, well-functioning individuals. Also, the study cohort was limited to recently retired adults in a narrow age range. Therefore, study findings may not be generalizable to the older population as a whole, especially to those older than age 67 years. Second, the low prevalence of low lean mass using some thresholds and the overwhelming recruitment of women, which may be partly explained by demographic factors (ie, in Switzerland, women age 65 years and older outnumber men by approximately 1.35 to 1), may have compromised statistical power and therefore increased the likelihood of type 2 errors, and prevented us from further fully assessing whether there were gender-specific associations. Third, the number of participants with incident fracture was relatively small. Fourth, falls' risk status, an important contributor to fracture as mentioned above, and physical performance data were not available for this cohort at baseline examination. Also, it remains to be determined whether composite definitions of sarcopenia, requiring both low lean mass and reduced physical performance or weakness, improve low trauma fracture risk prediction and discriminative ability. Numerous longitudinal studies have revealed that measures of muscle function may better predict poor health outcomes than measures of muscle mass alone, explaining the shift of emphasis toward a sarcopenia definition based not solely on reduced muscle mass but also on impaired muscle function.[10,13,52–54]

In conclusion, our study shows that low lean mass, as detected by applying Baumgartner et al. thresholds, is a predictor of incident fractures, independent of FRAX probability or BMD in a large cohort of healthy 65-year-old community dwellers. Our findings also add significant predictive value beyond FRAX. The increased risk is clearly related to the threshold for low lean mass selected. Whether assessing in addition muscle function improves low trauma fracture risk prediction remains to be determined.

Disclosures

All authors state that they have no conflicts of interest.

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