The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 12, e5180–e5194
https://doi.org/10.1210/clinem/dgab506
Clinical Research Article

Clinical Research Article

Bone Microarchitecture Decline and Risk of Fall and Fracture in Men With Poor Physical Performance—The STRAMBO Study

Philippe Paul Wagner,[1] Danielle E. Whittier,[3,4] Dominique Foesser,[1] Steven K. Boyd,[3,4] Roland Chapurlat,[1,2] and Pawel Szulc[1,2]

[1]INSERM UMR1033, Université de Lyon, 69008, Lyon, France; [2]Department of Rheumatology, Hospices Civils de Lyon, Hôpital Edouard Herriot, 69437 Lyon, France; [3]McCaig Institute for Bone and Joint Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta T2N 4Z6, Canada; and [4]Department of Radiology, Cumming School of Medicine, University of Calgary, Calgary, Alberta T2N 2T9, Canada

ORCiD number: 0000-0003-4168-6697 (P. Szulc).

Abbreviations: 17β-E_2, 17β-estradiol; 25OHD, 25-hydroxycholecalciferol; μFE, microfinite element; aBMD, areal bone mineral density; AFTC, apparent free testosterone concentration; ALM, appendicular lean mass; bio-17β-E_2, bioavailable 17β-estradiol; BMD, bone mineral density; COPD, chronic obstructive pulmonary disease; Ct.Ar, cortical area; Ct.Th^d, cortical thickness; Ct.BMD, cortical density of the volume of interest; CV, coefficient of variation; GFR, glomerular filtration rate; HR-pQCT, high-resolution peripheral quantitative computed tomography; hsCRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; inn.Tb.BMD, central inner trabecular density; PTH, parathyroid hormone; RALM-LL, relative appendicular lean mass of the lower limbs; RIA, radioimmunoassay; s.e.Tb.BMD, outer subendocortical trabecular bone density; T2DM, type 2 diabetes mellitus; Tb.1/N.SD, inhomogeneity of trabecular network; Tb.Ar, trabecular area; Tb.N, trabecular number; Tb.Sh^d, trabecular separation; Tb.Th^d, trabecular thickness; Tb.BMD, trabecular density; Tt.BMD, total volumetric bone mineral density.

Received: 29 December 2020; Editorial Decision: 6 July 2021; First Published Online: 12 July 2021; Corrected and Typeset: 3 August 2021.

Abstract

Context: High fracture risk in individuals with low muscle strength is attributed to high risk of falls.

Objective: This work aims to study the association of muscle mass and physical performance with bone microarchitecture decline and risk of fall and nonvertebral fracture in men.

Methods: A prospective, 8-year follow-up of a cohort was conducted among the general population. A total of 821 volunteer men aged 60 and older participated. Hip areal bone mineral density (aBMD) and appendicular lean mass (ALM) were assessed at baseline by dual x-ray absorptiometry. Lower-limb relative ALM (RALM-LL) is ALM-LL/(leg length)^2. The physical performance score reflects the ability to perform chair stands and static and dynamic balance. Bone microarchitecture was assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) at baseline and after 4 and 8 years.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Statistical analyses were adjusted for shared risk factors. Outcome measurements included the rate of change in the HR-pQCT indices, incident falls, and fractures.
Results: Cortical bone loss and estimated bone strength decline were faster in men with low vs normal RALM-LL (failure load: –0.74 ± 0.09 vs –0.43 ± 0.10%/year; $P < .005$). Differences were similar between men with poor and those with normal physical performance (failure load: –1.12 ± 0.09 vs –0.40 ± 0.05%/year; $P < .001$). Differences were similar between men having poor performance and low RALM-LL and men having normal RALM-LL and performance (failure load: –1.40 ± 0.17 vs –0.47 ± 0.03%/year; $P < .001$). Men with poor physical performance had a higher risk of fall (hazard ratio [HR] = 3.52; 95% CI, 1.57-7.90, $P < .05$) and fracture (HR = 2.68; 95% CI, 1.08-6.66, $P < .05$).
Conclusion: Rapid decline of bone microarchitecture and estimated strength in men with poor physical performance and low RALM-LL may contribute to higher fracture risk.

Key Words: bone microarchitecture, physical performance, fall, fracture, aging, sarcopenia

Fragility fractures are a major public health problem. Age-related bone loss and loss of muscle mass and strength increase the fracture risk jointly and independently of each other (1-4). Their association is characterized by a disproportionately high fracture risk, suggesting an interaction between them (2, 5, 6). The link between low muscle strength and poor bone status is supported by the concept of "mechanostat" (7-9). Experimental data suggest that osteocytes orchestrate the regulation of bone remodeling to adapt bone response to mechanical load (10, 11).

The results of clinical studies support this theory. In home-dwelling individuals, lower muscle mass and strength were associated with lower areal bone mineral density (aBMD) (12). In prospective studies, individuals with low muscle strength had a high risk of osteoporosis and rapid bone loss (9, 13). Studies on bone microarchitecture provided similar results. In the STRAMBO cohort, we have shown that older men with low grip strength had lower cross-sectional area and lower cortical area at the distal radius (14). In the same cohort, we have shown that, in older men, low grip strength at baseline was associated with a more rapid decline of cortical bone microarchitecture assessed prospectively at the distal radius (15).

