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Muscle density discriminates hip fracture better than computed tomography X-ray absorptiometry hip areal bone mineral density

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Abstract

Background   Muscle weakness is a key factor in the increase risk of falls and might also play a significant role in the increase of risk of hip fracture. Computed tomography-measured muscle size and muscle density are well-established imaging biomarkers used in studies of physical function, frailty or cancer, but limited to hip fracture. In particular, it is warranted to have a better understanding of the performance of muscle size and density in the discrimination of acute hip fractures. We also aim to determine age-related differences of muscle size and density in healthy controls and hip fracture patients.
Methods   Four hundred thirty-eight low-energy acute hip fracture cases and 316 healthy controls from the China Action on Spine and Hip Status study were included in the study. Muscle cross-sectional area and density were measured for the gluteus maximus and gluteus medius and minimus. Areal bone mineral density (aBMD) of the femoral neck and total hip was measured. Using propensity score matching, we generated three samples with cases and controls matched for age, body mass index, and gender: femoral neck fracture (FNF), intertrochanteric fracture (ITF), and any hip fracture vs. controls, respectively.
Results   Handgrip strength, gluteus muscle area and density, and bone parameters of the matched hip fracture groups were lower than those of the correspondence control groups, respectively ($P < 0.05$). The univariate analysis showed that associations of aBMD with FNF and with ITF were significantly weaker than associations between fracture and muscle parameters. Gluteus medius and minimus muscle density showed the highest areas under the curve (AUC) with FNF (0.88, 95% confidence interval, 0.85–0.92) and trochanteric fracture (0.95, 95% confidence interval, 0.92–0.97). The model including all muscle and bone parameters provided the highest AUC (FNF: AUC 0.912; ITF: AUC 0.958), and AUC results of another selected model without muscle density showed that association with fracture significantly dropped (FNF: AUC 0.755; ITF: AUC 0.858). Separate results for the two age groups younger and older than 70 years showed no age-related significant differences in discriminate models.
Conclusions   Muscle density performs better than aBMD from hip computed tomography X-ray absorptiometry and muscle size in discrimination of hip fracture. Combination of aBMD and muscle density provided the best discrimination. The integration of muscle assessments may trigger a paradigm shift in hip fracture prediction. Gluteus muscle density should also be evaluated as treatment outcome.

Keywords   Acute hip fracture; Muscle density; Muscle size; Bone mineral density

Introduction

Hip fractures (HFs) in the elderly are often referred to as 'The Last Fracture of Life', with a high degree of morbidity, mortality, and disability.[1] Therefore, it is important to identify subjects with a high HF risk to start preventive actions as soon as possible. Areal bone mineral density (aBMD) determined by dual-energy X-ray absorptiometry (DXA) is an established parameter for the diagnosis of osteoporosis and the prediction of HF risk. However, predictive capabilities of aBMD for HF are moderate.[2–4] Three-dimensional (3D) distribution of bone mineral density (BMD) and geometrical parameters such as cortical thickness measured by quantitative computed tomography (CT) have not substantially improved HF prediction.[5] With the development of computed tomography X-ray absorptiometry (CTXA), two-dimensional aBMD of the proximal femur can be derived from a 3D CT dataset. CTXA aBMD values of the total femur and femoral neck (FN) are equivalent to DXA aBMD values and can be used to calculate *T*-scores according to the World Health Organization definition of osteoporosis.[6]

Apart from a decrease of bone strength, muscle weakness might also play a significant role in the increase of risk of HF. Falls are common in the elderly, and almost all osteoporotic HFs are associated with falls. The risk of falls is multifactorial, but muscle weakness is a key factor in the increase risk of falls.[7–10] Reduction in muscle performance is associated with the loss of skeletal muscle mass.[11] However, substantial decreases in skeletal muscle function with ageing can occur with only minimal loss of skeletal muscle mass.[12,13] The interdependence may be partially related to the presence of fatty infiltration, which is one aspect of muscle quality. The assessment of muscle quality may be more important than the quantification of muscle mass. One aspect of muscle quality, namely, muscle density measured by CT as mean attenuation of skeletal muscle in Hounsfield units (HU), has already been widely used in research studies to assess muscle quality.[14]

Computed tomography-measured muscle size [cross-sectional area (CSA)] and muscle density (mean HU) of the abdomen and mid-thigh muscle bundle are well-established measurements parameters used in studies of physical function, frailty, or cancer.[14–16] However, only a few studies targeted the relationship of hip muscle characteristics with HF.[17–19] In particular, it is warranted to have a better understanding of the performance of muscle size and density in the discrimination of acute HFs.

The main aim of this study is to explore the value of muscle parameters for the discrimination of acute HFs. For this purpose, we used data from the China Action on Spine and Hip Status study including acute low-energy HFs cases and healthy controls. We also aim to determine age-related differences of muscle size and density in healthy controls and HF patients. We hypothesize that HF patients have lower muscle density than age-matched controls, and muscle density performs better than bone variables and muscle size in discriminating HFs.

Methods

Study design

China Action on Spine and Hip Status is a study to determine prevalence of osteoporotic fracture, osteoporosis, and osteoarthritis in an elderly Chinese population using quantitative CT and/or DXA.[20] The present subanalysis used CT scans from subjects obtained immediately after fragility HF and CT scans obtained from number of matched subjects without HFs. In this cross-sectional case–control analysis, we investigated and compared the gluteal muscle size and CT density for the discrimination of HF.

Participants

A total of 918 subjects with suspected HFs, admitted to the Beijing Jishuitan Hospital emergency department of orthopaedic trauma between January 2012 and May 2016, were recruited for this study. In this institution, CT scans are performed routinely for subjects with suspected or already confirmed HFs. Based on the CT images, fractures were categorized into FN fracture (FNF) or trochanteric fracture by an experienced musculoskeletal radiologist (Y. S.). A one-page questionnaire inquiring demographic data (e.g. age, gender, height, and weight), details of the fall (when, how, and where), fracture history, and medical history was completed by the patients or their relatives after the CT examination. Three hundred and sixteen community-dwelling subjects without HF of at least 60 years and in good health were recruited as controls from the neighbourhood of Beijing Jishuitan Hospital (*Figure* 1).

Inclusion and exclusion criteria of the HF patients were similar to those described by Su *et al.*[21] In brief, only fully ambulatory, community-dwelling Chinese Han adults with an HF resulting from low-energy injury were included. Thus, only falls from standing or sitting height were considered as cause for HF. In addition, CT had to be taken within 48 h after injury in order to minimize changes in aBMD and body composition due to bed rest after fracture. Subjects with prior and with bilateral HFs or inability to stand or walk before the event of HF were excluded.

