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Compartment-specific effects of muscle strength on bone microarchitecture in women at high risk of osteoporosis

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Abstract

Background It is well known that skeletal integrity is influenced by the musculature. Poor muscle strength (i.e. sarcopenia) is considered a major predictor of fragility fractures. While this observation appears particularly relevant for older women with increased risk of osteoporosis, there has been no comprehensive investigation to determine the influence of muscle performance on compartment-specific bone microarchitecture in multiple body regions.

Methods We retrospectively analysed data from different muscle performance and bone microarchitecture assessments in 230 women (aged 21 to 87 years) at high risk of osteoporosis. Muscle performance tests included grip strength and chair rising test (CRT) combined with mechanography. Balance was determined by Romberg posturography. Areal bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) at the hip and lumbar spine. Compartment-specific volumetric BMD, microarchitecture, and geometry were assessed by second-generation high-resolution peripheral quantitative computed tomography (HR-pQCT) at multiple skeletal sites (distal radius, tibia, and fibula). Regression models were applied to test for interactions between muscle and bone parameters. Subgroups were defined to compare women with osteoporosis and osteosarcopenia regarding BMD and microarchitecture.

Results While osteoporosis was diagnosed in 115/230 (50.0%) women, sarcopenia was detected in 38/230 (16.5%). Positive associations of both grip strength and CRT maximum force with cortical geometric and microarchitectural parameters were detected at all measured sites, with the strongest effect applying to CRT maximum force and tibial parameters (e.g. tibial cortical area $R^2 = 0.36$, $P < 0.0001$, and tibial cortical thickness $R^2 = 0.26$, $P < 0.0001$). Balance parameters showed much weaker or no associations with HR-pQCT parameters. Major associations between muscle strength and trabecular parameters could not be confirmed. Age and body mass index were confirmed as negative and positive predictors for several microarchitectural parameters, respectively. An independent predictive value of grip strength on radial, tibial, and fibular (all $P < 0.01$) cortical area and of CRT maximum relative force on cortical thickness (all $P < 0.05$) was revealed. Women with osteosarcopenia showed significantly reduced cortical HR-pQCT parameters but no differences in DXA values compared with women with osteoporosis but no sarcopenia. Stratification by fracture and treatment status revealed that vertebral fractures and denosumab treatment altered the muscle–bone interaction.

Conclusions A systemic interaction between muscle strength and bone microarchitecture was demonstrated, and this interaction appears to be primarily with the cortical bone compartment. The value of muscle assessments in fracture risk evaluation may be partly mediated by their effects on bone microarchitecture.

Keywords Osteoporosis; Sarcopenia; Muscle performance; Mechanography; Microarchitecture; HR-pQCT

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Introduction

Osteoporosis is a widespread disease defined by low bone mass and fragility fractures.[1] Next to age and female sex, impaired muscle status is considered a relevant risk factor of fragility fractures.[2] Sarcopenia refers to a loss of muscle mass and muscle strength with far-reaching consequences such as increased risk of osteoporosis,[3] falls and fragility fractures,[4,5] and increased overall mortality.[6] The term osteosarcopenia describes a condition in which osteoporosis and sarcopenia coexist.[7,8] Osteosarcopenia is strongly associated with frailty.[9] We and others have previously reported that poor muscle performance and balance are associated with fragility fractures.[10,11] Furthermore, it has been demonstrated that poor muscle performance predicts fragility fractures in elderly women and men.[2]

The gold standard for assessing bone mineral density (BMD) and risk of fragility fractures is dual-energy X-ray absorptiometry (DXA), where a standard deviation (i.e. *T*-score) ≤ -2.5 is considered osteoporosis.[12] However, as DXA has some methodological weaknesses, three-dimensional methods directed at bone microarchitecture are gaining importance. High-resolution peripheral quantitative computed tomography (HR-pQCT) is a non-invasive technique measuring bone microarchitecture at the distal radius and tibia.[13] It has been shown that impaired microarchitecture represents an important predictor of fragility fractures beyond low BMD measured by DXA.[14]

In recent years, the importance of muscle–bone interaction (crosstalk) has been increasingly explored in the scientific community.[15] Various bone-derived and muscle-derived molecules such as RANKL[16] and irisin[17] have been identified in this context, with systemic and local effects being differentiated. In the clinical setting, precise data on site-specific and compartment-specific interactions between muscle and bone are not available. Therefore, we assessed bone microarchitectural parameters by HR-pQCT at three skeletal sites (distal radius, tibia, and fibula) and performed several muscle performance and balance tests (grip strength, chair rising test (CRT), and Romberg posturography) in a cohort of 230 women at high risk of osteoporosis. We hypothesized that muscle strength tests perform better than posturography in their predictive value on skeletal microarchitecture and that local effects can be differentiated from systemic associations. The detailed knowledge of the associations between these measurements could not only provide information about the muscle–bone interaction but also improve the prediction of fragility fractures.

Methods

Study design

We retrospectively included 230 women in our study who presented to our specialized outpatient clinic for musculoskeletal disorders due to the presence of individual risk factors or established osteoporosis. As part of the routine diagnostic workup, demographic (age, weight, and height) and disease-specific characteristics (previous fragility fractures and bone-specific medication) were obtained from the women and various skeletal assessments including DXA and HR-pQCT were performed. Additionally, a suite of muscle and balance assessments such as grip strength, CRT, and Romberg posturography were applied. All measurements for each patient were taken on the same day. Women with medical conditions causing major effects on bone status and/or muscle function were excluded: high-dose corticosteroid treatment ($\geq$ 7.5 mg/day of prednisolone or equivalent), chronic kidney disease (glomerular filtration rate $<$ 30 mL/min), conditions or neurological disorders associated with prolonged generalized or local immobilization (e.g. Parkinson's disease, multiple sclerosis, and apoplexy), genetic bone diseases (e.g. osteogenesis imperfecta, osteopetrosis, and osteosclerosis), and active cancer or tumours with potential systemic or local effects on BMD (e.g. myeloma and skeletal metastases). Ethics approval was obtained from the local ethics committee (Ethikkomission der Ärztekammer Hamburg, PV3874; WF-028/21).

