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Original Article

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Bone-muscle indices as risk factors for fractures in men: the Osteoporotic Fractures in Men (MrOS) Study

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Abstract

Objective: To assess bone-muscle (B-M) indices as risk factors for incident fractures in men. **Methods:** Participants of the Osteoporotic Fractures in Men (MrOS) Study completed a peripheral quantitative computed tomography scan at 66% of their tibial length. Bone macrostructure, estimates of bone strength, and muscle area were computed. Areal bone mineral density (aBMD) and body composition were assessed with dual-energy X-ray absorptiometry. Four year incident non-spine and clinical vertebral fractures were ascertained. B-M indices were expressed as bone-to-muscle ratios for: strength, mass and area. Discriminative power and hazards ratios (HR) for fractures were reported. **Results:** In 1163 men (age: 77.2±5.2 years, body mass index (BMI): 28.0±4.0 kg/m^2, 4.1±0.9 follow-up years, 7.7% of men ≥1 fracture), B-M indices were smaller in fractured men except for bending and areal indices. Smaller B-M indices were associated with increased fracture risk (HR: 1.30 to 1.74) independent of age and BMI. Strength and mass indices remained significant after accounting for lumbar spine but not total hip aBMD. However, aBMD correlated significantly with B-M indices. **Conclusion:** Mass and bending B-M indices are risk factors for fractures in men, but may not improve fracture risk prediction beyond that provided by total hip aBMD.

Keywords: Bone-Muscle Indices, Men, Incident Fractures, Osteoporosis, Discriminative Power, pQCT, Full Body Composition, DXA

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Introduction

Bone is a dynamic tissue that remodels itself according to sensory thresholds governing the degree to which bone responds to strain[1]. Bone is differentially sensitive to loads depending on genetically determined set points that can be influenced by endocrine factors[2]. A variety of forces act on bone both when stationary and during physical activities, including gravitational force, force of muscles and tendons to maintain posture and perform activities, as well as ground re-action forces during gait.

Since muscle is one of the strongest voluntary loads acting on bone[3,4], there is much incentive to study how bone responds to muscular contraction forces across the population. Muscles must generate sufficient force close to their points of attachments in order to mobilize the bone lever arm. As such, bone must adapt sufficiently to withstand the high dynamic loads

imparted by muscle[5]. Ferretti et al described the bone-muscle interaction by quantifying the balance of mass and strength properties in bone versus muscle[4,6,7]. Although these measures are not accurate reflections of the response of bone on muscle, they illustrate a cross-sectional relationship between them.

Several investigators have described the bone-muscle interaction by using the ratio of bone-to-muscle strength, mass and area. Frost and colleagues called these measurements bone-muscle (B-M) strength indices[4]. The rationale for the use of these B-M strength indices is that greater strength in bone is coupled proportionally to stronger forces of muscle acting on it. Hypothetically, if a lack of bone strength were observed where muscle strength is elevated, the bone may be mechanically compromised. Although the term strength was used by Frost et al to describe B-M relationships, a series of mass and areal indices have also been examined[8-10]. Ferretti et al illustrated that higher bone strength[11] and bone mass[12] measurements were associated with correspondingly greater muscle force, and lean mass, as determined by peripheral quantitative computed tomography (pQCT) and dual energy X-ray absorptiometry (DXA). A similar study by Rittweger et al supported these findings[13]. Hereon forward, the general term, B-M indices, will be used to describe the series of strength, mass, and areal relationships between bone and muscle.

B-M indices appear to vary by sex[10,12], hormonal status[14] and menopausal status[9,12]. However, B-M indices of tissue mass remained relatively constant with aging[9]. So far, there has been only one report on standardizing B-M mass relationships using DXA[9]. Few studies examined the relationship between B-M indices and fractures. In one analysis, lower bone mineral content (BMC) coupled to larger muscle cross-sectional area (MCSA) (a low BMC:MCSA ratio) was observed in children who have undergone renal transplant and who sustained multiple fractures[15].

Combining muscle and bone measures for assessing fracture risk is a novel approach that has yet to be explored. Here, the diagnostic value of several B-M indices for assessing fractures was examined. It was hypothesized that a decrease in B-M indices is associated with an increased fracture risk in men to a degree that is at least similar to and independent of areal bone mineral density (aBMD). It was further speculated that B-M indices can improve the ability of aBMD to identify those with incident fractures.