Lower mechanical strain may not counteract pathways leading to bone loss. In particular, differences between the radius and tibia may be partly due to the impact of body weight. Previous studies suggested poor mobility (eg, slow gait speed) as a risk factor for fracture (6, 16). Poor mobility is associated with a high risk of fall (16). In the cross-sectional part of the STRAMBO study, we found poor bone microarchitecture in older men with impaired physical performance (17). A study of mobility may permit the assessment of muscle-bone interaction on load-bearing bones. In addition, microfinite element analysis, combining bone mass and microarchitecture, shows lower estimated bone strength (eg, failure load) in men with fracture (18). Thus, poor physical performance could contribute to higher fracture risk via accelerated deterioration of bone strength and higher risk of falling. However, to the best of our knowledge, no study has explored the impact of poor physical performance of the lower limbs on the decline in bone microarchitecture and strength and on the risk of fall and fracture in the same cohort.

Some factors (hypogonadism, vitamin D deficit, diabetes) may have parallel but independent effects on bone and muscle, their interaction, and the risk of falls (19-24). Thus, the link between bone, muscle and risk of fall found in previous studies may be spurious and related to insufficient control for the confounding effect of these shared risk factors.

Thus, our aim was to assess the link of poor physical performance of the lower limbs with the deterioration of bone microarchitecture at the tibia, the risk of fall and that of non-vertebral fracture in a cohort of older men followed prospectively for 8 years, after accounting for possible confounders.

Materials and Methods

Cohort

The STRAMBO study is a prospective, single-center cohort study designed to explore fracture prediction by bone microarchitecture measures in men (25). The study was accepted by the local ethics committee and carried out according to the 1975 and 1983 Declaration of Helsinki. It was performed as a collaboration between INSERM (Institut National de la Santé et de la Recherche Médicale) and a health insurance company MTRL (Mutuelle des Travailleurs de la Région Lyonnaise). The cohort was enrolled during 2006 to 2008 from the Greater Lyon MTRL lists. Invitations were sent to a random sample of men aged

20 and older. We included 1169 men who gave their informed consent, answered questionnaires, and had diagnostic exams. Among them, 821 men aged 60 and older at baseline were followed prospectively for 8 years.

Physical Performance

The score of physical performance was described previously (25, 26). A 5-time chair stand test was used to evaluate power on vertical movement and the hip surrounding muscle function. The inability to perform the test was diagnosed when a man was unable to complete 5 chair stands (score 0). Men were classified as able if they managed to get up 5 times regardless of the time required. They were separated according to the quartiles of time required to complete the 5 chair stands (scored 1 to 4 according to the quartiles). Static balance was evaluated by 10 seconds standing with feet in the side-by-side position. Every interruption during this time (grasp, inability to maintain the position) ended the test. The time was recorded when it was less than 10 seconds. For standing balance, the test was scored as follows: unable to stand in the positions (score 0), less than 10 seconds with eyes open (score 1), 10 seconds with eyes open and less than 5 seconds with eyes closed (score 2), 10 seconds with eyes open and 5 to 9 seconds with eyes closed (score 3), and 10 seconds in each position (score 4). The dynamic balance was evaluated with a forward and backward 10-step tandem walk on a drawn line on the floor. The examiner recorded the time, number of steps, and number of errors. The men who did not perform a 10-step tandem walk forward or backward were scored unable (score 0). For men who accomplished 10 steps, time was scored 1 to 4 according to the quartiles (4 for the shortest). The composite physical performance score was obtained by summing up the 4 scores (0-16).

Dual X-Ray Absorptiometry and Anthropometric Measurements

Body composition and hip areal BMD (aBMD) were assessed at baseline by dual x-ray absorptiometry (Hologic Discovery A, Hologic). Long-term coefficient of variation (CV) of aBMD of the commercial spine phantom was 0.35%. Body composition was assessed by the 12.4.3 software. Standing and sitting heights were measured using a standard stadiometer. Upper segment length is the difference between the sitting height and height of the chair. The difference between the standing height and the upper segment length is the lower segment length. CVs of the standing and sitting heights were 0.5% and 1.3% (27). Relative appendicular lean mass of the lower limbs (RALM-LL) was calculated as the sum of lean mass of both legs divided by lower segment length squared. RALM-LL is supposed to reflect muscle mass of lower limbs better than RALM because it is not biased by lean mass of the upper limbs or by variability of the upper segment length.