Exclusion criteria of the control subjects were inability to sit and stand independently or inability to walk with or without an assistive device. Further exclusion criteria for both groups were stroke, neurological disorders, metabolic diseases, rheumatic diseases, heart failure, severe chronic
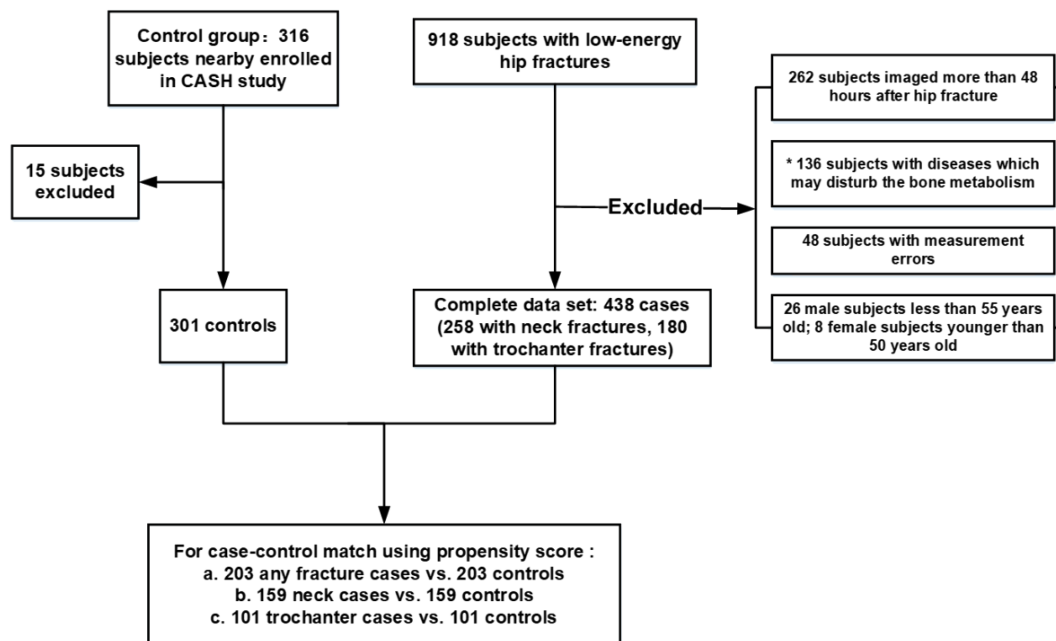
Figure 1 Flow chart of participant selection for the study. *Subjects with diseases potentially affecting bone metabolism, or having received treatments with potential or known effects on bone metabolism. Details are as follows: malignant tumours (*n* = 30); paralysis due to cerebrovascular accident (*n* = 35); the poor healed lower extremity fracture, avascular necrosis, or hip dysplasia (*n* = 23); bone metastases (*n* = 3); proximal femur osteochondroma (*n* = 1); lumbar fractures or proximal humerus fractures occurred within the last 3 months (*n* = 6); recently staying in bed due to acute pancreatitis (*n* = 2); ovariectomy (*n* = 2); medical usage of glucocorticoid hormone or Cushing's syndrome (*n* = 6); elevated parathyroid hormone level (*n* = 1); rheumatoid arthritis (*n* = 22); psoriasis (*n* = 2); severe renal insufficiency (*n* = 2); and myasthenia gravis (*n* = 1). CASH, China Action on Spine and Hip Status.

obstructive pulmonary disease and coagulation disorders, and other diseases that limited function.

The study was approved by the ethics committee of Beijing Jishuitan Hospital. Informed consent was obtained from each participant.

Computed tomography acquisition

Spiral CT imaging of the hip was performed for all study participants using two Toshiba Aquilion CT scanners (Toshiba Medical Systems Division, Tokyo, Japan). Scans were acquired in supine position from the top of the acetabulum to 3 cm below the lesser trochanter and included both legs. Scan parameters were 120 kVp, 125 mAs, 50 cm field of view, 512 × 512 matrix, 1 mm reconstructed slice thickness, and a standard reconstruction kernel with filtered back-projection.

Muscle density assessments

Cross-sectional area and density were measured of the gluteus maximus (G.max) at the level of the greater trochanter and of the gluteus medius and minimus (G.med/min) muscle at the level of the third sacral (S3) (*Figure* 2). In subjects with HF, the non-fractured hip was analysed. In 97 participants, the CT scan did not cover the S3 level; therefore, G.med/

min muscle density and area were measured at S4 or S5 levels, only. Supporting Information, *Table S1* shows that there was no significant difference (0.8 HU) in muscle density between the S3 and non-S3 levels. Difference in muscle area between the S3 and non-S3 levels was not significant either; however, the absolute difference of about 4.1 cm^2 accounted for a bias of up to 10% compared with the mean area value at the S3 level. For this reason, we did not include G.med/min muscle CSA in the analysis.

OsiriX software (Lite Version 10.0.2, Pixmeo, Geneva, Switzerland) was used for analysis. Muscle segmentation was performed manually using the 'pencil' tool to outline muscle contours. Within the resulting muscle regions of interest, a threshold of −29 HU was used to distinguish muscle tissue from fat. All muscle measurements were performed by the same investigator (Y. Z.) who had received training by an expert radiologist in CT muscle imaging prior to the analysis. For practice purposes, a sample of about 20 images had been analysed together with the expert prior to the beginning of the measurement study.

Muscle strength assessments

Handgrip strength of the dominant hand was measured using a Jamar dynamometer (Jamar®, Los Angeles, CA, USA). Details of measuring grip strength were reported previously.[22]
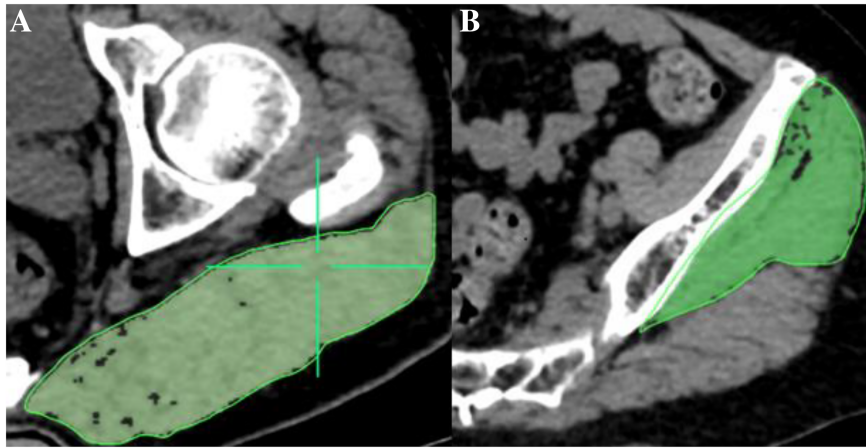
Figure 2 (A) Measurement of cross-sectional area and mean computed tomography values of the gluteus maximus muscle at the level of the greater trochanter of the femur. (B) Measurement of the gluteus medius and minimus muscle at the third sacral level. Muscle region is represented by the area highlighted in green.

Bone mineral density

Areal BMD (g/cm^2) of the FN and total hip (TH) was calculated from the hip CT scans using the CTXA technique (Version 4.2.3, Mindways Inc).[23] The Medical Image Analysis Framework option Femur (MIAF Femur Version 7.1.0MRH) was used to measure 3D FN cortical thickness (FN CortThick).[20]

Statistical analysis

Study participants were categorized as healthy controls, with an FNF, or with an intertrochanteric fracture (ITF). The two fracture groups were also combined as any HF group. Continuous variables are presented as mean ± standard deviation. Categorical variables are described as counts and corresponding percentages.

In order to minimize the between-group selection bias and to control for potential confounding factors, including age, gender, and body mass index (BMI), propensity score matching (PSM) was applied to match subjects for the following analyses: (i) subjects with FNF vs. control subjects; (ii) subjects with ITF vs. control subjects; and (iii) subjects with any HF vs. control subjects.