Materials and methods

Study design

The current study is an ancillary component of the Osteoporotic Fractures in Men (MrOS) Study. MrOS is a large prospective epidemiological study designed to identify osteoporotic risk factors in men. Between March of 2000 to April of 2002, 5994 men over 65 years of age were recruited from six sites across the United States, including: Birmingham, AL, Minneapolis, MN, Palo Alto, CA, Pittsburgh, PA, Portland, OR and San Diego, CA by local advertisement and by mass mailing. Those unable to walk without the assistance of another person or who have had bilateral hip replacement were excluded from the study. Details of the study have been published previously[16,17].

This ancillary study measured bone and muscle mass, and macrostructure at visit two (March 2005-May 2006) of the MrOS Study using pQCT and DXA at two study centers: Pittsburgh, PA and Minneapolis, MN. Information on participants' anthropometrics, self-reported medical history, and catalogued medication use was collected annually. All prescription and non-prescription medications taken in the past 30 days were recorded by the clinics and stored in an electronic medications database (San Francisco Coordinating Centre, San Francisco, CA). Each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA). Information on whether or not calcium or vitamin D was used was obtained from this database. Every four months, participants reported fractures, if any, through a questionnaire (>99% response rate). Fractures were centrally adjudicated by physician review of radiographic reports. Fractures, including incident post-visit two traumatic and non-traumatic cases of both non-vertebral and vertebral fractures were reported. Morphometric and asymptomatic vertebral fractures were not examined. Participants were followed for approximately four years (mean 4.1±0.9 years) from visit two of MrOS to obtain incident fracture data.

Physical performance was measured by walking speed and grip strength tests during visit two of MrOS. All participants provided written informed consent to study procedures in accordance to the Declaration of Helsinki. The study protocol was approved by local institutional research ethics boards.

The Pittsburgh MrOS site consisted of 886 participants eligible for study, 632 of whom completed pQCT. A total of 540 participants completed pQCT scans out of 906 Minneapolis participants who were eligible. Collectively, 1172 men from the two study centers were scanned on both pQCT and DXA machines. After exclusion of 2 men with missing or erroneous data, and 7 men exhibiting abnormal bone mechanical measures due to image artifact, the final analysis was performed on 1163 men. Of these 1163 men, 1138 performed grip strength walking speed and grip strength tests.

Physical function tests

Grip strength (kg) was measured using a Jamar hand-held dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). The dynamometer was held in the dominant hand and squeezed to a maximum isometric force. The maximum of two trials was obtained. To convert grip strength to force in Newtons, a correction factor of 9.81 N/kg was multiplied, as suggested by Rauch et al[18]. Walking speed was measured in meters per second for a usual pace walk over a six meter course. The mean of two trials was employed in these analyses.

DXA scans

All DXA scans were performed on the Hologic QDR-4500 W. Total body composition including total lean tissue mass (LTM, g),

Bone & muscle mechanical indices	Equation	Definition	Units
CSMI (cross-sectional moment of inertia	$\sum(d_i^2*A)$	Resistance of bone to bending and torsional force as a result of inertial properties of mass distributed around the torsional or bending axis[4]	mm^4
SM (section modulus)	$\sum(d_i^2*A)/d_{max}$	The ratio of the bone's resistance to bending and torsion to its maximally distributed distance about the bending or torsional axis[37]	mm^3
BSI (bending strength index)	$SM/(L_{tib}*0.66)$	A more reliable predictor of bone strength in bending and torsion related to SM – dependent on length of lever arm[8]	mm^2
SSI_p (polar stress-strain index)	$\frac{pCSMI \cdot cortical\ vBMD_i}{d_{max} \cdot vBMD_{max}}$	Estimates bone strength in bending and torsion based on distribution of density-weighted bone voxels from polar axis	mm^3
MSS (muscle-specific strength)	$\frac{Grip\ strength\ (kg) \times 9.81\ N/kg}{MCSA}$	Muscular strength as defined by muscular force over a given cross-sectional area	N/mm^2
MBM (muscle bending moment)	$MCSA \times L_{tib} \times 66\%$ x tension of muscle acting on bone (9.5 N/mm^2) *	The work implicated by muscle acting to bend bone, related to the length of the moment arm and muscle cross-sectional area	N·mm

* Tension of muscle acting on bone was estimated by Rittweger et al[13] based on a peak muscle tension measured at 650 kPa at the calf muscles, assuming 60% of the total MCSA is effective during peak force production, with the force concentrated over 4.1% of the tibia= 650 kPa x 60%/4.1%= 9500 kPa x 0.001 N/mm^2 / kPa = 9.5 N/mm^2.