High-Resolution Peripheral Quantitative Computed Tomography

Bone microarchitecture was assessed at the right distal tibia by the XtremeCT device (Scanco Medical) at baseline and after 4 and 8 years. An anteroposterior scout view was used to set a reference line at the end plate of the distal tibia. The volume of interest composed of 110 slices was acquired starting at a fixed offset of 22.5 mm from the reference line with an isotropic voxel size of 82 µm (17). Standard analysis was used to separate the trabecular and cortical compartments. Derived parameters (as opposed to measured) are denoted with a superscript "d" (28). Trabecular (Tb.Ar) and cortical area (Ct.Ar) are cross-sectional areas of each compartment. Cortical thickness ($Ct.Th^{d}$) is the mean cortical volume divided by the outer bone surface. Average volumetric bone mineral density (BMD) in each compartment of volume of interest were calculated as cortical (Ct.BMD) and trabecular density (Tb.BMD). In the trabecular bone, outer, subendocortical Tb.BMD (s.e.Tb.BMD) and central, inner (inn.Tb.BMD) were calculated. Trabecular thickness ($Tb.Th^{d}$) and separation ($Tb.Sp^{d}$) were derived from bone volume/tissue volume and trabecular number (Tb.N) (28). The heterogeneity of the trabecular network was quantified from the intraindividual distribution of Tb.N (Tb.1/N.SD, µm). Quality control was performed by daily scan phantom measurements. The short-term and long-term CV for the phantom densities were 0.05% to 0.9% and 0.5% to 1.7%, respectively. The in vivo reproducibility of the bone microarchitectural variables was 0.7% to 4.5% (29). Overlap between baseline follow-up scans was determined based on slice-matching, and movement artifacts were graded from a scale from 1 (no motion) to 5 (severe motion) (30). All scans with a motion score of 4 or greater and/or overlap of 85% or less were excluded.

Finite Element Analysis

Microfinite element (µFE) analysis was performed using the unregistered segmented HR-pQCT images to determine reaction force and estimated failure load. Linear µFE models were generated by using the voxel-by-voxel approach. Poisson ratio of 0.3 and a homogeneous Young modulus of 6829 GPa were assigned as bone tissue properties (31, 32). The model boundary conditions were an

axial compression test with 1% compressive strain, and resultant reaction force of the bone was measured. Failure load was estimated from the models using a yield criterion of 2% critical volume and 0.7% critical strain (33). μFE models were solved using a conjugate gradient approach with a convergence criterion of 1×10^{-6} (FAIM v8.0, Numerics88 Solutions Ltd) on the University of Calgary's high-performance computing cluster.

Incidence of Falls and Nonvertebral Fragility Fractures

Participants were interviewed annually for 8 years with an interviewer-assisted questionnaire to assess falls, injurious falls (ie, necessitating hospitalization) and nonvertebral fragility fractures. We retained self-reported low-trauma fractures (a fall from a standing position or less) confirmed by a health professional (x-ray, medical, or surgical report). Fractures of the skull, face, hand, fingers, and toes as well as those related to high trauma were not retained.

Epidemiologic Questionnaire

At baseline, men replied to an interviewer-administered questionnaire covering self-reported lifestyle factors and health status. Smoking was assessed as current smoker vs nonsmoker. Alcohol intake was calculated as the average amount of alcohol consumed weekly. Calcium intake was assessed by a food-frequency questionnaire adapted to French alimentary habits (34). Current leisure physical activity was calculated as the amount of time spent walking, gardening, and participating in leisure sport activity including seasonal activities. Occupational physical activity was self-reported and classified as weak, average, high, or very high. Intrinsic falls during the year preceding the recruitment and prior fractures were self-reported. Comorbidities (ischemic heart disease [IHD], hypertension, diabetes mellitus, prior stroke, Parkinson disease, cancer, chronic obstructive pulmonary disease [COPD], type 2 diabetes mellitus [T2DM], rheumatoid arthritis, and digestive diseases) were self-reported, classified as present or absent, and not further ascertained.

Hormonal Assessment

Testosterone was measured by radioimmunoassay (RIA) with diethyl ether extraction. Limit of detection was 0.06 nM. Interassay CV was 8% (22). 17β-estradiol (17β-E_2) was measured by ultrasensitive RIA (CISBio-International) (22). Intra-assay and interassay CV of 17β-E_2 were 5.7% and 18%, respectively. The detection limit was 5 pM. Sex hormone–binding globulin was measured by RIA (CISBio-International) (22). Intra-assay and interassay CV were 4% and 5%, respectively. Apparent free testosterone concentration (AFTC) and bioavailable 17β-E_2 (bio-17β-E_2) were calculated as described previously (22, 35). 25-hydroxycholecalciferol (25OHD) was assessed by RIA (DiaSorin) after acetonitrile extraction (23). The detection limit was 3 ng/mL. Intra-assay and interassay CV were 5% to 7% and 9% to 11%, respectively. Serum parathyroid hormone (PTH) was measured by human-specific, 2-site immunochemiluminescence assay. The detection limit was 3 pg/mL (23). Intra-assay and interassay CV were less than 5%. High-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetric latex assay (Roche Diagnostics). The detection limit was 0.15 mg/L. Intra-assay and interassay CV were 8%. Serum creatinine was measured using a modified kinetic Jaffé method (36). Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation (36).