Mean differences between two groups each were analysed using the Mann–Whitney *U* test. Three different multivariable subsets were used for independent binary logistic regression models to calculate odds ratios of fracture per standard deviation increase: (i) the muscle model included G.max muscle CSA and density and G.med/min muscle density; (ii) the BMD model included TH aBMD and FN aBMD; and (iii) the bone structure model included FN CortThick. Results of the muscle strength model, which included handgrip strength, are not shown because of the low number of only 66 HF

patients. Receiver operating characteristic (ROC) curve analyses were applied, and area under the curve (AUC) values with 95% confidence intervals (CIs) were used as performance characteristics. The Hosmer–Lemeshow tests were used to evaluate model robustness by calculating the Pearson χ^2 statistic from the table of observed and expected frequencies. Results are not significant if models fit well. Four selected logistic regression models were used to determine best variable subsets for fracture discrimination: (i) G.max muscle CSA and density, G.med/min muscle density, and FN aBMD; (ii) G.max muscle density, G.med/min muscle density, and FN aBMD; (iii) G.med/min muscle density and FN aBMD; and (iv) G. max muscle CSA and FN aBMD. One-degree-of-freedom tests were used to compare the latter three ROC curves with the first selected model. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study sample characteristics

Figure 1 illustrates the recruitment of study participants. Fifteen participants (from 316) were excluded from the control group: eight because of invalid handgrip strength measurements and seven because of missing CT scans or inadequate image quality (i.e. motion artefacts). Of the 301 control participants, 107 were male and 194 female. After the review of the questionnaire, of medical records, and of the CT images, 480 cases of the 918 low trauma HF patients were excluded. After exclusion, the study cohort included 739 participants: 301 non-fracture controls, 258 subjects with FNF, and 180 subjects with ITF. Characteristics of the study cohort are shown in *Table* 1. The HF patients were older

Table 1 Characteristics of study participants

Characteristics	Unmatched population [mean ± SD or % (n)]				Mean difference[a]			P value[b]		
	HC (n = 301) (1)	FNF (n = 258) (2)	ITF (n = 180) (3)	HF (n = 438) (4)	(2) vs. (1)	(3) vs. (1)	(4) vs. (1)	(2) vs. (1)	(3) vs. (1)	(4) vs. (1)
Male gender, % (n)	35.6 (107)	20.9 (54)	25.6 (46)	22.8 (100)	n/a	n/a	n/a	n/a	n/a	n/a
Age (years)	68.4 ± 6.1	74.0 ± 10.0	78.5 ± 8.6	75.8 ± 9.7	5.6 (7.6)	10.1 (12.9)	7.5 (9.8)	<0.01	<0.01	<0.01
Weight (kg)	66.8 ± 10.0	60.2 ± 10.7	61.1 ± 12.0	60.6 ± 11.3	−6.6 (−11.0)	−5.7 (−9.3)	−6.2 (−10.3)	<0.01	<0.01	<0.01
Height (cm)	162.5 ± 7.5	161.6 ± 7.4	160.9 ± 8.6	161.3 ± 7.9	−0.9 (−0.5)	−1.5 (−0.9)	−1.1 (−0.7)	0.14	0.01	0.02
BMI (kg/cm^2)	25.2 ± 2.9	22.9 ± 3.4	23.6 ± 4.1	23.2 ± 3.7	−2.3 (−10.0)	−1.7 (−7.1)	−2.0 (−8.8)	<0.01	<0.01	<0.01
Handgrip (kg)	25.6 ± 8.5	14.3 ± 9.6	11.9 ± 9.7	13.1 ± 9.7	−11.3 (−79.0)	−13.7 (−114.4)	−12.5 (−95.5)	<0.01	<0.01	<0.01
G.MaxM area (cm^2)	39.4 ± 7.4	31.8 ± 7.1	29.7 ± 7.4	31.0 ± 7.3	−7.5 (−23.7)	−9.6 (−32.3)	−8.4 (−27.1)	<0.01	<0.01	<0.01
G.MaxM density (HU)	33.5 ± 6.6	25.1 ± 7.0	21.9 ± 7.3	23.8 ± 7.3	−8.4 (−33.5)	−11.6 (−52.9)	−9.7 (−40.8)	<0.01	<0.01	<0.01
G.Med/MinM density (HU)	42.4 ± 4.4	31.9 ± 6.4	29.4 ± 5.8	30.9 ± 6.3	−10.5 (−32.8)	−12.9 (−43.9)	−11.5 (−37.2)	<0.01	<0.01	<0.01
SBP (mmHg)	126.5 ± 8.6	144.2 ± 19.4	145.4 ± 22.8	144.8 ± 20.8	17.7 (12.3)	18.9 (13.0)	18.2 (12.6)	0.11	0.30	0.09
DBP (mmHg)	74.1 ± 7.6	74.5 ± 18.2	75.6 ± 13.7	75.0 ± 16.4	0.4 (0.6)	1.5 (2.0)	0.9 (1.2)	<0.01	<0.01	<0.01
TH aBMD (g/cm^2)	0.8 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	−0.2 (−31.6)	−0.2 (−45.4)	−0.2 (−36.9)	<0.01	<0.01	<0.01
FN aBMD (g/cm^2)	0.7 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	−0.2 (−32.9)	−0.2 (−42.9)	−0.2 (−36.8)	<0.01	<0.01	<0.01
FN CortThick (mm)	1.8 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	−0.2 (−11.0)	−0.2 (−9.9)	−0.2 (−10.5)	<0.01	<0.01	<0.01

BMI, body mass index; DBP, diastolic blood pressure; FN aBMD, femoral neck areal bone mineral density; FN CortThick, cortical thickness of femoral neck; FNF, femoral neck fracture; G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HC, healthy control; HF, any hip fracture; HU, Hounsfield units; ITF, intertrochanteric fracture; SBP, systolic blood pressure; SD, standard deviation; TH aBMD, total hip areal bone mineral density.
[a]Data in parentheses are percentage mean differences.
[b]P values were obtained for fracture risk using two-sample Wilcoxon tests for continuous variables.

and had higher systolic blood pressure, lower BMI, lower handgrip strength, lower gluteus muscle CSA and density, lower aBMD in TH and FN regions, and lower cortical thickness of FN.

After PSM using age, gender, and BMI, 159 FNF cases were matched with 159 controls and 101 ITF cases with 101 controls (*Table* 2). Two hundred three cases with any HF were matched with 203 controls. The HF group was further divided in a younger group (age <70 years) consisting of 100 HF cases matched with 115 controls and an older group (age ≥70 years) consisting of 103 HF cases and 88 controls (*Table* 3).

Handgrip strength, gluteus muscle area and density, and bone parameters of the matched HF groups were lower than those of the correspondence control groups, respectively ($P < 0.05$).

Relationship between muscle parameters and age

To explore the age-related TH fracture risk discrimination, we therefore stratified the analyses by age (age cut point 70 years). *Figure* 3 shows of G.med/min muscle density and G.max muscle density and CSA stratified for the two age ranges below and above 70 years. For all three muscle parameters, variables were significantly different between the two age groups, with the exception of G.max muscle CSA in control group ($P = 0.278$). Interestingly in HF group, G.max muscle CSA differed by 13% between the two age groups. However, the age-related difference in G.max muscle CSA

was numerically lower than the corresponding difference of 18% of G.max muscle density.