Table 1. Definitions for tibial bone and muscle mechanical parameters. SM= section modulus, L_{tib}= length of tibia, pCSMI= polar cross-sectional moment of inertia, $vBMD_i$= volumetric BMD, d_i= distance of individual voxel from torsional (z) or bending (x,y) axis, d_{max}= maximum distance among all voxels from torsional (z) or bending (x,y) axis, A_i= area of individual bone pixel, $vBMD_{max}$= maximum bone density (1.2 g/cm^3), MCSA= muscle cross-sectional area.

Bone-Muscle indices	Equation	Units	Reference
B-MBI$_D$ (density-weighted B-M bending index)	SSI/MBM	mm^2/N	Rittweger et al, 2000[13]
B-MSI$_D$ (density-weighted B-M strength index)	SSI/MSS	mm^5/N	Adapted from Rittweger at al, 2000[13] by Wong, A.K.O
B-MBI$_U$ (non-density-weighted B-M bending index)	BSI/MBM	mm/N	Adapted from Macdonald et al, 2005[8] and Rittweger et al, 2000 (13) by Wong, A.K.O.
B-MSI$_U$ (non-density-weighted B-M strength index)	BSI/MSS	mm^4/N	Adapted from MacDonald et al, 2005[8] by Wong, A.K.O.
B-MMI$_{W/L}$ (whole body (w) and lower limb (L) B-M mass index)	BMC/LTM	Index	Cure-Cure et al, 2005[9]
B-MAI (B-M areal index)	CoA/MCSA	Index	Macdonald et al, 2005[8]

Table 2. Definitions for tibial bone-muscle (B-M) indices. B-M indices were defined according to mechanical, densitometric and areal indices of bone and muscle. BMC= bone mineral content, LTM= lean tissue mass, CoA= cortical bone area, MCSA= muscle cross-sectional area.

whole body BMC (BMC_W, g), lower limb BMC (BMC_L, g) and aBMD (g/cm^2) of the lumbar spine and total hip were measured. Scans of the right hip were collected in most cases. The left hip was scanned if there was a fracture, implant, hardware or other problems preventing the right hip from being imaged. Strict quality assurance efforts were made to ensure high measurement precision and correct positioning, as previously described[16]. T-scores for aBMD were computed using normative values previously reported by Looker et al[19].

pQCT scans & image analyses

All pQCT scans were performed on the non-dominant lower limb using the Stratec XCT-2000 (Pittsburgh) and the XCT-3000 (Minneapolis) scanners (Stratec Medizintechnik, Pforzheim, Germany). Inter-modality precision error on the two models was within 0.5% for bone area, 3.0% for muscle area, and 1.0% for total bone density as determined from phantom measurements[20]. Tibial length was measured as the distance between the medial malleolus and the medial

Variable/Parameter	No Fracture	Fractured	p-value
	(N= 1073)	(N= 90)	
Age (years)	77.16 +/- 5.13	78.09 +/- 5.38	0.099
BMI (kg/m²)	28.01 +/- 3.93	27.43 +/- 4.25	0.187
Rheumatoid arthritis	62 (5.8)	7 (7.8)	0.441
Osteoarthritis	235 (21.9)	24 (26.7)	0.297
Osteoporosis	33 (3.1)	8 (8.9)	0.004
Diabetes	166 (15.5)	13 (14.4)	0.796
Family history of OP	360 (52.1)	27 (54.0)	0.795
Osteoporosis Medication	33 (3.1)	9 (10.0)	0.001
Glucocorticoids	24 (2.2)	5 (5.6)	0.053
Calcium supplement use	275 (25.6)	32 (35.6)	0.041
Vitamin D supplement use	653 (60.9)	61 (67.8)	0.199
Walking speed (m/s)	1.15 +/- 0.24	1.10 +/- 0.26	0.057
Grip strength (kg)	37.68 +/- 7.56	34.82 +/- 8.24	0.001
$B\text{-}MBI_D$ (mm^2/N)[a]	4.89 +/- 1.00	4.71 +/- 0.97	0.114
$B\text{-}MSI_D$ (mm^5/N)[a]	3.54 +/- 1.01	3.28 +/- 0.86	0.021
$B\text{-}MBI_U$ (mm/N)[a]	4.2 +/- 1.01	4.01 +/- 0.88	0.089
$B\text{-}MSI_U$ (mm^4/N)[a]	3.54 +/- 1.01	3.26 +/- 0.90	0.012
$B\text{-}MMI_W$, %[a]	6.82 +/- 0.99	6.39 +/- 1.00	<0.001
$B\text{-}MMI_L$, %[a]	4.36 +/- 0.99	4.12 +/- 1.08	0.029
B-MAI, %[a]	4.57 +/- 1.00	4.43 +/- 0.96	0.216
aBMD Lumbar Spine (g/cm^2)	1.21 +/- 0.26	1.13 +/- 0.27	0.004
aBMD Total Hip (g/cm^2)	0.97 +/- 0.14	0.87 +/- 0.14	<.0001
Lumbar Spine aBMD T-score	0.20 +/- 1.80	-0.53 +/- 1.70	<0.001
Total Hip aBMD T-score	-0.50 +/- 1.00	-1.16 +/- 1.00	<.0001