Statistical Analysis

The analyses were performed using the R version 3.3.3 software (2017, R Foundation for Statistical Computing). Simple correlations were assessed using the Pearson correlation coefficient. Comparisons according to the quartile of RALM-LL or of the physical performance score were performed by analysis of covariance with and without adjusting for age. Chi-square test or Fisher exact test was used for categorical variables. Linear mixed-effect models were used to explore the evolution of bone parameters according to age decade. Multivariable-adjusted linear mixed-effect models were used to explore the evolution of bone indices according to the classes of RALM-LL and physical performance score. To construct the model, a bivariate analysis was performed to explore the association between independent variables and each bone parameter with a simple linear regression and an α risk of 10%. Model assumptions were checked by histograms and quantile-to-quantile plots of residuals. Variables were selected based on biological plausibility, previous published data, and bivariable analyses with bone microarchitectural measures. The selected variables were integrated into a multivariate model to adjust partial correlation coefficients of the comparison groups. The quality of the statistical model for a given set of variables was assessed with the Akaike information criterion and the coefficient of determination (R^2). For strongly correlated variables (AFTC and bio-17β-E_2, PTH, and 25OHD), 2 models were checked and the variable with a stronger effect was retained. The final mixed models were adjusted for age, body mass index, calcium intake, leisure and occupational physical activity, length

of leg, bio-17β-E_2 or AFTC, 25OHD or PTH, GFR, IHD, cancer, COPD, T2DM, and Parkinson disease. The conditions for the validity of fixed-effect models have been verified graphically. Random-effect models were added to characterize individual trajectories to allow individual specific prediction. Then, log-transformed variables were analyzed to obtain results as percentages.

Adjusted Cox proportional hazard analyses were performed to assess hazard ratios and 95% CI for incident multiple falls, incident injurious falls, and incident nonvertebral fractures according to the defined risk groups of physical performance. The quality of statistical models for a given set of variables was checked with Schönfeld residuals. The final Cox model for falls was adjusted for age, prior falls, RALM-LL, systolic blood pressure, hsCRP, and AFTC. The final Cox model for fractures was adjusted for age, weight, hip aBMD, prior fractures and falls, RALM-LL, IHD, and 25OHD. Other potential confounders such as lifestyle factors, comorbidities, and hormones were checked; however, they were not significant and not retained in the final model.

Results

Among 821 men, 795 (97%), 620 (78%), and 456 (54%) had good-quality scans at baseline and 4 and 8 years, respectively. The causes of attrition were death (61 and 168 after 4 and 8 years), poor health (32 and 126 after 4 and 8 years), relocation (3 and 7 after 4 and 8 years), and poor quality of scans (53 and 42 after 4 and 8 years). The 343 men who did not have complete follow-up were older than those who did (age 79 vs 74 years, $P < .001$). After adjustment for age, they were heavier, had lower grip strength, less leisure physical activity, and lower testosterone and 25OHD levels ($P < .001$ for all).

Aging-related Deterioration of Bone Microarchitecture

Total BMD (Tt.BMD) decreased significantly in all the age groups, that is, the means differed significantly from 0 (Table 1). In all the age groups, Ct.Ar, Ct.Th^d, and Ct.BMD decreased, whereas Tb.Ar and s.e.Tb.BMD increased. Tb.BMD and inn.Tb.BMD increased in the first 2 younger age groups, but not in the oldest one. Tb.N increased, whereas Tb.1/N.SD and Tb.Sp^d decreased in the 2 younger groups. Failure load and reaction forces decreased in all the groups. Aging-related decrease in Tt.BMD, cortical measures, Tb.BMD, reaction force and failure load, as well as endocortical expansion (Tb.Ar) accelerated across all age groups. Similar results were found when the changes were expressed as percentages.

Lower-Limb–Relative Appendicular Lean Muscle Mass

Men in the 2 lower RALM-LL quartiles were older than the 2 higher quartiles ($P < .001$) (37). After adjustment for age, men in the lowest quartile had lower weight and higher GFR and testosterone level. Ct.Th^d, Ct.Ar, and Ct.BMD decreased significantly in all the quartiles; however, the loss was 23% to 28% (0.23-0.30 SD) more rapid in the first quartile than in the 3 upper quartiles jointly ($P < .001$) (Table 2). Tb.Ar and s.e.Tb.vBMD increased significantly in all the quartiles, the increase being 31% (0.25 SD, $P < .005$) and 26% (0.18 SD, $P < .05$) more rapid in the first quartile vs the 3 upper quartiles combined. No consistent patterns were found for the other trabecular indices. Failure load and reaction force decreased in all the quartiles. Their rates of decrement increased across the RALM-LL quartiles and were more rapid by 30% (0.24 SD) and 45% (0.21 SD), respectively, in the first vs the fourth quartile. Results were similar in the analysis using the percentage values of changes.

Score of Physical Performance

Men in the lowest quartile of the physical performance score were older (Table 3). After adjustment for age, they were heavier and had lower leisure physical activity and lower AFTC and 25OHD levels. They had higher concentrations of PTH and hsCRP. Prevalence of COPD, Parkinson disease, stroke, and IHD were higher in the lowest compared with the highest quartile.