Associations of muscle and bone parameters with hip fracture

Table 4 shows the associations of G.max muscle CSA and density, G.med/min muscle density, FN and TH aBMD, and FN CortThick with HF after matching for age, BMI, and gender by PSM. *Figure* 4 shows ROC curves for bone and muscle variables shown in *Table* 4. The univariate analysis showed that associations of aBMD with FN and with trochanteric fracture were significantly weaker than associations between fracture and muscle density parameters. G.med/min muscle density showed the highest AUC with FNF (0.88; 95% CI, 0.85–0.92) and trochanteric fracture (0.95; 95% CI, 0.92–0.97). Association with fracture was significantly higher than for G.max muscle area (FNF: $P < 0.0001$; ITF: $P < 0.0001$) and for FN aBMD (FNF: $P = 0.008$; IFT: $P < 0.0001$). AUC values of multivariate bone and muscle models (*Table* 3) were almost identical to those of FN aBMD and G.med/min muscle density, respectively. In contrast, the AUC value of FN cortical thickness (*Table* 3) was rather low (FNF: 0.62; ITF: 0.70).

Association with fracture was also determined for four selected models (Models 1–4) combining bone and muscle parameters. Numerically, the highest AUC values were obtained for Model 1 (FNF: AUC 0.912; ITF: AUC 0.958), but AUC values for selected Model 2 (FNF: AUC 0.908; ITF: AUC 0.957) and Model 3 (FNF: AUC 0.902; ITF: AUC 0.956) were not dominantly lower (Model 2 vs. Model 1: FNF: $P = 0.417$;

Table 2 Characteristics of matched participants using propensity score in FNF, ITF, and HC groups

Characteristics [mean ± SD or % (*n*)]	Matched population				Matched population			
	HC (*n* = 159)	FNF (*n* = 159)	Mean difference[a]	*P* value[b]	HC (*n* = 101)	ITF (*n* = 101)	Mean difference[a]	*P* value[b]
Male gender, % (*n*)	23.3 (37)	26.4 (42)	n/a	n/a	39.6 (40)	28.7 (29)	n/a	n/a
Age (years)	69.9 ± 6.3	69.8 ± 9.4	−0.1 (−0.2)	0.8	73.2 ± 6.8	73.6 ± 6.0	0.4 (0.5)	0.8
Weight (kg)	64.4 ± 10.8	64.5 ± 9.5	0.1 (0.1)	0.8	64.9 ± 8.8	64.4 ± 11.1	−0.5 (−0.7)	0.8
Height (cm)	161.0 ± 7.4	163.1 ± 7.5	2.2 (1.3)	0.01	162.1 ± 7.7	162.2 ± 8.6	0.1 (0.1)	0.8
BMI (kg/cm^2)	24.8 ± 3.1	24.2 ± 3.4	−0.6 (−2.3)	0.1	24.7 ± 2.2	24.5 ± 4.05	−0.2 (−0.6)	0.7
Handgrip (kg)	23.7 ± 7.9	16.6 ± 9.6	−7.1 (−42.8)	<0.01	24.9 ± 9.0	15.4 ± 10.3	−9.6 (−62.2)	<0.01
G.MaxM area (cm^2)	37.1 ± 6.9	34.0 ± 7.0	−3.1 (−9.1)	<0.01	38.8 ± 7.4	31.8 ± 7.2	−7.1 (−22.2)	<0.01
G.MaxM density (HU)	32.5 ± 6.4	26.0 ± 6.9	−6.5 (−24.9)	<0.01	33.1 ± 6.3	22.7 ± 7.9	−10.4 (−45.9)	<0.01
G.Med/MinM density (HU)	41.6 ± 4.5	33.0 ± 6.1	−8.3 (−25.1)	<0.01	41.1 ± 4.6	30.5 ± 5.3	−10.6 (−34.9)	<0.01
SBP (mmHg)	126.9 ± 8.9	143.1 ± 20.3	16.2 (11.4)	<0.01	128.0 ± 7.8	146.7 ± 21.5	18.7 (12.7)	<0.01
DBP (mmHg)	74.0 ± 8.6	72.7 ± 20.0	−1.3 (−1.8)	0.7	75.1 ± 7.1	79.7 ± 11.8	4.6 (5.8)	0.03
TH aBMD (g/cm^2)	0.8 ± 0.12	0.6 ± 0.1	−0.1 (−19.8)	<0.01	0.8 ± 0.2	0.6 ± 0.1	−0.2 (−34.5)	<0.01
FN aBMD (g/cm^2)	0.7 ± 0.1	0.5 ± 0.1	−0.1 (−21.5)	<0.01	0.7 ± 0.1	0.5 ± 0.09	−0.2 (−33.1)	<0.01
FN CortThick (mm)	1.8 ± 0.3	1.7 ± 0.3	−0.1 (−8.6)	<0.01	1.9 ± 0.3	1.7 ± 0.3	−0.2 (−12.6)	<0.01

BMI, body mass index; DBP, diastolic blood pressure; FN aBMD, femoral neck areal bone mineral density; FN CortThick, cortical thickness of femoral neck; FNF, femoral neck fracture; G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HC, healthy control; HU, Hounsfield units; ITF, intertrochanteric fracture; SBP, systolic blood pressure; SD, standard deviation; TH aBMD, total hip areal bone mineral density.
[a]Data in parentheses are percentage mean differences.
[b]*P* values were obtained for fracture risk using two-sample Wilcoxon tests for continuous variables.

Table 3 Characteristics of matched participants using propensity score in total fracture group and HC group