Bone mineral density, microarchitecture, and geometry

Areal bone mineral density (aBMD, with *T*-score and *Z*-score) was measured by DXA (Lunar iDXA, GE Healthcare, Madison, WI, USA). Both sides (left/right) of the femoral neck and the total hip as well as the lumbar spine (L1–L4) were examined. The lowest *T*-score of each of the hip evaluations (with corresponding absolute BMD and *Z*-score) was used for further analysis. In addition, lumbar spine BMD was recorded as the lowest *T*-score (with corresponding absolute BMD and *Z*-score) of at least two adjacent vertebrae. Daily calibration scans with a dedicated phantom according to the manufacturer's recommendations were performed for DXA quality assurance. This involves precision tests including least significant change calculations following the recommendations of the International Society for Clinical Densitometry.[18]

Furthermore, all women were examined by second-generation HR-pQCT (XtremeCT II, Scanco Medical, Brüttisellen, Switzerland) on the non-dominant distal radius and the opposite distal tibia using the standard *in vivo* scan protocol (68 kVp, 1470 μA, 43 ms integration time, 60.7 μm voxel size). The scan region begins at a fixed offset distance of 9 and 22 mm proximal to the reference line, which is placed at the inflection point of the endplate of the distal radius and tibia plafond, respectively. The total scan region extends 168 slices (10.2 mm) proximally from this point.[19] We additionally analysed the microarchitecture of the distal fibula, which has been done in a similar manner for first-generation HR-pQCT.[20] HR-pQCT images were examined for motion artefacts and excluded if motion artefacts grade 4 or 5 were present.[21] Volumetric bone mineral density was expressed as total BMD (Tt.BMD, mg HA/cm^3), cortical BMD (Ct.BMD, mg HA/cm^3), and trabecular BMD (Tb.BMD, mg HA/cm^3). Microarchitectural parameters follow the standardized nomenclature of the IOF-ASBMR-ECTS working group[19] and included the bone volume to total volume ratio (BV/TV), trabecular number (Tb.N, mm^{-1}), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), cortical thickness (Ct.Th, mm), and cortical porosity (Ct.Po, pore volume to total volume ratio). Geometrical values included total bone area (Tt.Ar, mm^2), trabecular bone area (Tb.Ar, mm^2), cortical bone area (Ct.Ar, mm^2), and cortical perimeter (Ct.Pm, mm). HR-pQCT results were compared with device-specific, age-specific, and sex-specific reference values.[22]

Muscle performance

Maximum grip strength (kg) was evaluated during muscular isotonic contraction using a hand-held dynamometer (Leonardo Mechanograph® GF, Novotec Medical, Pforzheim, Germany). Women were instructed to sit steadily on a chair and place their arms flat on their thighs.[23] Three measurements with each arm (left/right) were performed of which the highest value of the six measurements was used for further analysis as reported previously.[11] CRT was performed using a ground reaction force plate (Leonardo Mechanograph® GRFP STD, Novotec Medical). For this purpose, a special bench was installed on the force plate at a height of 45 cm. After sitting on the bench with both feet on the floor, the women were instructed to fold their arms in front of their chest and stand up and sit down again as quickly as possible for five cycles. Both CRT maximum force (kN) and CRT time per repetition (s) were documented for the stand-up tests with the mechanograph, as described previously.[10] The presence of sarcopenia was defined by using cut-off points for low muscle performance determined by grip strength and CRT time per repetition according to the recommendations of the EWGSOP2 consensus.[24]

Balance

Romberg posturography was also performed with the Leonardo Mechanograph® GRFP. Women were guided to stand upright on the GRFP with their feet together and their arms in front of their body at shoulder height. Next, they were instructed to stand as still as possible with their eyes open for 10 s. After a gap of a few seconds, the women were instructed to repeat the test with their eyes closed. Centre of pressure (CoP) movements were tracked using the GRFP and the corresponding path length was defined as the length of the CoP path (mm) for 10 s, as reported previously.[11]

Laboratory assessment

To assess the bone metabolism of the women, blood and urine samples were collected at the time of presentation. Serum calcium, phosphate, 25-hydroxyvitamin D, parathyroid hormone (PTH), bone-specific alkaline phosphatase (bone ALP), and the urinary bone resorption marker deoxypyridinoline (DPD)/creatinine were measured. All parameters were compared with the reference ranges derived from the local laboratory.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 28.0.1 (IBM, Armonk, NY, USA) and GraphPad Prism 9.3.1 (GraphPad Software, San Diego, CA, USA). Results are reported as absolute values or as means ± standard deviations with mean percentages of the median of the reference values. The Shapiro–Wilk test was used to evaluate the normal distribution of the data. To test for differences between two subgroups, the unpaired two-tailed *t* test was used for normally distributed data and the Mann–Whitney *U* test was used for non-parametric data. One-way analysis of covariance (ANCOVA) was performed to evaluate differences in bone microarchitecture between women with osteosarcopenia and women with osteoporosis while controlling for the covariate age. Homogeneity of regression slopes was not violated regarding the dependent variable, as the interaction terms were not statistically significant ($P > 0.05$). To evaluate the associations between muscle and HR-pQCT parameters, linear regression analyses were performed and the confidence intervals (CIs) of the respective regression slopes, the coefficients of determination R^2, and the *P*-values were calculated. Furthermore, a multiple linear regression model (enter method) was applied to evaluate the predictive value of the independent variables age, body mass index (BMI), grip strength, and CRT maximum relative force on selected HR-pQCT parameters (dependent variables). Next to overall model characteristics (R^2, adjusted R^2, *F*, and *P*-value), indi-

vidual regression coefficients (B, β, and P-value) were calculated.

Results

Characterization of the study cohort

Overall characteristics of the study cohort including demographic, densitometric, mechanographic, and disease-specific data are presented in *Table* 1. DXA revealed that most women were within the range of osteoporosis (50.0%) or osteopenia (36.1%). Furthermore, a high number of women had previously suffered from fragility fractures (vertebral 28.7%, peripheral 17.4%), underscoring that a high-risk population was studied. We were able to cover a wide range of age, BMI, and muscle performance, including women with values in the reference range and severely reduced muscle strength (i.e. sarcopenia). Namely, we identified sarcopenia in 16.5% of the included women. HR-pQCT examination yielded site-specific results for the distal radius, tibia, and fibula, with overall low values as compared with age-specific and sex-specific reference values (*Table* 2).