Tt.BMD decreased significantly in all the quartiles, and the decrease was 2.5-fold more rapid in the first quartile compared with the 3 upper ones combined (0.68 SD, $P < .001$) (Table 4). Ct.Th^d, Ct.Ar, and Ct.BMD decreased significantly in all the quartiles and the decrease was 63%j to 100% (0.54-0.62 SD) more rapid in the first quartile compared with the 3 upper ones combined ($P < .001$). Tb.Ar increased in all the quartiles and the expansion was 2.2-fold more rapid in the first quartile than in the 3 upper ones combined (0.66 SD, $P < .001$). Tb.BMD was stable in the first quartile and increased in the 3 other ones. Inn. Tb.BMD decreased significantly in the first quartile and was stable in the other ones ($P < .001$). S.e.Tb.BMD increased significantly in all the quartiles. Tb.N increased in all the quartiles, and the rate of increase was 11% higher in the first compared with the fourth quartile (0.06 SD, $P < .05$). Tb.Th^d and Tb.Sp^d decreased in the first quartile and were stable in other ones. Failure load and reaction forces decreased in all the quartiles. The rate of decrease in reaction force and failure load were 2-fold more rapid in the lowest quartile compared with the 3 upper ones jointly

Table 1. Prospectively assessed aging-related deterioration of bone microarchitecture at the distal tibia according to age group

Age range	60-70 y (n = 336) Ref.	70-80 y (n = 359)	> 80 y (n = 128)	*P* for trend
Change of bone microarchitecture as absolute values				
Tt.BMD, mg HA/cm^3/y	**–0.55 ± 0.07**	**–1.15 ± 0.19**[d]	**–2.86 ± 0.30**[d]	< .001
Ct.Th^d, µm/y	**–0.63 ± 0.06**	**–1.21 ± 0.15**[d]	**–2.75 ± 0.24**[d]	< .001
Ct.Ar, mm^2/y	**–0.66 ± 0.07**	**–1.41 ± 0.17**[d]	**–3.12 ± 0.27**[d]	< .001
Ct.BMD, mg HA/cm^3/y	**–3.04 ± 0.17**	**–4.40 ± 0.44**[d]	**–7.89 ± 0.70**[d]	< .001
Tb.Ar, mm^2/y	*0.40 ± 0.05*	*1.00 ± 0.14*[d]	*2.34 ± 0.22*[d]	< .001
Tb.BMD, mg HA/cm^3/y	*0.35 ± 0.04*	*0.30 ± 0.10*	0.00 ± 0.16[c]	< .05
inn.Tb.BMD, mg HA/cm^3/y	*0.31 ± 0.04*	*0.17 ± 0.11*[a]	**–0.24 ± 0.13**[d]	< .001
s.e.Tb.BMD, mg HA/cm^3/y	*0.41 ± 0.04*	*0.49 ± 0.11*	0.35 ± 0.18	.70
Tb.N, 1/mm/year, 10^3	*3.81 ± 1.15*	*8.39 ± 2.93*	–0.50 ± 4.62	.50
Tb.Th^d, µm/y	0.02 ± 0.53	**-0.20 ± 0.14**[b]	0.13 ± 0.21	.20
Tb.Sp^d, µm/y	**–1.21 ± 0.33**	**–2.30 ± 0.84**[a]	0.64 ± 1.33	.98
Tb.1/N.SD, µm/y	**–0.40 ± 0.21**	**–0.73 ± 0.53**	0.54 ± 0.84	.70
Reaction force, No.	**–41.5 ± 5.4**	**–99.2 ± 8.2**[d]	**–176.7 ± 16.3**[d]	< .001
Failure load, No.	**–21.8 ± 2.4**	**–49.1 ± 3.7**[d]	**–83.4 ± 7.3**[d]	< .001
Change of bone microarchitecture as percentage				
Tt.BMD, %/y	**–0.19 ± 0.03**	**–0.46 ± 0.07**[d]	**–1.16 ± 0.12**[d]	< .001
Ct.Th^d,%/y	**–0.59 ± 0.08**	**–1.40 ± 0.20**[d]	**–3.29 ± 0.32**[d]	< .001
Ct.Ar, %/y	**–0.55 ± 0.08**	**–1.41 ± 0.20**[d]	**–3.34 ± 0.31**[d]	< .001
Ct.BMD, %/y	**–0.37 ± 0.02**	**–0.58 ± 0.06**[d]	**–1.05 ± 0.10**[d]	< .001
Tb.Ar, %/y	*0.06 ± 0.01*	*0.14 ± 0.02*[d]	*0.35 ± 0.03*[d]	< .001
Tb.BMD, %/y	*0.20 ± 0.02*	*0.17 ± 0.06*	**–0.05 ± 0.10**[d]	< .005
inn.Tb.BMD, %/y	*0.22 ± 0.04*	0.06 ± 0.11[a]	*–0.36 ± 0.18*[d]	< .001
s.e.Tb.BMD, %/y	*0.18 ± 0.02*	*0.21 ± 0.05*	0.12 ± 0.07	.94
Tb.N, %/y	*0.21 ± 0.06*	*0.45 ± 0.16*[a]	–0.08 ± 0.26	.64
Tb.Th^d, %/y	0.01 ± 0.07	–0.26 ± 0.17[a]	0.11 ± 0.26	.17
Tb.Sp^d, %/y	**–0.24 ± 0.06**	**–0.48 ± 0.16**[a]	0.07 ± 0.26	.74
Tb.1/N.SD, %/y	**–0.20 ± 0.07**	–0.40 ± 0.19	0.22 ± 0.30	.84
Reaction force, %/y	**–0.30 ± 0.03**	**–0.79 ± 0.07**[d]	**–1.96 ± 0.13**[d]	< .001
Failure load, %/y	**–0.31 ± 0.03**	**–0.77 ± 0.06**[d]	**–1.93 ± 0.12**[d]	< .001

Bold indicates a decrease significantly different from zero. Italic indicates an increase significantly different from zero. Derived parameters (as opposed to measured) are denoted with a superscript "d."