Characteristics [mean ± SD or % (n)]	Total population				<70 years old				≥70 years old			
	HC (n = 203)	HF (n = 203)	Mean difference[a]	P value[b]	HC (n = 115)	HF (n = 100)	Mean difference[a]	P value[b]	HC (n = 88)	HF (n = 103)	Mean difference[a]	P value[b]
Male gender, % (n)	28.6 (58)	28.6 (58)	n/a	n/a	25.2 (29)	22.0 (22)	n/a	n/a	33.0 (29)	35.0 (36)	n/a	n/a
Age (years)	69.6 ± 6.7	69.3 ± 8.0	−0.3 (−0.4)	0.87	64.5 ± 2.7	62.5 ± 4.5	−2.0 (−3.2)	<0.01	76.2 ± 4.1	75.9 ± 4.3	−0.3 (−0.4)	0.40
Weight (kg)	65.1 ± 9.9	65.1 ± 10.1	0.02 (0.03)	0.90	66.5 ± 11.1	62 ± 9.8	−4.5 (−7.3)	<0.01	63.2 ± 7.7	68.1 ± 9.6	4.9 (7.8)	<0.01
Height (cm)	161.3 ± 7.3	163.1 ± 7.8	1.8 (1.1)	0.02	161.7 ± 7.6	163.1 ± 7.2	1.4 (0.8)	0.13	160.8 ± 6.9	163.2 ± 8.3	2.4 (1.5)	0.08
BMI (kg/cm²)	25.0 ± 3.0	24.5 ± 3.6	−0.5 (−1.9)	0.11	25.4 ± 3.3	23.3 ± 2.9	−2.1 (−9.0)	<0.01	24.4 ± 2.5	25.7 ± 3.8	1.2 (5.0)	0.02
Handgrip (kg)	24.3 ± 8.1	14.8 ± 10.2	−9.5 (−39.2)	<0.01	25.6 ± 8.3	14.8 ± 10.2	−10.8 (−72.7)	<0.01	22.6 ± 7.5	14.8 ± 10.4	−7.9 (−34.8)	<0.01
G.MaxM area (cm²)	37.8 ± 6.6	34.1 ± 7.2	−3.7 (−9.8)	<0.01	38.4 ± 6.5	35.5 ± 7.7	−2.9 (−8.2)	<0.01	37 ± 6.7	32.7 ± 6.3	−4.2 (−11.5)	<0.01
G.MaxM density (HU)	32.8 ± 6.5	25.8 ± 7.1	−7.1 (−21.5)	<0.01	33.5 ± 6.4	28.3 ± 6	−5.2 (−18.4)	<0.01	31.9 ± 6.6	23.3 ± 7.2	−8.6 (−27.1)	<0.01
G.Med/MinM density (HU)	42.1 ± 4.5	32.8 ± 6.0	−9.1 (−21.6)	<0.01	43.3 ± 4.5	34.1 ± 5.5	−9.1 (−26.7)	<0.01	40.5 ± 4.1	31.9 ± 5.4	−8.6 (−21.4)	<0.01
SBP (mmHg)	126.6 ± 8.5	143.7 ± 22.3	17.1 (13.5)	<0.01	125.2 ± 8.6	136.6 ± 20.5	11.5 (8.4)	<0.01	128.4 ± 8.1	150.2 ± 22.2	21.8 (17.0)	<0.01
DBP (mmHg)	74.2 ± 6.3	75.4 ± 18.7	1.2 (1.6)	0.03	74.4 ± 5.9	70.3 ± 22.4	−4.1 (−5.9)	0.65	73.9 ± 6.8	80.1 ± 13.1	6.2 (8.4)	0.01
TH aBMD (g/cm²)	0.8 ± 0.2	0.6 ± 0.1	−0.2 (−19.3)	<0.01	0.8 ± 0.1	0.6 ± 0.1	−0.1 (−21.8)	<0.01	0.8 ± 0.2	0.6 ± 0.1	−0.2 (−20.6)	<0.01
FN aBMD (g/cm²)	0.7 ± 0.1	0.5 ± 0.09	−0.1 (−20.5)	<0.01	0.7 ± 0.1	0.5 ± 0.1	−0.1 (−23.8)	<0.01	0.7 ± 0.2	0.5 ± 0.1	−0.1 (−21.6)	<0.01
FN CortThick (mm)	1.9 ± 0.3	1.7 ± 0.3	−0.1 (−8.1)	<0.01	1.8 ± 0.3	1.7 ± 0.3	−0.2 (−8.9)	0.03	1.9 ± 0.3	1.7 ± 0.3	−0.2 (−8.2)	<0.01

BMI, body mass index; DBP, diastolic blood pressure; FN aBMD, femoral neck areal bone mineral density; FN CortThick, cortical thickness of femoral neck; G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HC, healthy control; HF, any hip fracture; HU, Hounsfield units; SBP, systolic blood pressure; SD, standard deviation; TH aBMD, total hip areal bone mineral density.

[a]Data in parentheses are percentage mean differences.

[b]P values were obtained for fracture risk using two-sample Wilcoxon tests for continuous variables.
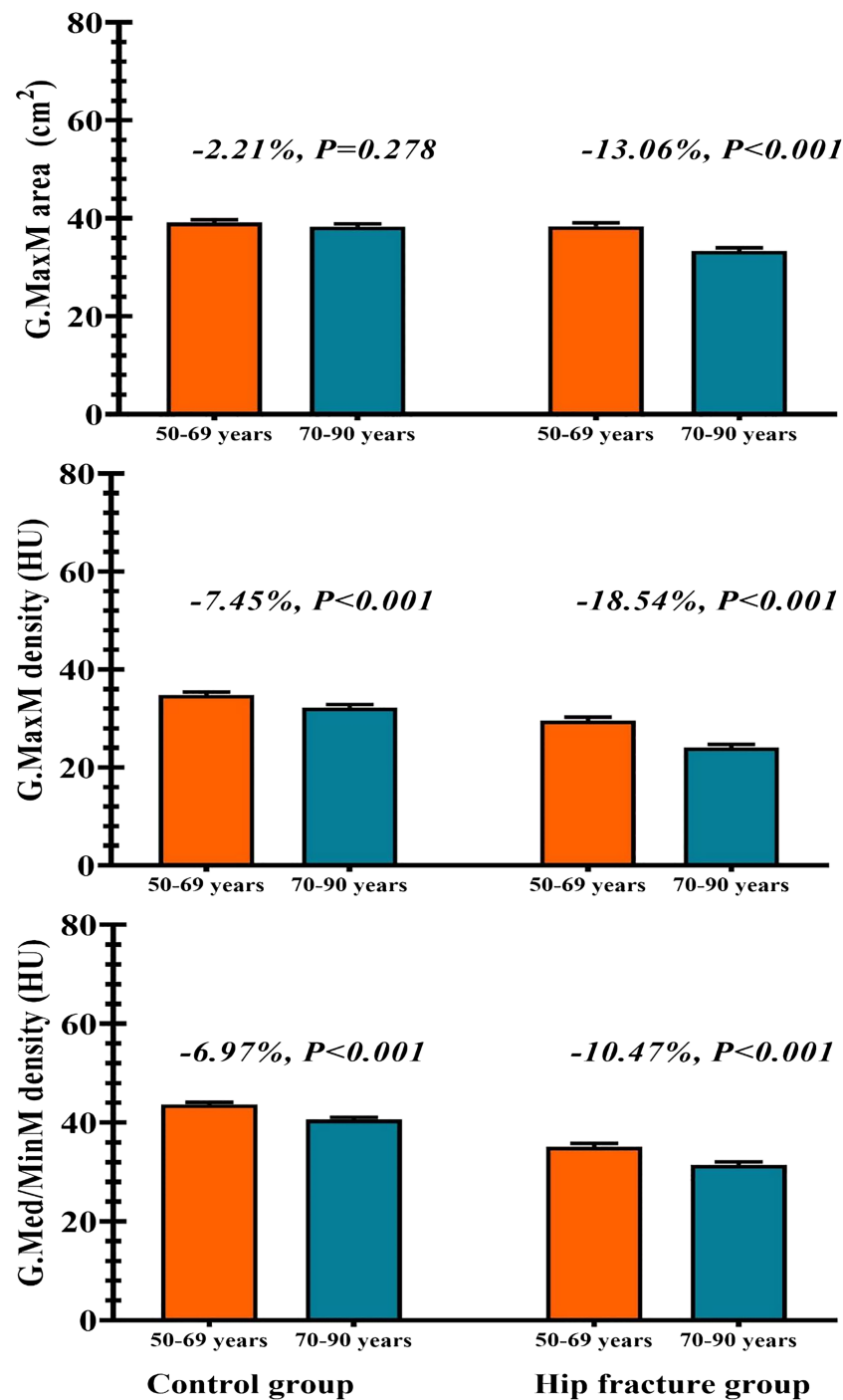
Figure 3 Gluteus muscle area and density by age groups in control and fracture groups. G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HU, Hounsfield units.

ITF: $P = 0.149$; Model 3 vs. Model 1: FNF: $P = 0.115$; ITF: $P = 0.551$). AUC results of Model 4 (FNF: AUC 0.755; ITF: AUC 0.858) showed that association with fracture significantly dropped when not including muscle density (Model 4 vs. Model 1: FNF: $P < 0.001$; ITF: $P < 0.001$). AUC values for Model 1 were higher than for the other three models in

any HF (Model 2: $P = 0.311$; Model 3: $P = 0.132$; and Model 4: $P < 0.001$).