Table 1 Overview of the study cohort

	Total (n = 230)			
Parameter	Mean	SD	Min	Max
Demographics				
Age (years)	61.6	14.4	21	87
Weight (kg)	66.4	13.9	41.8	132.4
Height (m)	1.66	0.07	1.51	1.85
BMI (kg/m^2)	24.2	5.0	15.7	49.5
DXA				
Femoral T-score	−1.9	1.1	−4.1	1.6
Femoral Z-score	−0.8	0.8	−3.3	1.6
Spinal T-score	−2.1	1.4	−5.1	2.1
Spinal Z-score	−0.9	1.1	−3.2	1.6
Normal BMD	32 of 230 (13.9%)			
Osteopenia (< -1.0)	83 of 230 (36.1%)			
Osteoporosis (≤ -2.5)	115 of 230 (50.0%)			
Mechanography				
Grip strength (kg)	22.8	5.1	8.0	39.1
CRT maximum force (kN)	0.85	0.17	0.47	1.62
CRT time per repetition (s)	2.02	0.90	0.83	8.26
Romberg path length EO (mm)	142.7	84.2	57.0	635.8
Romberg path length EC (mm)	219.4	151.8	78.0	1438.4
Normal muscle performance	192 of 230 (83.5%)			
Sarcopenia	38 of 230 (16.5%)			
Fragility fractures				
No fracture	136/230 (59.1%)			
Fragility fracture	94/230 (40.9%)			
Vertebral fracture	66/230 (28.7%)			
Peripheral fracture	40/230 (17.4%)			
Specific osteoporosis treatment				
Bisphosphonates	18/230 (7.8%)			
Denosumab	31/230 (13.5%)			

BMI, body mass index; CRT, chair rising test; DXA, dual-energy X-ray absorptiometry; EC, eyes closed; EO, eyes open; SD, standard deviation.
Women were classified into normal bone mineral density (BMD), osteopenia, and osteoporosis based on T-score. Sarcopenia was assessed according to EWGSOP2 sarcopenia cut-off points for low muscle strength by grip strength and chair rising test.[24]

Compartment-specific associations between muscle performance and bone microarchitecture parameters

When comparing the different muscle assessments, it was apparent that grip strength and CRT maximum force showed the strongest associations with HR-pQCT parameters at all skeletal sites. A colour-coded panel with all parameters is provided in Supporting Information, *Figure S1*. Specifically, we found that the effect of grip strength and CRT maximum force on Tt.BMD (e.g. tibia R^2 = 0.081, R^2 = 0.210, both $P < 0.0001$) was primarily due to their effects on Ct.Ar (R^2 = 0.180, R^2 = 0.356, both $P < 0.0001$) and Ct.Th (R^2 = 0.093, R^2 = 0.260, both $P < 0.0001$) (*Figure* 1A and 1B). With respect to trabecular bone volume, only weak associations were found between grip strength and BV/TV at the distal radius (R^2 = 0.036, $P < 0.05$) as well as CRT maximum force and BV/TV at the distal radius and tibia (R^2 = 0.066, $P < 0.0001$, R^2 = 0.044, $P < 0.05$). It was also noticeable that grip strength was most strongly associated with radial cortical microarchitecture, whereas CRT maximum force was most strongly associated with tibial cortical microarchitecture, highlighting an additional local interaction. While we could not find any associations with HR-pQCT parameters for CRT time per repetition (*Figure* 1C), some significant albeit weak associations were found regarding balance (i.e. Romberg posturography). These included, for example, Romberg path length with eyes open and Tt.BMD, Ct.Th, and Ct.Ar at the distal tibia (R^2 = 0.041, R^2 = 0.023, R^2 = 0.026, all $P < 0.05$) (*Figure* 1D and 1E).

Additional visualization of the parameters with the strongest associations confirmed a positive effect of grip strength on Tt.BMD, Ct.Th, and Ct.Ar (*Figure* 2A–2C). For example, a change in grip strength of 1 kg was associated with a change in tibial Ct.Ar of 1.7 mm^2 (95% CI 1.3 to 2.2). Similarly, CRT maximum force was positively associated with Tt.BMD, Ct. Th, and Ct.Ar (*Figure S2*).

Effects of age and body mass index on bone microarchitecture and adjusted analysis regarding site-specific muscle–bone interactions

Based on the assumption that lower extremity muscle strength is influenced by body mass and to avoid multicollinearity in the regression model, we first evaluated the association of BMI and body weight on CRT maximum force. Overall, the strongest associations were noted for body

Table 2 Volumetric BMD, bone microarchitecture, and geometry results at the distal radius, tibia, and fibula as assessed by HR-pQCT

	Radius			Tibia			Fibula	
Parameter	Mean	SD	% median	Mean	SD	% median	Mean	SD
HR-pQCT								
Tt.BMD (mg HA/cm^3)	232.2	58.6	76.2	222.1	53.7	77.1	444.1	123.0
Tt.Ar (mm^2)	271.9	42.5	110.5	721.1	108.6	111.1	112.3	21.3
Tb.BMD (mg HA/cm^3)	107.3	37.9	77.4	128.9	36.9	82.3	142.2	52.9
BV/TV	0.158	0.048	84.9	0.200	0.047	87.9	0.211	0.066
Tb.N (mm^{-1})	1.128	0.297	85.2	1.140	0.253	89.7	0.960	0.315
Tb.Th (mm)	0.219	0.012	99.0	0.249	0.020	98.4	0.278	0.032
Tb.Sp (mm)	0.963	0.413	132.2	0.925	0.362	121.5	1.203	0.650
Tb.Ar (mm^2)	227.8	42.4	117.2	627.2	113.4	117.2	66.6	22.4
Ct.BMD (mg HA/cm^3)	819.1	89.5	90.9	793.9	91.9	91.7	819.8	89.0
Ct.Th (mm)	0.812	0.165	81.9	1.138	0.254	80.5	1.585	0.429
Ct.Po	0.007	0.004	117.9	0.030	0.015	131.2	0.034	0.016
Ct.Pm (mm)	69.9	6.0	—	105.1	8.1	—	43.0	4.0
Ct.Ar (mm^2)	47.9	8.9	87.8	99.0	20.8	83.2	47.9	11.0

BMD, bone mineral density; BV/TV, bone volume to tissue volume; Ct.Ar, cortical area; Ct.BMD, cortical BMD; Ct.Pm, cortical perimeter; Ct.Po, cortical porosity (pore volume to total volume ratio); Ct.Th, cortical thickness; HA, hydroxyapatite; HR-pQCT, high-resolution peripheral quantitative computed tomography; SD, standard deviation; Tb.Ar, trabecular area; Tb.BMD, trabecular BMD; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; Tt.Ar, total area; Tt.BMD, total BMD.
For each patient, HR-pQCT results of the distal radius and tibia were compared with the median of device-specific, age-specific, and sex-specific reference values.[22]