Abbreviations: BMD, bone mineral density; Ct.Ar, cortical area; Ct.BMD, cortical vBMD; Ct.Th^d, cortical thickness; inn.Tb.BMD, inner, central Tb.BMD; mg HA, mg hydroxyapatide; RALM-LL, relative appendicular lean mass of the lower limbs; Ref., reference; s.e.Tb.vBMD, subendocortical Tb.BMD; Tb.N, trabecular number; Tb.1/N.SD, inhomogeneity of trabecular network; Tb.BMD, trabecular vBMD; Tb.Sp^d, trabecular separation; Tb.Th^d, trabecular thickness; Tt.BMD, total volumetric bone mineral density (vBMD).

[a]*P* less than .05,

[b]*P* less than .01,

[c]*P* less than .005, and

[d]*P* less than .001 for comparisons vs reference group.

(0.61 SD and 0.63 SD, respectively, $P < .001$). Results were similar in the analysis using the percentage values of changes in the HR-pQCT indices.

Lower-Limb–Relative Appendicular Lean Muscle Mass, Physical Performance, and Bone Microarchitecture

Four groups were created according to the lowest quartiles of the physical performance score and RALM-LL (Table 5). Men having both RALM-LL and the physical performance score in the 3 upper respective quartiles were the reference group. Tt.BMD, cortical indices, reaction force, and failure load decreased significantly in all the groups, and more rapidly in the groups with low physical performance compared with the reference group. Tt.BMD decreased more rapidly in both groups with low performance with differences of 0.90 SD and 0.56 SD compared with the reference group ($P < .001$). Failure load decreased more rapidly in both groups with low physical performance with differences of 0.92 SD and 0.44 SD compared with the reference group ($P < .001$). Tb.Ar increased significantly in all the groups. It increased more rapidly in both groups with low performance with

Table 2. Bone microarchitecture according to the quartiles of relative appendicular lean mass of the lower limbs