For all multivariate and selected models, AUC values for any type of HF were in between those of FNF and trochanteric fracture. Separate results for the two age groups younger and older than 70 years were only performed for the any fracture

Table 4 ORs of fracture risk per SD increase in PS-matched population by fracture type

Model/variables	Femoral neck fracture risk (N = 318)		Intertrochanteric fracture risk (N = 202)		Any hip fracture risk (N = 406)	
	ORs (95% CIs)	P value	ORs (95% CIs)	P value	ORs (95% CIs)	P value
Univariate muscle parameters						
G.MaxM area (cm²)	0.63 (0.50, 0.80)	<0.01	0.35 (0.24, 0.50)	<0.01	0.58 (0.47, 0.71)	<0.01
G.MaxM density (HU)	0.34 (0.25, 0.45)	<0.01	0.17 (0.11, 0.28)	<0.01	0.31 (0.24, 0.41)	<0.01
G.Med/MinM density (HU)	0.10 (0.06, 0.16)	<0.01	0.03 (0.01, 0.08)	<0.01	0.07 (0.04, 0.12)	<0.01
Multivariate muscle model						
G.MaxM area (cm²)	1.06 (0.76, 1.49)	0.72	0.65 (0.36, 1.16)	0.15	1.01 (0.74, 1.38)	0.96
G.MaxM density (HU)	1.76 (1.04, 2.98)	0.03	1.97 (0.79, 4.90)	0.15	1.64 (1.03, 2.62)	0.04
G.Med/MinM density (HU)	0.06 (0.03, 0.12)	<0.01	0.02 (0.004, 0.08)	<0.01	0.05 (0.02, 0.09)	<0.01
AUC (95% CIs), P value[a]	0.887 (0.850, 0.923), 0.50		0.945 (0.916, 0.974), 0.55		0.904 (0.875, 0.933), 0.89	
Univariate BMD variables						
TH aBMD (g/cm²)	0.30 (0.22, 0.42)	<0.01	0.18 (0.11, 0.29)	<0.01	0.24 (0.17, 0.33)	<0.01
FN aBMD (g/cm²)	0.35 (0.26, 0.48)	<0.01	0.16 (0.09, 0.28)	<0.01	0.27 (0.20, 0.37)	<0.01
Multivariate BMD model						
TH aBMD (g/cm²)	0.74 (0.44, 1.23)	0.24	0.42 (0.19, 0.90)	0.03	0.31 (0.19, 0.52)	<0.01
FN aBMD (g/cm²)	0.93 (0.23, 0.68)	<0.01	0.34 (0.15, 0.78)	0.01	0.71 (0.43, 1.19)	0.20
AUC (95% CIs), P value[a]	0.759 (0.706, 0.812), 0.46		0.851 (0.798, 0.904), 0.46		0.799 (0.756, 0.842), 0.54	
Bone structure model						
FN CortThick (mm)	0.57 (0.43, 0.75)	<0.01	0.41 (0.28, 0.62)	<0.01	0.57 (0.45, 0.73)	<0.01
AUC (95% CIs), P value[a]	0.618 (0.553, 0.682), 0.01		0.702 (0.626, 0.777), 0.18		0.617 (0.561, 0.674), <0.01	
Selected Model 1						
G.MaxM area (cm²)	1.54 (1.03, 2.29)	0.03	0.92 (0.47, 1.79)	0.80	1.53 (1.05, 2.24)	0.04
G.MaxM density (HU)	1.76 (1.01, 3.09)	0.05	1.90 (0.73, 4.98)	0.19	1.76 (1.05, 2.95)	0.04
G.Med/MinM density (HU)	0.06 (0.03, 0.13)	<0.01	0.03 (0.01, 0.11)	<0.01	0.05 (0.02, 0.10)	<0.01
FN aBMD (g/cm²)	0.34 (0.21, 0.55)	<0.01	0.26 (0.11, 0.60)	<0.01	0.29 (0.18, 0.48)	<0.01
AUC (95% CIs), P value[a]	0.912 (0.88, 0.944), 0.71		0.958 (0.932, 0.984), 0.66		0.930 (0.905, 0.955), 0.28	
Selected Model 2						
G.MaxM density (HU)	1.90 (1.07, 3.39)	0.02	1.84 (0.73, 4.65)	0.20	1.83 (1.10, 3.03)	0.02
G.Med/MinM density (HU)	0.06 (0.03, 0.14)	<0.01	0.03 (0.01, 0.11)	<0.01	0.06 (0.03, 0.11)	<0.01
FN aBMD (g/cm²)	0.42 (0.27, 0.66)	<0.01	0.25 (0.11, 0.56)	<0.01	0.34 (0.23, 0.52)	<0.01
AUC (95% CIs), P value[a]	0.908 (0.877, 0.941), 0.40		0.957 (0.93, 0.983), 0.58		0.927 (0.903, 0.952), 0.71	
Selected Model 3						
G.Med/MinM density (HU)	0.11 (0.07, 0.19)	<0.01	0.05 (0.02, 0.13)	<0.01	0.09 (0.05, 0.16)	<0.01
FN aBMD (g/cm²)	0.42 (0.28, 0.64)	<0.01	0.26 (0.12, 0.61)	<0.01	0.35 (0.23, 0.53)	<0.01
AUC (95% CIs), P value[a]	0.902 (0.869, 0.935), 0.74		0.956 (0.930, 0.982), 0.98		0.923 (0.898, 0.948), 0.89	

(Continues)

Table 4 (continued)

Model/variables	Femoral neck fracture risk (N = 318)		Intertrochanteric fracture risk (N = 202)		Any hip fracture risk (N = 406)	
	ORs (95% CIs)	P value	ORs (95% CIs)	P value	ORs (95% CIs)	P value
Selected Model 4						
G.MaxM area (cm²)	1.04 (0.78, 1.39)	0.81	0.61 (0.39, 0.94)	0.02	0.94 (0.72, 1.21)	0.62
FN aBMD (g/cm²)	0.3 (0.21, 0.43)	<0.01	0.20 (0.11, 0.36)	<0.01	0.25 (0.18, 0.35)	<0.01
AUC (95% CIs), P value^a	0.755 (0.702, 0.808), 0.73		0.858 (0.806, 0.910), 0.69		0.797 (0.754, 0.840)	

AUC, area under curve; BMD, bone mineral density; CIs, confidence intervals; FN aBMD, femoral neck areal bone mineral density; FN CortThick, cortical thickness of femoral neck; G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HU, Hounsfield units; ORs, odds ratios; PS, propensity score; SD, standard deviation; TH aBMD, total hip areal bone mineral density.

^a P values were obtained using the Hosmer–Lemeshow tests. P > 0.05 indicates that the null hypothesis (observed event rates match expected event rates in subgroups of the model population) is not rejected.

due to the limited number of participants' age differentiation (*Table* 5). AUC values of multivariate models were numerically higher in the younger age group with the exception of Model 4, but none of the differences were statistically significant.

Results for handgrip strength and a corresponding muscle strength model are not shown in *Tables* 4 and 5, because in the HF group, handgrip measurements were available only from 66 subjects. Using these limited numbers, AUC results for a muscle strength model to discriminate fracture were as follows: HF: AUC 0.751, *P* for Hosmer–Lemeshow test = 0.53; ITF: AUC 0.722, *P* = 0.58; and FNF: AUC 0.706, *P* = 0.02. For age stratified, AUC results for any HF were as follows: age <70 years: AUC 0.771, *P* = 0.49, and age >70 years: AUC 0.714, *P* = 0.16.