[a] parameters were expressed in terms of its standard deviation.

Table 3. Comparison of participant characteristics between those with and without incident fractures. Means were expressed ± standard deviations and frequencies were expressed with (percentage of cohort).

condyle of the tibia. Measurements were acquired in the transaxial plane at 66% of the tibial length, proximal to the distal aspect of the medial malleolus. One slice measured at 2.5±0.3 mm was obtained. Images were acquired with isotropic pixel resolution of 500 μm by using the following acquisition parameters: CT speed of 20 mm/s, 38 kVp X-ray beam energy and matrix size of 256 x 256. Quality control was performed on a daily basis using a hydroxyapatite European forearm phantom.

Bone and muscle at pQCT images obtained 66% of the tibial length were semi-automatically segmented by a single user (CLG). Peel mode 2 and contour mode 3 on Stratec analysis software (Version 5.5E) was applied to analyze pQCT images using an inner density threshold of 400 mg/cm^3 and an outer density threshold of 130 mg/cm^3 to separate the cortical from cancellous bone, and to separate bone from soft tissue, respectively[21]. A series of densitometric and macrostructural measurements were automatically computed using the Stratec software package. Formulae used to calculate cross-sectional moments of inertia (CSMI), section modulus (SM), and polar stress-strain index (SSI_p) were described previously by Schoenau et al[22], and the definitions are summarized here in Table 1.

	Pearson Correlations	
B-M Index Parameter	**LS aBMD T-score**	**TH aBMD T-score**
$B\text{-}MBI_D$	0.286[a]	0.131[a]
$B\text{-}MSI_D$	0.289[a]	0.286[a]
$B\text{-}MBI_U$	0.262[a]	0.146[a]
$B\text{-}MSI_U$	0.294[a]	0.311[a]
$B\text{-}MMI_W$	0.631[a]	0.517[a]
$B\text{-}MMI_L$	0.397[a]	0.381[a]
B-MAI	0.300[a]	0.261[a]

[a] significant correlation at the 99% confidence level.

Table 4. Correlations between bone-muscle (B-M) indices and aBMD. Pearson correlation coefficients were reported for each B-M index and both total hip (TH) and lumbar spine (LS) areal bone mineral density (aBMD) T-scores. TH aBMD T-scores were computed using a normal race-specific population of men previously described by Looker et al[19].

Computation of B-M indices

B-M indices were computed based on the combination of DXA and pQCT-derived bone and muscle measurements. In general, bone parameters were divided by muscle parameters to give a B-M index. Here, seven B-M indices described in Table 2 were examined. The B-M bending index (B-MBI) was defined in terms of the propensity of muscle to generate a bending force acting on bone (muscle-bending moment (MBM)) versus the resistance of bone from bending and torsion (SSI_p). Although SSI_p logically also represents torsion, Kontulainen et al showed that SSI_p explained 76% of the variance in failure moment in three point bending tests performed at the 66% site, justifying its representation of bending resistance overall[23]. Alternatively, B-M strength index (B-MSI) quantified a similar relationship but reflected the amount of force the participants' muscle actually generated in the upper limb, scaled by muscle area of the lower limb (muscle-specific strength). Although only upper extremity strength was measured, it was extrapolated to represent total muscle strength as previously reported[24]. Hence, caution is used in interpreting how muscle strength affects the 66% tibia in these analyses. Both B-MBI and B-MSI were examined with (subscript-D) and without (subscript-U) adjustment for density of individual bone voxels. Bone-muscle relationships were further expressed in terms of bone-to-muscle mass indices (B-MMI) as determined across the whole body ($B\text{-}MMI_w$) and at the leg where pQCT scans were performed ($B\text{-}MMI_L$). Finally, the B-M areal index (B-MAI) examined how muscle area related to bone area.