RALM-LL	Q1 < 5.27 kg/m^2(n = 206)	Q2 (5.27-5.63 kg/m^2) (n = 205)	Q3 (5.63-6.07 kg/m^2) (n = 205)	Q4 (Ref.) ≥ 6.07 kg/m^2 (n = 206)
Change in bone microarchitectural variables as absolute values				
Tt.BMD, mg HA/cm^3/y	**–1.18 ± 1.80**[a]	**–0.97 ± 0.29**	**–0.88 ± 0.28**	**–0.76 ± 0.28**
Ct.Th^d, µm/y	**–12.59 ± 1.00**[d]	**–9.58 ± 2.41**	**–9.38 ± 2.37**	**–8.39 ± 2.36**
Ct.Ar, mm^2/y	**–1.40 ± 0.11**[c]	**–1.05 ± 0.27**	**–1.03 ± 0.26**	**–0.97 ± 0.26**
Ct.BMD, mg HA/cm^3/y	**–4.73 ± 0.28**[d]	**–3.94 ± 0.67**	**–3.71 ± 0.66**	**–3.28 ± 0.66**
Tb.Ar, mm^2/y	*0.98 ± 0.21*[c]	*0.68 ± 0.20*	*0.73 ± 0.20*	*0.63 ± 0.08*
Tb.BMD, mg HA/cm^3/y	*0.37 ± 0.06*	0.28 ± 0.15	*0.31 ± 0.15*	0.27 ± 0.15
inn.Tb.BMD, mg HA/cm^3/y	*0.25 ± 0.07*	0.14 ± 0.17	0.25 ± 0.16	0.21 ± 0.16
s.e.Tb.BMD, mg HA/cm^3/y	*0.55 ± 0.07*[a]	*0.46 ± 0.16*	*0.42 ± 0.16*	*0.36 ± 0.16*
Tb.N, 1/mm/y*10^3)	4.85 ± 4.22	4.66 ± 4.33	4.39 ± 4.25	7.09 ± 4.24
Tb.Th^d, µm/y	0.12 ± 0.19	–0.01 ± 0.08	–0.03 ± 0.20	–0.04 ± 0.20
Tb.Sp^d, µm/y	**–1.81 ± 0.52**	**–1.62 ± 0.72**	–1.40 ± 0.70	**–1.14 ± 0.50**
Tb.1/N.SD, µm/y	–0.81 ± 0.41	–0.49 ± 0.44	–0.40 ± 0.43	–0.11 ± 0.29
Reaction force, No.	**–88.0 ± 11.6**[a]	**–72.7 ± 11.6**	**–72.1 ± 11.2**	**–62.0 ± 7.8**
Failure load, No.	**–44.5 ± 5.2**[b]	**–37.1 ± 5.2**	**–36.8 ± 5.0**	**–30.8 ± 3.1**
Change in bone microarchitectural variables as percentage				
Tt.BMD, %/y	**–0.45 ± 0.05**[d]	**–0.36 ± 0.11**	**–0.36 ± 0.11**	**–0.27 ± 0.11**
Ct.Th^d, %/y	**–1.45 ± 0.30**[c]	**–0.96 ± 0.31**	**–1.06 ± 0.30**	**–0.87 ± 0.31**
Ct.Ar, %/year	**–1.45 ± 0.13**[d]	**–0.95 ± 0.31**	**–1.02 ± 0.30**	**–0.85 ± 0.30**
Ct.BMD, %/y	**–0.62 ± 0.03**[d]	**–0.49 ± 0.10**	**–0.48 ± 0.10**	**–0.41 ± 0.10**
Tb.Ar, %/y	*0.15 ± 0.03*[a]	*0.10 ± 0.03*	*0.10 ± 0.03*	*0.09 ± 0.03*
Tb.BMD, %/y	*0.22 ± 0.04*	0.17 ± 0.09	0.16 ± 0.09	0.15 ± 0.09
inn.Tb.BMD, %/y	*0.18 ± 0.07*	0.18 ± 0.07	0.10 ± 0.17	0.15 ± 0.17
s.e.Tb.BMD, %/y	*0.23 ± 0.03*[a]	*0.20 ± 0.07*	*0.17 ± 0.07*	0.15 ± 0.07
Tb.N, %/y	*0.27 ± 0.10*	0.26 ± 0.24	0.23 ± 0.24	0.37 ± 0.24
Tb.Th^d, %/y	–0.00 ± 0.10	–0.07 ± 0.24	–0.04 ± 0.24	–0.19 ± 0.24
Tb.Sp^d, %/y	**–0.31 ± 0.10**	–0.29 ± 0.24	–0.26 ± 0.24	–0.40 ± 0.24
Tb.1/N.SD, %/y	–0.18 ± 0.11	–0.16 ± 0.27	–0.16 ± 0.27	–0.20 ± 0.27
Reaction force, %/y	**–0.74 ± 0.09**[b]	**–0.56 ± 0.12**	**–0.54 ± 0.10**	**–0.44 ± 0.10**
Failure load, %/y	**–0.74 ± 0.09**[c]	**–0.57 ± 0.08**	**–0.55 ± 0.11**	**–0.43 ± 0.10**

Bold indicates a decrease significantly different from zero. Italic indicates an increase significantly different from zero. Results presented as adjusted means ± SEM. Derived parameters (as opposed to measured) are denoted with a superscript "d." Models adjusted for age, body mass index, calcium intake, leisure and occupational physical activity, length of leg, apparent free testosterone ***or*** bioavailable 17β-estradiol, 25-hydroxycholecalciferol ***or*** parathyroid hormone, log-transformed high-sensitivity C-reactive protein, glomerular filtration rate, cancer, diabetes, prior stroke, ischemic heart disease, COPD, and Parkinson disease.

Abbreviations: BMD, bone mineral density; Ct.Ar, cortical area; Ct.BMD, cortical vBMD; Ct.Th^d, cortical thickness; inn.Tb.BMD, inner, central Tb.BMD; mg HA, mg hydroxyapatide; Q, quartile; RALM-LL, relative appendicular lean mass of the lower limbs; Ref., reference; s.e.Tb.BMD, subendocortical Tb.BMD; Tb.N, trabecular number; Tb.1/N.SD, inhomogeneity of trabecular network; Tb.BMD, trabecular vBMD; Tb.Sp^d, trabecular separation; Tb.Th^d, trabecular thickness; Tt.BMD, total volumetric bone mineral density (vBMD).

[a]Less than 0.05,

[b]less than 0.01,

[c]less than 0.005, and

[d]less than 0.001 for comparisons vs reference group (Q4).

differences of 1.45 SD and 0.40 SD compared with the reference group ($P < .001$). In the group with low physical performance but higher RALM-LL, the loss of Tb.BMD and inn.Tb.BMD was more rapid compared with the reference group ($P < .001$). No consistent patterns were found for the other trabecular variables. Results expressed as percentages were similar.

We compared both groups with low physical performance. Men having high RALM-LL and low physical performance were the reference group. Ct.Th^d decreased more rapidly in men with low RALM-LL compared with the reference group (0.76 SD, $P < .05$). Ct.Ar and Ct.BMD decreased and Tb.Ar increased twice as rapidly in men with low RALM-LL compared with men with higher RALM-LL, with differences of 1.05 to 1.31 SD between the groups ($P < .001$ for all). Results expressed as percentages were similar.