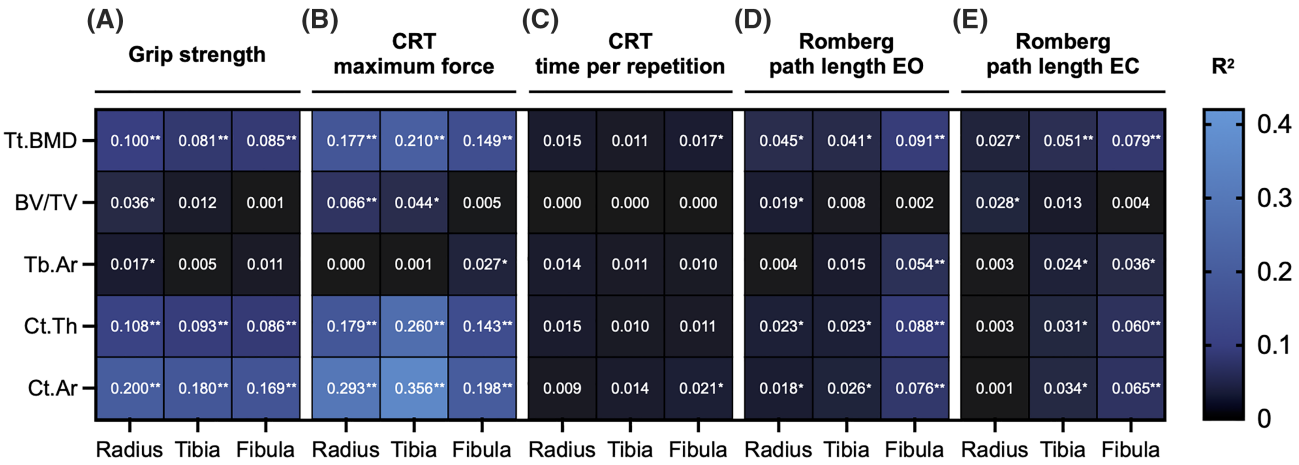

Figure 1 Associations of muscle performance and balance measures with HR-pQCT parameters assessed at multiple sites. Influence of *(A)* grip strength, *(B)* chair rising test (CRT) maximum force, *(C)* CRT time per repetition, *(D)* Romberg path length eyes open (EO), and *(E)* Romberg path length eyes closed (EC) on HR-pQCT parameters at the distal radius, tibia, and fibula. Colour-coded charts represent the coefficients of determination R^2 determined by linear regression analyses. *$P < 0.05$, **$P < 0.001$.

weight and CRT maximum force (*Figure S3A*). We therefore additionally calculated CRT maximum relative force adjusted for body weight (N/kg), which showed a weak negative association with body weight (*Figure S3B*).

To identify independent predictors of HR-pQCT parameters, a multiple linear regression model was applied in which we tested the influence of age, BMI, grip strength, and CRT maximum relative force (*Table* 3). Age was identified as a moderate to strong negative influencing factor on Tt.BMD, Ct.Th, and Ct.Ar in all skeletal regions. BMI was also shown to have a significant positive effect on all investigated parameters in all skeletal regions. In this regression model, grip strength emerged as an independent influencing factor for radial, tibial, and fibular Ct.Ar, but not Tt.BMD or Ct.Th, suggesting that grip strength exerts systemic effects in cortical area. Interestingly, CRT maximum relative force could be confirmed as an independent influencing factor for Ct.Ar at the tibia, but not at the radius and fibula. Moreover, CRT maximum relative force was found to be independently affecting Ct.Th at the radius, tibia, and fibula, although the effects were strongest for the distal tibia, confirming an additional local effect.