Data analysis

Participant characteristics were compared between those with and without incident fractures using an analysis of variance (ANOVA), Kruskal-Wallis and Chi square tests for normal continuous, skewed continuous and categorical variables, respectively. Pearson correlation coefficients were computed for B-M indices with each of total hip and lumbar spine aBMD T-scores. Cox proportional hazards models estimated the hazard ratios (HR) (95% confidence intervals) for incident fractures based on B-M indices and for aBMD of the total hip and lumbar spine. Because B-M indices are ratiometric outcomes, the resultant variance is reduced compared to the individual variances of each bone and muscle parameter. The diminished ability to represent bone-muscle relationships based on these quotients can be addressed by examining fracture's interaction with muscle on bone in a bone-muscle linear regression. A significant interaction term would indicate an association between fractures and bone-muscle relationships. In detail, bone parameters were entered into the model as dependent variables, and muscle parameters, fracture status, and an interaction term between muscle and fracture status were entered as independent variables. Parameter estimates between bone and muscle variables were reported for those with and without an incident fracture. A significant interaction term signified an association between fracture status and bone-muscle relationships. A receiver-operator characteristics (ROC) analysis was used to determine the ability of B-M indices and aBMD T-scores for identifying those with incident fractures post-visit two. Areas under the ROC curves (AUC) were reported for each of aBMD T-score and B-M indices separately and when combined in the same model. A Chi-square analysis was used to determine whether there was a significant difference in AUC values between a model including B-M indices plus aBMD T-score versus aBMD T-score alone. All Cox regression, linear regression and ROC analyses were performed with age and body mass index (BMI) as covariates. All statistics were assessed at the 95% confidence level using SAS/STAT v9.3 (SAS Institute Inc, Cary, NC, USA).

Results

During 4.1±0.9 years of follow-up, 90 men (7.7%) experienced a fracture (20 hip, 78 non-spine and 12 clinical vertebral fractures of which 3 were cervical). In those with incident fractures, B-MSI and B-MMI indices were significantly smaller than those without fractures (Table 3). Similarly, fractured participants had a lower lumbar spine aBMD, lower total hip aBMD, and weaker grip strength. A greater proportion of fractured participants were diagnosed with osteoporosis by their physicians, were on osteoporosis medication or taking calcium supplements. There were significant correlations between all B-M indices and each of aBMD T-scores of the total hip and lumbar spine ranging from 0.13 to as high as 0.63 ($p<0.01$ for all correlations) (Table 4).

B-M indices and fracture risk

Each standard deviation (SD) decrease in B-MBI and B-MMI was associated with an increased fracture risk that remained significant after accounting for age, BMI, grip strength, walking speed and aBMD of the lumbar spine (Table 5). Lower $B\text{-}MMI_w$ showed a higher association with fracture risk than all other B-M indices. Although SD decreases in B-MSI and B-MAI were associated with an increased risk of fractures alone, these associations were attenuated after accounting for walking speed and lumbar spine aBMD. Adjustment for total hip aBMD rendered all HR's for B-M indices statistically non-significant. While B-MBI unadjusted for density tended towards an increased risk of fracture after accounting for total hip aBMD, this was not significant. Measures of lumbar spine and total hip aBMD were both independent risk factors for incident fractures. Total hip aBMD demonstrated the highest fracture risk, persisting after accounting for age and BMI.