Discussions

Based on the analysis of 739 participant of the large China Action on Spine and Hip Status case–control cohort, our study demonstrates that CT muscle density is higher associated with acute HF than muscle size or aBMD measured by CTXA of the hip. To our knowledge, this is the largest CT study so far that demonstrated an important contribution of muscle characteristic to HF discrimination. In addition, the relevance of muscle size vs. muscle density for HF discrimination has not been addressed so far.

Muscle density as determined by CT is measured as X-ray attenuation of muscle reported as CT value in HU. Elevated levels of intramuscular fat accumulation[24] reduce CT muscle density but do not affect muscle area. Thus, muscle area is insensitive to intramuscular fat accumulation, which is an important cause of age-related muscle degradation.[25–27] However, in the vast majority of imaging studies targeting muscle, muscle area, not density, was obtained as a primary outcome.[14,16] An abundance of previous research has shown that fatty infiltration of muscle gradually increases with age.[26] A study of the spine showed that muscle density profoundly declined with age (−17% per decade in women and −11% in men).[28] In another longitudinal study of trunk muscle with 6 year follow-up, a 20–30% decline of lumber muscles density was observed.[29] Age-related decreases in muscle density were also reported from several studies. In the AGES Reykjavik Study, quadriceps muscle density decreased by about 12.5% between 65 and 85 years.[30] Several cross-sectional or longitudinal studies of the Health ABC project also confirmed decreases of thigh muscle density or increases of thigh muscle fatty infiltration with age.[12,24,31] Another study[32] found that fat content of the hip muscles remained relatively stable between 20 and 50 years of age and then increased with age. Further, the increase in fat content with age in individuals over 50 years of age was greater for the gluteal muscles than for the other hip muscles. Therefore, we believe that changes in muscle density precede HF and may be a long-term predictor of frailty leading to HF.
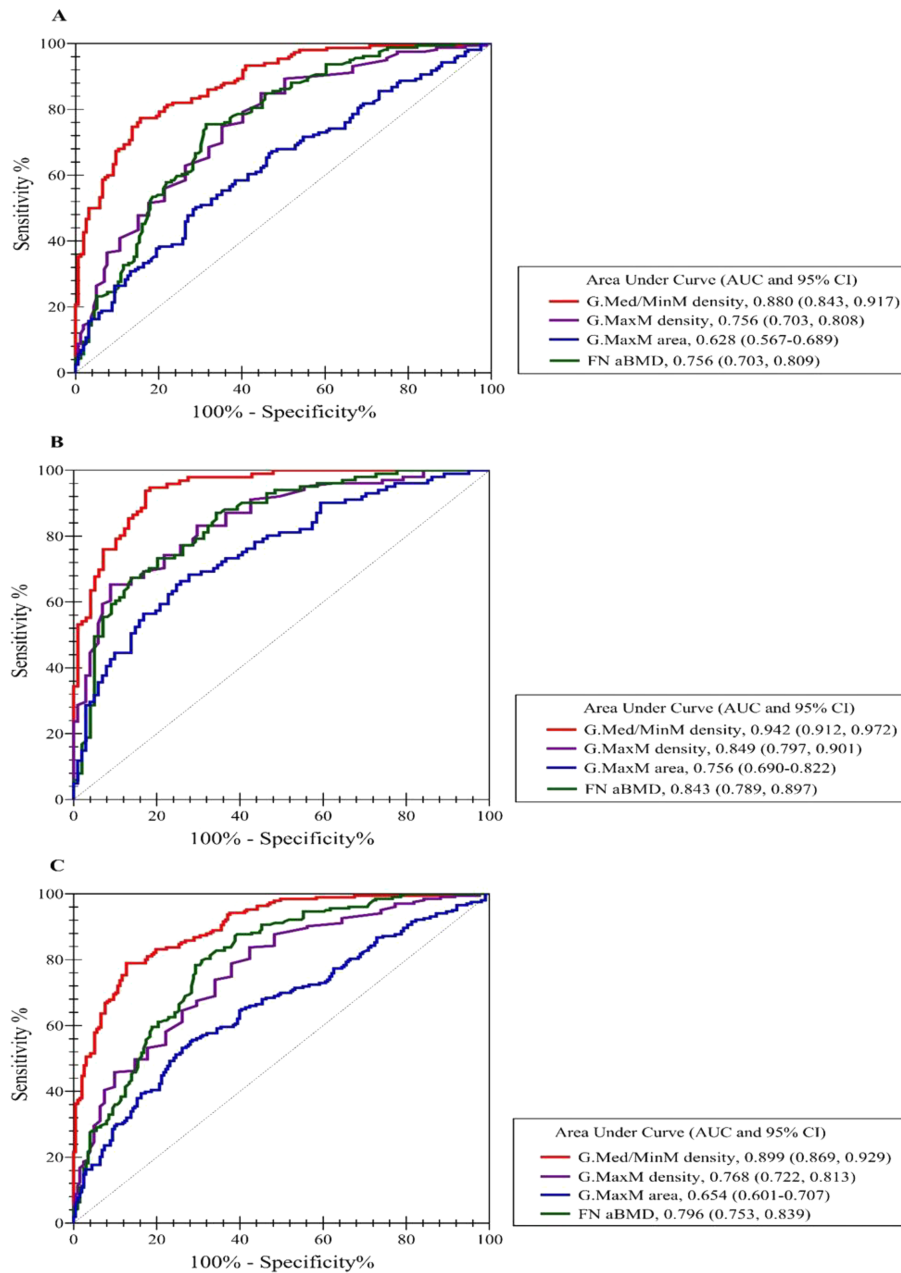
Figure 4 Receiver operating characteristic curves for muscle and bone parameters in propensity score-matched population: (A) femoral neck fracture, (B) intertrochanteric fracture, and (C) any hip fracture. CI, confidence interval; FN aBMD, femoral neck areal bone mineral density; G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle.

Of course, under certain circumstances, for example, treatment with corticosteroids, there may be an additional, rapid increase in fatty infiltration leading to progressive frailty shortening the time to HF.

In agreement with the three basic studies cited earlier,[25–27] our results confirm that with respect to HF discrimination, muscle density is the more important parameter than muscle area. This is in particular obvious when comparing Models 3 and 4. The combination of aBMD with muscle area resulted in the same AUC value as the BMD model alone, while the

combination of aBMD with G.med/min muscle density significantly improved HF discrimination. The G.med/min muscle, referred to as the 'rotator cuff of the hip', plays an important role in gait stability.[18] It inserts on the greater trochanter of the femur and serves as major abductors and rotators of the hip during normal gait for maintenance of balance.[33,34] A recent study also found a significant correlation of smaller gluteus muscle with higher loads during daily activities like stair climbing and sit-down/stand-up from a chair or walking for patients after TH arthroplasty.[35] Therefore, ageing of the

Table 5 ORs of any fracture risk per SD increase in PS-matched population by age group