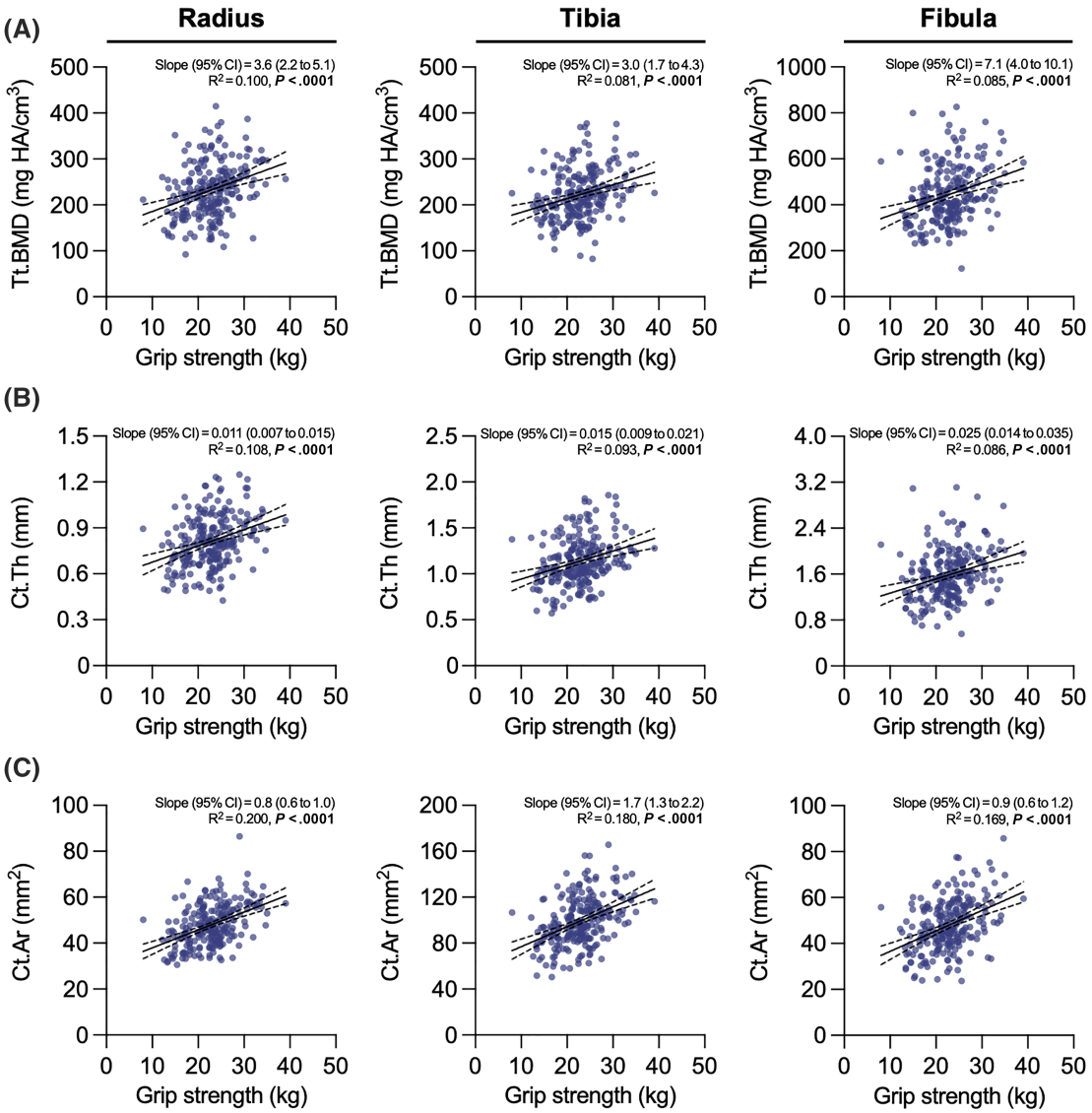

Figure 2 Influence of grip strength on volumetric BMD and cortical parameters at different skeletal sites. Visualization of the associations between grip strength and *(A)* total BMD (Tt.BMD), *(B)* cortical thickness (Ct.Th), and *(C)* cortical area (Ct.Ar) at the distal radius, tibia, and fibula. Linear regression analyses were performed and confidence intervals (CIs) of the respective regression slopes, the coefficients of determination R^2, and the *P*-values were calculated. Numbers in bold indicate statistical significance ($P < 0.05$).

Impact of osteosarcopenia on skeletal microarchitecture

To investigate potential differences in HR-pQCT parameters based on the presence of sarcopenia in women with osteoporosis, we divided the group of 115 women with osteoporosis into two subgroups. The first group included women with osteoporosis but without sarcopenia (Opo, *n* = 90), while the other group contained women with both osteoporosis and sarcopenia (i.e. osteosarcopenia) (Osa, *n* = 25). We detected distinct alterations when comparing the HR-pQCT results in Opo versus Osa. Significantly lower values for Tt.BMD were measured at all skeletal sites in Osa compared with Opo (*Figure* 3A). While no differences were found in BV/TV (*Figure* 3B), significantly lower Ct.Th was observed in Osa compared with Opo at all three skeletal sites (*Figure* 3C). To evaluate whether these group differences are also detectable in measurements using DXA, we evaluated the two subgroups with respect to femoral and spinal aBMD, *T*-score, and *Z*-score, where we found no significant differences between Opo and Osa (*Figure S4*). Because the Osa group was slightly older than the Opo group (72.0 vs. 66.0 years, $P < 0.001$) but similar in weight, height, and BMI, we applied additional adjustment for age by ANCOVA. In this analysis, Ct.Th was still

Table 3 Results of a multiple linear regression model analysing independent factors associated with volumetric BMD and cortical HR-pQCT parameters at different skeletal sites

	Radius			Tibia			Fibula		
Parameter	*B*	β	*P*	*B*	β	*P*	*B*	β	*P*
Tt.BMD (mg HA/cm^3)									
(Constant)	137.920		0.014	70.045		0.164	356.374		0.001
Age (years)	−1.629	−0.401	<**0.0001**	−1.357	−0.365	<**0.0001**	−4.587	−0.538	<**0.0001**
BMI (kg/m^2)	3.730	0.321	<**0.0001**	4.213	0.396	<**0.0001**	5.918	0.243	<**0.0001**
Grip strength (kg)	0.620	0.054	0.379	0.060	0.006	0.924	−0.836	−0.035	0.547
CRT maximum relative force (N/kg)	7.043	0.136	**0.026**	10.327	0.217	<**0.001**	19.213	0.176	**0.002**
	R^2 = 0.366			R^2 = 0.393			R^2 = 0.438		
	R^2 adjusted = 0.354			R^2 adjusted = 0.382			R^2 adjusted = 0.428		
	F (4, 225) = 32.405, $P <$ **0.0001**			F (4, 225) = 36.430, $P <$ **0.0001**			F (4, 225) = 43.924, $P <$ **0.0001**		
Ct.Th (mm)									
(Constant)	0.457		0.006	0.333		0.161	0.852		0.048
Age (years)	−0.004	−0.317	<**0.0001**	−0.005	−0.310	<**0.0001**	−0.011	−0.374	<**0.0001**
BMI (kg/m^2)	0.010	0.318	<**0.0001**	0.022	0.441	<**0.0001**	0.022	0.253	<**0.0001**
Grip strength (kg)	0.003	0.106	0.095	0.003	0.055	0.360	0.004	0.043	0.501
CRT maximum relative force (N/kg)	0.019	0.132	**0.036**	0.042	0.188	**0.002**	0.064	0.167	**0.009**
	R^2 = 0.314			R^2 = 0.393			R^2 = 0.304		
	R^2 adjusted = 0.302			R^2 adjusted = 0.383			R^2 adjusted = 0.291		
	F (4, 225) = 25.768, $P <$ **0.0001**			F (4, 225) = 36.493, $P <$ **0.0001**			F (4, 225) = 24.530, $P <$ **0.0001**		
Ct.Ar (mm^2)									
(Constant)	27.582		0.001	40.255		0.029	36.494		<0.001
Age (years)	−0.187	−0.304	<**0.0001**	−0.478	−0.332	<**0.0001**	−0.281	−0.369	<**0.0001**
BMI (kg/m^2)	0.563	0.320	<**0.0001**	1.659	0.403	<**0.0001**	0.400	0.184	**0.002**
Grip strength (kg)	0.427	0.245	<**0.0001**	0.756	0.185	**0.001**	0.431	0.199	**0.002**
CRT maximum relative force (N/kg)	0.664	0.084	0.155	2.411	0.131	**0.020**	0.724	0.074	0.234
	R^2 = 0.393			R^2 = 0.456			R^2 = 0.330		
	R^2 adjusted = 0.382			R^2 adjusted = 0.446			R^2 adjusted = 0.319		
	F (4, 225) = 36.432, $P <$ **0.0001**			F (4, 225) = 47.079, $P <$ **0.0001**			F (4, 225) = 27.756, $P <$ **0.0001**		

BMD, bone mineral density; BMI, body mass index; CRT, chair rising test; Ct.Ar, cortical area; Ct.Th, cortical thickness; HR-pQCT, high-resolution peripheral quantitative computed tomography; Tt.BMD, total BMD.
B and β represent unstandardized and standardized regression coefficients, respectively. Next to individual coefficients for each independent variable, overall model characteristics and coefficients are presented for each parameter. Numbers in bold indicate statistical significance ($P < 0.05$).

significantly lower in Osa than in Opo at the distal radius (F (1,112) = 4.473, P = 0.037, partial η^2 = 0.038). This difference was also confirmed when converting the results to available age-matched reference values (*Figure S5*).