Difference in bone-muscle correlations between fracture groups

Aside from $B\text{-}MSI_U$, there were significant correlations between bone and muscle for each pair of parameters examined as part of B-M index definitions. All regression coefficients tended to be larger for the fractured group than the non-fractured group, but only for the SSI_p-MSS pair this was statistically significant (Table 6). BSI and MSS exhibited an inverse relationship for the non-fractured group that was not signifi-

	No Further Adjustments[a]		Further Adjusted for LS aBMD[a]		Further Adjusted for TH aBMD[a]	
A) Parameter	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
B-MBID	1.30	(1.03, 1.64)	1.33	(1.03, 1.71)	1.22	(0.94, 1.59)
B-MBIU	1.35	(1.06, 1.73)	1.45	(1.10, 1.90)	1.28	(0.97, 1.70)
B-MSID	1.28	(1.00, 1.64)	1.17	(0.91, 1.51)	1.07	(0.84, 1.37)
B-MSI$_U$	1.34	(1.04, 1.73)	1.21	(0.94, 1.56)	1.08	(0.84, 1.39)
B-MMI$_W$	1.64	(1.30, 2.07)	1.65	(1.22, 2.24)	1.13	(0.84, 1.52)
B-MMI$_L$	1.39	(1.06, 1.83)	1.35	(1.00, 1.83)	1.02	(0.79, 1.33)
B-MAI	1.23	(0.96, 1.56)	1.22	(0.93, 1.59)	0.99	(0.78, 1.24)
Lumbar spine aBMD T-score	1.28	(1.12, 1.45)				
Total Hip aBMD T-score	2.08	(1.64, 2.64)				

[a] Models were adjusted for age and body mass index

Table 5. Fracture risk associated with bone-muscle (B-M) indices and aBMD. Hazard ratios (HR) for fractures were reported for B-M indices and aBMD per standard deviation decrease in each measure. All HRs were adjusted for age and body mass index. Further adjustment for walking speed and either lumbar spine (LS) or total hip (TH) areal bone mineral density (aBMD) was applied to all models. Only models that did not contain B-M bending indices were further adjusted for grip strength.

Parameters Correlated	Groups	N	R	Regression coefficient*	P-value
SSI$_p$ & MBM (B-MBI$_D$)	**Fx**	87	0.436	274.30 (154.03, 394.58)	<0.001
	No-Fx	1031	0.435	245.65 (214.59, 276.71)	<0.001
BSI & MBM (B-MBI$_U$)	**Fx**	87	0.348	0.79 (0.34, 1.25)	0.001
	No-Fx	1028	0.264	0.53 (0.41, 0.64)	<0.001
SSI$_p$ & MSS[a] (B-MSI$_D$)	**Fx**	85	0.257	161.41 (31.04, 291.78)	0.017
	No-Fx	1016	-0.013	-7.46 (-43.24, 28.33)	0.683
BSI & MSS (B-MSI$_U$)	**Fx**	85	0.136	0.3 (-0.17, 0.77)	0.214
	No-Fx	1013	-0.024	-0.05 (-0.17, 0.08)	0.452
BMC$_W$ & LTM$_W$ (B-MMI$_W$)	**Fx**	89	0.628	309.4 (228.87, 389.93)	<0.001
	No-Fx	1068	0.552	261.94 (238.2, 285.68)	<0.001
BMC$_L$ & LTM$_L$ (B-MMI$_L$)	**Fx**	89	0.440	61.28 (35.02, 87.55)	<0.001
	No-Fx	1068	0.412	53.71 (46.14, 60.25)	<0.001
CoA & MCSA (B-MAI)	**Fx**	87	0.345	22.53 (9.49, 35.58)	0.001
	No-Fx	1031	0.287	15.56 (12.39, 18.74)	<0.001

[a] There is a significant interaction between muscle and fracture when regressed on bone.
* Unstandardized regression coefficients were reported as changes per standard deviation increase of dependent muscle variable.

Table 6. Comparison of bone-muscle correlations between fracture and non-fractured groups. A multivariable linear regression model examined the effect of the interaction between muscle measures and fracture status regressed on bone parameters. A significant interaction term indicated difference in bone-muscle relationships between fractured and non-fractured groups. All bone measures were used as dependent variables.

cant. A similar non-significant pattern was observed for the relationship between SSI$_p$ and MSS in those without a fracture. A significant interaction of muscle and fracture status on bone was only identified for SSI$_p$ versus MSS.

Discriminative power of B-M indices on fractures

In unadjusted models, AUC values were in general small for B-M indices and for aBMD T-scores (Table 7). However, most AUCs for B-M indices were significantly larger than 0.50. B-MMI$_w$ showed discriminative power above 60% for men with one or more incident fractures, which was similar to discriminative power of aBMD T-score of the lumbar spine, but lower than that of the total hip. When B-M indices were incorporated with total hip aBMD T-score in the same model, the ability to identify those with one or more incident fractures did not significantly improve compared to using total hip aBMD T-score alone.