Model/variables	<70 years old (N = 215)		≥70 years old (N = 191)	
	ORs (95% CIs)	*P* value	ORs (95% CIs)	*P* value
Univariate muscle parameters				
G.MaxM area (cm^2)	0.66 (0.50, 0.87)	<0.01	0.49 (0.35, 0.69)	<0.01
G.MaxM density (HU)	0.36 (0.25, 0.53)	<0.01	0.25 (0.17, 0.39)	<0.01
G.Med/MinM density (HU)	0.07 (0.03, 0.14)	<0.01	0.06 (0.02, 0.13)	<0.01
Multivariate muscle model				
G.MaxM area (cm^2)	1.05 (0.68, 1.60)	0.84	0.91 (0.56, 1.5)	0.72
G.MaxM density (HU)	2.45 (1.23, 4.88)	0.01	1.07 (0.55, 2.08)	0.85
G.Med/MinM density (HU)	0.03 (0.01, 0.09)	<0.01	0.05 (0.02, 0.16)	<0.01
AUC (95% CIs), *P* value[a]	0.917 (0.879, 0.954), 0.12		0.904 (0.861, 0.947), 0.64	
Univariate BMD variables				
TH aBMD (g/cm^2)	0.22 (0.14, 0.36)	<0.01	0.32 (0.21, 0.48)	<0.01
FN aBMD (g/cm^2)	0.22 (0.14, 0.34)	<0.01	0.27 (0.17, 0.41)	<0.01
Multivariate BMD model				
TH aBMD (g/cm^2)	0.63 (0.29, 1.40)	0.25	0.77 (0.40, 1.51)	0.45
FN aBMD (g/cm^2)	0.31 (0.15, 0.66)	<0.01	0.33 (0.16, 0.66)	<0.01
AUC (95% CIs), *P* value[a]	0.806 (0.748, 0.864), 0.31		0.788 (0.723, 0.853), 0.52	
Bone structure model				
FN CortThick (mm)	0.59 (0.43, 0.81)	<0.01	0.53 (0.36, 0.78)	<0.01
AUC (95% CIs), *P* value[a]	0.589 (0.510, 0.668), 0.01		0.658 (0.577, 0.74), 0.09	
Selected Model 1				
G.MaxM area (cm^2)	1.69 (1.01, 2.82)	0.04	1.22 (0.68, 2.17)	0.51
G.MaxM density (HU)	2.59 (1.20, 5.58)	0.02	1.02 (0.50, 2.08)	0.95
G.Med/MinM density (HU)	0.03 (0.01, 0.09)	<0.01	0.07 (0.02, 0.20)	<0.01
FN aBMD (g/cm^2)	0.17 (0.08, 0.36)	<0.01	0.40 (0.22, 0.75)	<0.01
AUC (95% CIs), *P* value[a]	0.946 (0.918, 0.974), 0.18		0.923 (0.884, 0.961), 0.29	
Selected Model 2				
G.MaxM density (HU)	2.76 (1.29, 5.91)	0.01	1.07 (0.53, 2.16)	0.85
G.Med/MinM density (HU)	0.03 (0.01, 0.09)	<0.01	0.07 (0.02, 0.21)	<0.01
FN aBMD (g/cm^2)	0.22 (0.11, 0.43)	<0.01	0.44 (0.25, 0.77)	<0.01
AUC (95% CIs), *P* value[a]	0.943 (0.915, 0.971), 0.88		0.923 (0.884, 0.961), 0.53	
Selected Model 3				
G.Med/MinM density (HU)	0.07 (0.03, 0.15)	<0.01	0.07 (0.03, 0.18)	<0.01
FN aBMD (g/cm^2)	0.23 (0.12, 0.44)	<0.01	0.44 (0.25, 0.77)	<0.01
AUC (95% CIs), *P* value[a]	0.934 (0.904, 0.964), 0.27		0.923 (0.884, 0.961), 0.58	
Selected Model 4				
G.MaxM area (cm^2)	1.13 (0.80, 1.58)	0.50	0.72 (0.48, 1.09)	0.12
FN aBMD (g/cm^2)	0.20 (0.12, 0.33)	<0.01	0.30 (0.19, 0.47)	<0.01
AUC (95% CIs), *P* value[a]	0.801 (0.742, 0.861), 0.55		0.802 (0.738, 0.865), 0.65	

AUC, area under curve; BMD, bone mineral density; CIs, confidence intervals; FN aBMD, femoral neck areal bone mineral density; FN CortThick, cortical thickness of femoral neck; G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HU, Hounsfield units; ORs, odds ratios; PS, propensity score; SD, standard deviation; TH aBMD, total hip areal bone mineral density.
[a]*P* values were obtained using the Hosmer–Lemeshow tests. *P* > 0.05 indicates that the null hypothesis (observed event rates match expected event rates in subgroups of the model population) is not rejected.

gluteus muscle may lead to walking impairments and fall-related fractures.

Our emphasis of the importance of muscle density was further supported by the separate analysis of the two age groups. Muscle density was significantly lower at older age, in both the control participants and the HF patients, while in the control participants, muscle area did not change between the two age groups. In the control group, muscle degradation by fatty infiltration did not result in muscle atrophy; this combined effect was only observed in patients with acute HF.

In data from the Health ABC Study, Lang *et al.* showed that mid-thigh muscle CSA and density predicted fracture risk after adjustment for age, height, BMI, and some additional covariates, but only muscle density remained after an additional adjustment for DXA aBMD.[36] In a case–control study based on a Chinese female population, Lang *et al.*[17] showed that subjects with HFs had lower hip muscle density and lower muscle CSA values compared with controls, similar to our results. However, Lang *et al.* did not observe gluteus maximus muscle (extensor muscle) density differences between HF patients and controls. The discordance of Lang study to our study results might be due to a small sample size (45 HFs) and a slightly different muscle level of the measurement. In the EEFECT study, Mühlberg *et al.* found that the amount of adipose tissue and the distribution of the adipocytes in the muscles of the upper thigh were significantly associated with acute HF (AUC, 0.85; 95% CI: 0.78, 0.93). Muscle area did not discriminate HF, and muscle density became insignificant after adjustment for age height and weight.[19] But again, the sample size was small (40 HFs) and the location of the analysed muscles differed from the current study.

A strength of our study was the rather large number of included subjects. Controls and fractured cases could be matched with respect to age, gender, and BMI independently for FNF, trochanteric fracture, and all HFs as well as for the two age groups. In contrast to other studies, it was not necessary to use age, gender, and BMI as covariates or adjustments in the multivariate analyses. Another strength was that patients with incident HFs were scanned within 48 h, which would mostly minimize fracture-related changes of bone and muscle tissues, apart from oedema around the fractured hip.

A major limitation of the study was the cross-sectional design, limiting the analysis to evaluation associations with HF instead of HF prediction. Another limitation was the muscle assessments, which were based on the single slice instead of a full 3D analysis of the complete muscles. Further, a more advanced muscle analysis as performed in the EFFECT was beyond the scope of this study because it requires a 3D analysis and a complicated segmentation of the fascia.[14,37] Finally, we did not answer the question whether the HF risk varies with age. This requires more than two age groups and a separate analysis by gender, which requires a higher number of subjects than were available in this study the missing gender specific analysis.

In conclusion, our study results show that muscle density performs better than aBMD from hip CTXA and muscle size in discrimination of HF. Combination of aBMD and muscle density provided the best discrimination. The integration of muscle assessments may trigger a paradigm shift in HF prediction. Gluteus muscle density should also be evaluated as treatment outcome, and its use as a treatment endpoint for therapies that reduce HF risk should be further investigated.

Acknowledgement

Conflict of interest

K.E. is a part-time employee of BioClinica, Inc. Other authors declare no conflict of interest.

Funding

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparisons between area and density of gluteus medius and minimus muscle at 3rd sacral (S3) and non-3rd sacral (S4&S5) vertebrae levels

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