Stratification of associations between muscle performance and bone microarchitecture by fracture and treatment status

This unique cohort of women undergoing musculoskeletal assessment also allowed us to stratify muscle and bone microarchitecture associations by fragility fracture and treatment status. It was striking that the associations between muscle strength tests (grip strength and CRT maximum force) and bone microarchitecture parameters were significantly worsened in women with vertebral fractures, whereas they slightly improved in women with peripheral fractures compared with those without fragility fractures (*Figure* 4). We were also able to show that women under denosumab treatment presented significantly worsened associations compared with those in the nontreated or bisphosphonate cohorts (*Figure* 5).

Associations between muscle strength and laboratory bone metabolism parameters

Evaluation of potential relationships between muscle strength and laboratory bone metabolism parameters revealed no significant results for all parameters except for vitamin D, which showed a weak negative association with grip strength and CRT maximum force (*Figure S6*).

Discussion

In recent years, a large amount of clinical and experimental evidence for a dynamic muscle–bone crosstalk has been accumulated, but precise data on associations between muscle performance and bone microarchitecture in women at high risk of fragility fractures have remained largely unexplored.

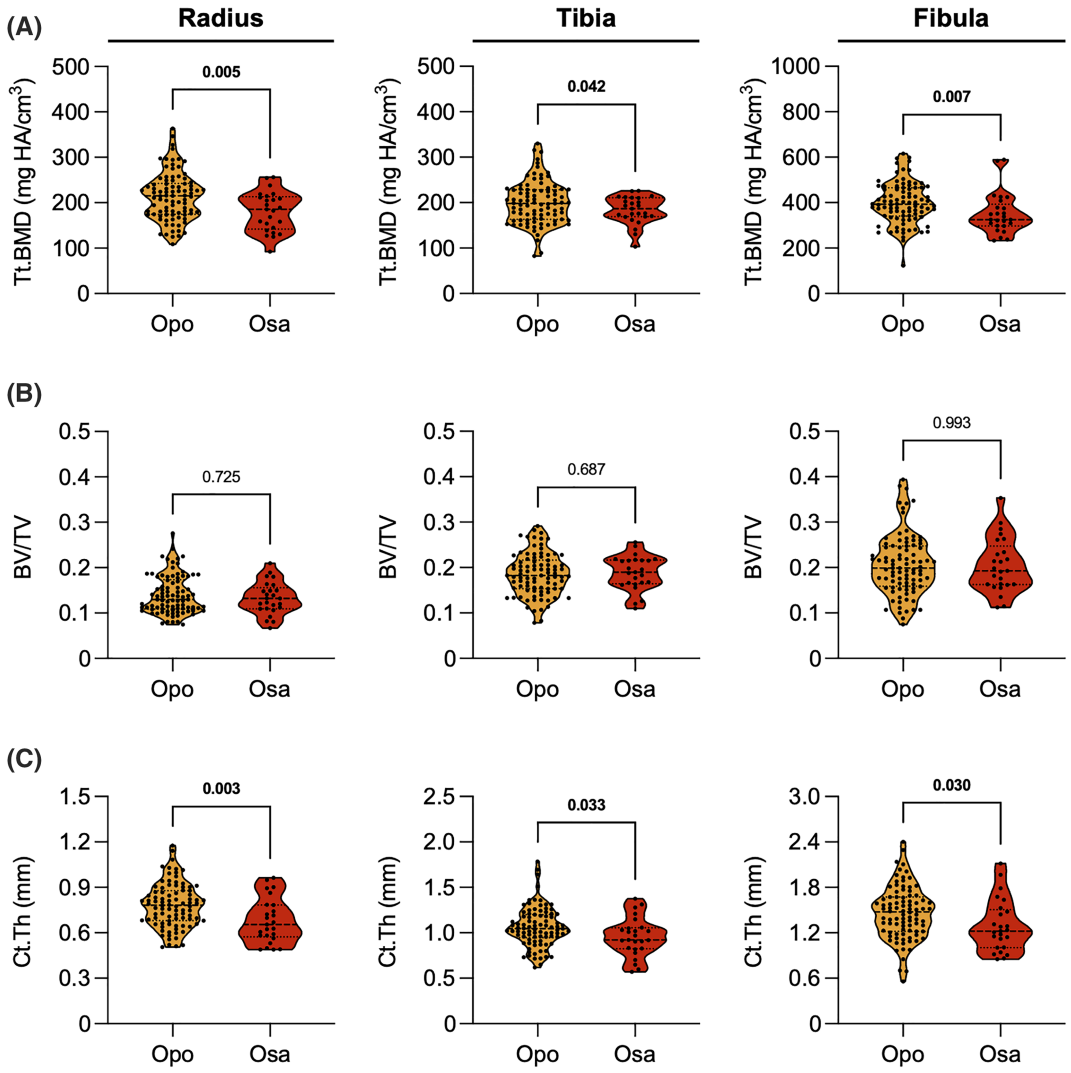

Figure 3 Differences in HR-pQCT parameters between women with osteoporosis (Opo) and women with osteosarcopenia (Osa) at different skeletal sites. Comparison of *(A)* total BMD (Tt.BMD), *(B)* bone volume to tissue volume (BV/TV), and *(C)* cortical thickness (Ct.Th) at the distal radius, tibia, and fibula. The Shapiro–Wilk test was used to evaluate the normal distribution of the data. Then, the unpaired two-sided *t* test was used for normally distributed data and the Mann–Whitney *U* test was used for non-parametric data. The dashed lines of violin plots represent the median and the quartiles. Exact *P*-values are displayed.