Discussion

The current study suggests that the ratio of bone-to-muscle mass and bone-to-muscle bending strength are associated with an increased risk of incident fractures independent of age, BMI,

Parameter	Independent AUC	Independent 95% CI	TH aBMD T-score + B-M Index Model AUC	TH aBMD T-score + B-M Index Model 95% CI	p-value for AUC > 0.50	p-value for AUC(Model) vs. AUC(TH aBMD)
B-MBI$_D$	0.570	(0.505,0.635)	0.678	(0.618, 0.737)	0.037[a]	0.806
B-MBI$_U$	0.571	(0.509,0.634)	0.679	(0.620, 0.738)	0.023[a]	0.680
B-MSI$_D$	0.575	(0.511, 0.639)	0.679	(0.620, 0.738)	0.018[a]	0.436
B-MSI$_U$	0.576	(0.512, 0.640)	0.680	(0.621, 0.739)	0.015[a]	0.391
B-MMI$_W$	0.606	(0.543, 0.670)	0.691	(0.634, 0.747)	0.001[a]	0.280
B-MMI$_L$	0.595	(0.530, 0.660)	0.686	(0.630, 0.743)	0.003[a]	0.733
B-MAI	0.541	(0.473, 0.608)	0.678	(0.619, 0.737)	0.192	0.700
Lumbar Spine aBMD T-score	0.619	(0.560, 0.679)	-	-	<0.001[a]	-
Total Hip aBMD T-score	0.681	(0.623, 0.738)	-	-	<0.001[a]	-

[a] significance at the 95% confidence level.

Table 7. Discriminative power of aBMD and B-M indices on fractures. Areas under the receiver operator characteristics curve (AUC) were reported for B-M indices alone and in combination with total hip aBMD T-score in the same model. A Chi-square analysis was used to determine whether AUC values for the B-M indices plus total hip aBMD T-score model were significantly different from AUC values for total hip aBMD T-score alone.

walking speed, bone density of the lumbar spine but not of the total hip. However, a significant percentage of variance in bone-muscle indices was already explained by aBMD. The degree to which bone measures correlated with muscle measures did not differ according to the presence or absence of an incident fracture for most cases, except for bone-muscle strength relations. Overall, bone-muscle indices did not provide added value above and beyond that of bone density measurements for discriminating between those with or without incident fractures.

Mechanical B-M indices & fracture risk

Among the mechanical B-M indices, bending index identified the highest risk for fractures independent of physical function, and aBMD at the lumbar spine. In the current study, bending index was measured as the relationship between muscle bending moment and bone resistance to bending and torsion. Muscle bending moment can be reasonably represented by angular torque introduced by flexor digitorum longus and tibialis anterior muscles. The degree of adaptation of bone strength to muscle bending moment has been found to be consistent across individuals of different ages in men[9], and between different anatomical locations[10]. However, variation in how weight-bearing and other external forces influence this relationship may be related to hormonal variation as suggested by menopause-related differences in bone-muscle relationships[9]. Our finding that strength indices did not associate with significant increases in fracture risk may at least in part be explained by poor representation of muscle-specific strength in the leg muscles since direct measures of lower limb strength were unavailable.

Density & size-related B-M indices & fracture risk

A more elevated HR was found for mass indices compared to other B-M indices. This observation, suggesting a larger role played by bone and muscle mass on fracture risk, supports the current use of bone density measures for diagnosing osteoporosis. Rittweger and colleagues saw a higher mass index at the lower limb compared to the whole body[13]. In contrast, the present study demonstrated that smaller total-body mass index was associated with a larger risk for fractures than an equally sized difference in mass index at the lower limb (Table 5). Although fracture groups were not separated according to fracture location due to limited sample size and power, a previous study suggested that bone density data are best used to identify risk of fractures at the same location in which measurements were made[25]. While Rittweger and Macdonald reported that areal index differed among maturity groups and sex in adolescent boys and girls[8,13], adjustment for age in the present study of men did not improve the ability of the areal index to associate with incident fracture risk (Table 5).