In the present study, we performed a suite of muscle and balance tests and evaluated their compartment-specific effect on mineralization, microarchitecture, and geometry obtained by second-generation HR-pQCT at the distal radius, tibia, and fibula. Grip strength and CRT maximum force were identified as the most predictive muscle tests in relation to HR-pQCT parameters, with the highest associations found for Tt.BMD, Ct.Th, and Ct.Ar. Overall, the effect of muscle strength on cortical bone was much larger, underscoring a compartment-specific effect. Beyond the systemic interactions, we were able to identify additional local effects, as grip strength showed the strongest associations with radial microarchitecture and CRT maximum force showed the strongest associations with tibial microarchitecture. The influence of the muscle status on cortical bone mass was supported by the finding that women with osteosarcopenia showed significantly reduced cortical thickness, even after adjusting for age.

The global gold standard for determining the risk of fragility fractures is DXA. However, DXA is known to miss a relevant portion of patients who sustain fragility fractures without meeting DXA criteria for osteoporosis (i.e. *T*-score ≤ -2.5). In this context, HR-pQCT was shown to improve the diagnostic prediction of fragility fractures, with microarchitectural parameters providing significantly improved predictive power for fractures in postmenopausal women.[25] The associations between muscle strength and bone microarchitecture by HR-pQCT demonstrated in this

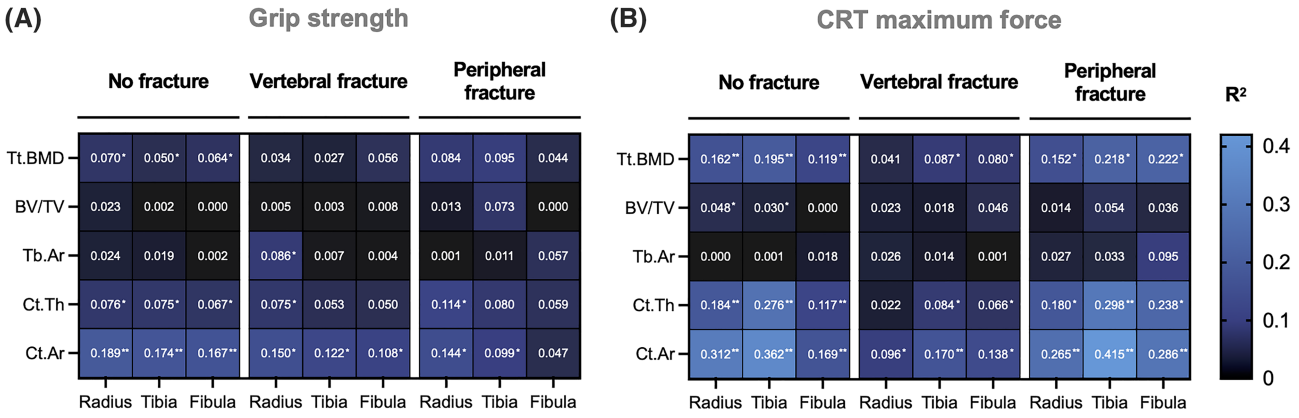

Figure 4 Associations between different muscle performance measures and HR-pQCT parameters stratified by fracture status. *(A)* Comparison of the associations between grip strength and HR-pQCT parameters at the distal radius, tibia, and fibula in women without fracture, with vertebral fracture, and with peripheral fracture. *(B)* Comparison of the associations between chair rising test (CRT) maximum force and HR-pQCT parameters at the distal radius, tibia, and fibula in women without fracture, with vertebral fracture, and with peripheral fracture. Colour-coded charts represent the coefficients of determination R^2 determined by linear regression analyses. $^*P < 0.05$, $^{**}P < 0.001$.

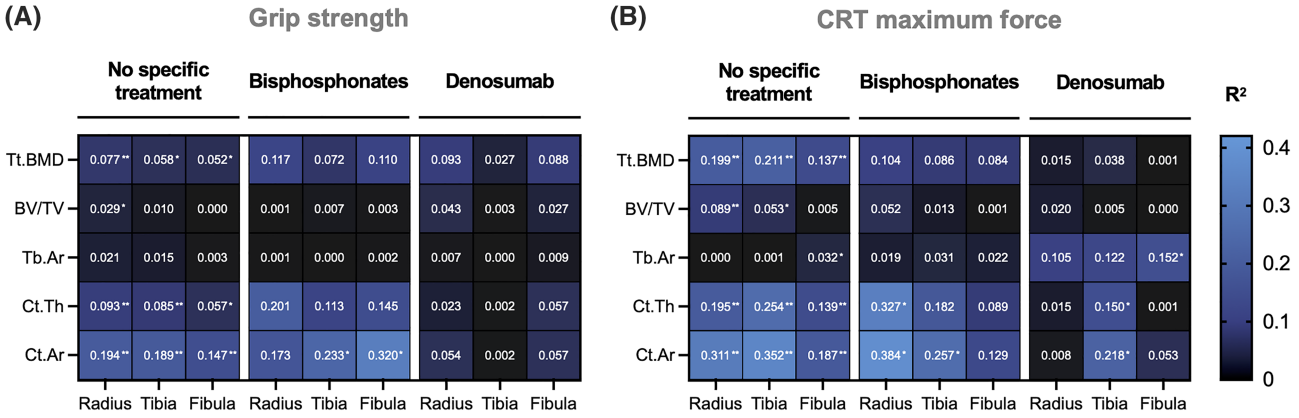

Figure 5 Associations between different muscle performance measures and HR-pQCT parameters stratified by treatment status. *(A)* Comparison of the associations between grip strength and HR-pQCT parameters at the distal radius, tibia, and fibula in women without specific treatment, treated with bisphosphonates, and treated with denosumab. *(B)* Comparison of the associations between chair rising test (CRT) maximum force and HR-pQCT parameters at the distal radius, tibia, and fibula in women without specific treatment, treated with bisphosphonates, and treated with denosumab. Colour-coded charts represent the coefficients of determination R^2 determined by linear regression analyses. $^*P < 0.05$, $^{**}P < 0.001$.

study are markedly higher than those between muscle strength and DXA from a previous study.[10] These associations suggest that the predictive value of muscle assessments for fragility fractures may function partly by influencing bone microarchitecture. Regarding the predictive power of muscle parameters, it was recently shown for elderly men that muscle performance tests such as grip strength and CRT could significantly improve fracture prediction.[26] Conversely, bone microarchitecture decline was also associated with the risk of falls and fractures in men with poor physical performance.[27] In our study on women, linear regression models suggested that around one-third of the changes in HR-pQCT parameters can be explained by muscle strength.