Correlations between bone and muscle parameters

Significant correlations between bone and muscle parameters observed here support the notion that muscle is in part responsible for variation in bone volumetric density, structural and mechanical properties. Rittweger et al demonstrated that correlations between bone bending resistance and muscle bending moment were strongest at the 33% site of the tibia as compared to the 66% site (more proximal). This observation was explained by greater proximity of the 33% site to the insertion point of the gastrocnemius muscle[13]. Here, a similar correlation was observed between bone bending resistance and muscle torque when examined at the 66% tibia, but it is more likely to be explained by forces exerted by a different set of muscle groups[13,26]. The lower limb has shown to exhibit stronger correlations between bone and lean tissue mass than at the upper limb or whole body[27]. In the present study, the opposite was

true ($p<0.001$). A possible reason for this discrepancy is the fact that only men were examined here, in whom fat distribution may not be as variable and may not be a significant confounder to muscle mass quantification as in women[28]. With higher fat content, lean tissue mass may be overestimated, therefore misrepresenting bone-muscle mass correlations derived by DXA.

Study limitations

In this bone-muscle study, B-M indices were used as indicators of the interrelation between bone and muscle as previously reported[8-10,13,29,30]. The B-M indices measured only at one point in time represented purely the association between bone and muscle but considered neither change nor causality of one component on the other. These cross-sectional measures of bone-muscle ratios may have resulted in poorer ability to detect those who fractured compared to a putative measure capable of representing bone mechano-responsiveness. The present study was limited to the idea that smaller B-M indices were associated with smaller correlations between bone and muscle. In addition, ratiometric outcomes reduce variance components in both variables, discounting the potential contribution of some aspect of each bone and muscle parameter to fractures. However, in bone-muscle correlation analyses where ratios were not applied, only one set of bone-muscle parameters exhibited significant interaction with fractures.

In this study, only men were examined, the majority of whom were in the 70-80 years old age category (Table 3), and their fracture risk is likely different from younger men and from post-menopausal women examined by other studies[9,10,12,13]. The fact that part of the variation in B-M indices was already explained by aBMD of the total hip can further explain the attenuated fracture risk observed after Cox models for fractures were adjusted for aBMD.

The current study was performed using pQCT at the 66% tibia because it corresponds with the largest reported cross-section of the leg muscles[13]. The advantage of pQCT is that both bone and muscle can be obtained from the same 66% site scan. A number of studies supported the fact that MCSA is an indicator of muscular strength[6,31-34]. However, the ability of muscle to produce force per given volume of tissue appears to decline with aging[35-37]. One study suggested the use of ground reaction forces for assessing bone loading environment and saw that bones in younger men were more capable of responding to forces than in older men[30]. While the current study included physical function measures in fracture prediction models, there were no direct measures of lower limb physical function. In addition, the way agonist and antagonist muscle groups contribute forces differently in the lower limb is important to consider when assessing torque on bone[38].

Clinical relevance

Poor bone-muscle relationships may be only one of several reasons why patients fracture. Although one may have normal B-M indices, it is possible to possess both low bone and low muscle mass. Consequently, these individuals may also be at risk for fracture despite having normal B-M indices. The current study suggested that smaller B-M mass and bending indices were associated with fractures, but did not provide added clinical value for discriminating those with or without a fracture. At present, the results here suggested that B-M indices are potential risk factors for incident fracture. However, further investigation is required to determine whether changes in B-M indices are better at representing bone's response to muscle, and whether they are independent predictors of fractures. As novel therapies targeting muscle and bone emerge, an improved understanding of bone-muscle relations may become of high priority.

Conclusion

Bone-muscle indices were explored here from an epidemiological and biomechanical perspective, consistent with the bone mechanostat theory. Bone-muscle indices derived from pQCT and DXA were potential risk factors for fractures in men, independent of walking speed, age, BMI and lumbar spine aBMD. They also demonstrated acceptable discrimination between individuals with and without an incident fracture. This study showed that fracture discrimination afforded by bone and muscle information from DXA and pQCT scans may be more valuable than simply examining lumbar spine aBMD using DXA. However, these results should be interpreted with caution as B-M indices may not appear to complement total hip aBMD for predicting fractures, partly due to their significant association with total hip aBMD. It is worth noting that B-M indices are only a first step towards understanding the true response of bone to muscle forces *in vivo*. Future studies focusing on longitudinal changes in B-M indices merit attention, particularly with respect to fracture risk.

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