Muscle strength was primarily associated with cortical thickness and area, which is in line with the previous observation that higher hand grip strength was associated with greater radius bone size and strength in elderly women and men.[28] It is interesting to note that the main effect of muscle strength was on the cortical compartment. This finding is supported by a previous bedrest study in which only the cortical thickness of the distal tibia was restored by physical activity countermeasures in women.[29] On a molecular level, it has been demonstrated that irisin, a myokine secreted in response to exercise, increased cortical but not trabecular bone mass in mice.[17] These collective observations suggest that the cortical bone compartment has a unique capacity

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for mechanosensation. However, there is evidence from mouse studies that the trabecular compartment has mechanoresponsive functions as well.[30,31] Our clinical data also showed an effect on trabecular bone volume, but this effect was much less pronounced. Mechanistically, matrix-embedded osteocytes are of central interest as they exert mechanotransductive functions through their lacunocanalicular system. While disuse was associated with osteocyte deficiency and cortical bone loss in women,[32] irisin resulted in increased bone formation mainly by suppressing osteocyte-secreted sclerostin[17] and prevented disuse osteoporosis in mice.[33] Together, it is likely that the musculature positively affects cortical bone mass via its effects on osteocyte function.

Loading is usually associated with increased periosteal and endocortical bone formation.[34] In our study, it was noticeable that cortical area and thickness were more influenced by muscle strength than cortical perimeter. An explanation for this may be provided by an experimental study in mice, which showed that after *in vivo* loading, the endocortical surface was more mechanoresponsive than the periosteal surface.[34] This may suggest that improved muscle strength (in general associated with more loading) affects endocortical rather than periosteal formation, leading to changes in cortical area and thickness but not in cortical perimeter.

That women with osteoporosis and poor muscle strength (i.e. osteosarcopenia) have significantly impaired cortical but not trabecular bone mass also has clinical implications. For example, denosumab, a RANKL monoclonal antibody, has a stronger effect on restoring cortical bone mass,[35,36] which may indicate the preferential use of this drug over bisphosphonates in women with osteosarcopenia. Another reason for the preferential administration of denosumab is the positive influence of this drug on muscle strength.[16] In this context, it was striking that in our cohort the subgroup of women receiving denosumab treatment showed impaired associations between muscle strength and bone microarchitecture, indicating differential effects on cortical bone properties and muscle strength. Of note, this association was also impaired in the subgroup of women with prior vertebral fractures compared with those with peripheral fractures or without fragility fractures. These results suggest that certain subgroups (such as women receiving denosumab treatment or suffering from previous vertebral fractures) reflect distinct phenotypes in which muscle strength measures are less predictive of bone microarchitecture.

The association between balance parameters, such as that of Romberg posturography, and bone microarchitecture was either very weak or absent, indicating a value of balance tests for evaluating the risk of falls independently of an association with bone quality. It must be noted that weak or no associations between Romberg posturography and bone microarchitecture do not necessarily indicate that these measures lack predictive power for fragility fractures. This is supported by the fact that muscle and balance tests are known to predict fragility fractures independently of skeletal parameters in both sexes.[2]

While our comprehensive analysis provides accurate information on the systemic and local effects of muscle strength on skeletal microarchitecture, other examples of the systemic interaction of bone and muscle exist. One of them is the recent observation that serum levels of the bone resorption marker C-terminal telopeptide (CTX) are associated with muscle function in community-dwelling older adults.[37] In our study, evidence for the systemic effect of muscle strength is provided by the significant influence of grip strength and CRT maximum force on the HR-pQCT parameters Tt.BMD, Ct.Th, and Ct.Ar at all three skeletal sites. Nonetheless, we could not detect associations between laboratory bone metabolism parameters and muscle strength, suggesting a rather minor role of these markers in general or a specific value of CTX in the assessment of muscle function.

The benefit of adequate muscle strength on bone quality is evidenced by the previous observation that both self-reported physical activity and impact loading during exercise are positively associated with bone microarchitecture.[38,39] Conversely, the negative impact of muscle atrophy on bone loss is illustrated by various disuse conditions,[40] such as spinal cord injury,[41] stroke,[42] or bed rest.[29] In our study, linear regression models indicated that muscle strength had a weaker influence on fibular than tibial or radial microarchitecture, which is likely related to generally reduced loading of the fibula. These findings are in line with the previous observation that patients with spinal cord injury show a weaker decline in fibular microarchitecture following immobilization.[43] The hypothesis of an additional local muscle–bone interaction was also supported by the fact that grip strength showed the strongest association with radial microarchitecture, while CRT maximum force generally showed the strongest association with tibial microarchitecture. Our results therefore support the direct benefit of exercising specific muscle groups on bone microarchitecture in the context of optimized fracture prevention.

We are aware that our research may have a few limitations. Due to the retrospective cross-sectional design of the study, associations could be investigated, but it is not feasible to derive conclusions regarding causality. Additional longitudinal studies involving larger study cohorts are required to determine the individual and combined effects of muscle performance tests and HR-pQCT parameters on fracture risk in patients across all age groups. Another limitation is that, according to the EWGSOP2 consensus,[24] the identification of low muscle strength (i.e. probable sarcopenia) should be confirmed by additional diagnostics, for example, measurement of appendicular skeletal muscle mass by DXA or bioelectrical impedance analysis. These parameters were not measured in our study and should be obtained in future studies to further

investigate the effects of additional sarcopenia-related parameters in terms of bone mineralization, microarchitecture, and geometry. Regarding the HR-pQCT method, it should be noted that we used fixed offsets for the determination of the scan region, which could be a possible source of error due to different bone lengths of the studied women.

In conclusion, we here provide a comprehensive analysis of the interactions between various muscle and balance tests with bone microarchitecture in women at high risk of osteoporosis. Our findings indicate that muscle strength is primarily associated with cortical area and thickness rather than trabecular microarchitecture. While osteosarcopenia represents an age-independent and aBMD-independent risk factor of poor microarchitecture, we also demonstrated that the muscle–bone interaction is altered by fragility fractures and bone-specific treatments. Together, our findings shed light on the value of muscle assessments as a part of fracture risk evaluation.

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Conflict of interest

All authors declare that they have no conflict of interest.

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Online supplementary material

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

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