Multiple Incident Falls

Over 8 years, 243 men sustained multiple intrinsic falls. The median time to the first fall was 944 days

Table 3. Characteristics of the cohort at baseline according to the score of physical performance

Test of physical performance	Q1 < 8 (n = 206)	Q2 (8-10) (n = 231)	Q3 (11-12) (n = 176)	Q4 (Ref.) (13-16), (n = 200)	P^e	P^f
Age, y	76.9 ± 6.5[a]	71.8 ± 6.7[a]	70.9 ± 6.3[a]	68.9 ± 6.8	< .001	
Weight, kg	79.1 ± 11.3	79.3 ± 11.9	77.4 ± 10.3	77.6 ± 11.3	.086	< .05
BMI	28.7 ± 0.24[a]	27.1 ± 0.26	27.1 ± 0.24	27.1 ± 0.25	< .001	< .001
Lower limb mass, kg	15.42 ± 2.05[b]	16.25 ± 2.20	16.23 ± 2.13[a]	16.67 ± 2.23	< .001	.051
RALM-LL, kg/m^2	5.6 ± 0.6[d]	5.7 ± 0.6	5.7 ± 0.6	5.8 ± 0.6	< .005	.24
Leisure physical activity, h/wk	3.3 ± 0.43[d]	5.6 ± 0.43	6.4 ± 0.46	5.8 ± 0.43	< .001	< .001
Time spent outdoors, h/wk	6.2 ± 0.32[d]	7.6 ± 0.30[c]	8.4 ± 0.35	9.0 ± 0.33	< .001	< .001
25OHD, nmol/L	18.5 ± 0.66[d]	21.5 ± 0.62[d]	23.8 ± 0.71	25.2 ± 0.67	< .001	< .001
Parathyroid hormone, pg/mL	56.9 ± 1.70[d]	47.8 ± 1.62	44.9 ± 1.85	44.7 ± 1.74	< .001	< .05
Calcium intake, mg/d	753 ± 254	766 ± 260	751 ± 223	791.6 ± 231.9	.32	.34
Testosterone, nmol/L	10.9 ± 0.38[a]	11.8 ± 0.35	12.5 ± 0.40	12.2 ± 0.37	< .05	< .05
AFTC, pmol/mL	211.7 ± 6.35[d]	246.9 ± 6.00	252.4 ± 6.87	260.1 ± 6.46	< .001	< .05
Total 17β-estradiol, pmol/L	52.6 ± 23.0[a]	53.1 ± 18.1	53.2 ± 21.0	54.8 ± 21.2	.73	.81
Bio-17β-estradiol, pmol/L	36.3 ± 1.45	38.0 ± 1.38	37.6 ± 1.57	39.8 ± 1.48	.15	.87
SHBG, nmol/L	46.85 ± 1.45[d]	41.71 ± 1.38	44.49 ± 1.57[a]	39.50 ± 1.48	< .005	.26
hsCRP, ng/mL	2.1 (1.2-5.0)[d]	1.6 (0.8-3.4)	1.6 (0.8-3.1)	1.3 (0.7-2.4)	< .001	< .005
Glomerular filtration rate, mL/min	67.3 ± 1.07[d]	70.8 ± 1.01	70.8 ± 1.02	73.0 ± 1.08	< .005	.59
Comorbidities						
Fall	54 (26.2%)	39 (16.9%)	37 (21%)	30 (15%)	< .05	.47
Cancer	27 (13.1%)	35 (15.2%)	23 (13.1%)	21 (10.5%)	.563	.44
COPD	20 (9.7%)	14 (6.1%)	7 (4%)	10 (5%)	.1	< .05
Parkinson disease	10 (4.9%)	3 (1.3%)	1 (0.6%)	1 (0.5%)	< .005	< .001
Diabetes	44 (5.4%)	24 (2.9%)	18 (2.2%)	11 (1.4%)	.29	.11
Stroke	15 (7.3%)	11 (4.8%)	3 (1.7%)	2 (1%)	< .005	< .05
Ischemic heart disease	52 (25.2%)	39 (16.9%)	20 (11.4%)	17 (8.5%)	< .001	< .001

Results are mean ± SD, median (interquartile range) or number of participants (proportion, %). Fall equals one or more self-reported intrinsic fall during the year prior to recruitment.

Abbreviations: 25OHD, serum 25-hydroxycholecalciferol; AFTC, apparent free testosterone concentration; BMI, body mass index; COPD, chronic obstructive pulmonary disease; hsCRP, high-sensitivity C-reactive protein; RALM-LL, relative appendicular lean mass of the lower limbs; Ref., reference; SHBG, sex hormone–binding globulin; Q, quartile.

[a]*P* less than .05,

[b]less than .01,

[c]less than .005, and

[d]less than .001 vs Q4 (Ref. group).

P^e equals without age adjustment.

P^f equals with adjustment for age.

(interquartile range, 548-1323 days). The percentage of men with falls was higher in the men with the poorest performance (41.6%) compared with those with the highest performance (24.4%) (Table 6). In the fully adjusted model, the risk of fall was higher in the poorest performance class compared with the class with the highest performance (hazard ratio = 1.72; 95% CI, 1.17-2.54, $P < .05$). The risk of multiple falls was higher in the class with the poorest performance compared with the 3 upper classes combined (hazard ratio = 1.67; 95% CI, 1.24-2.23, $P < .001$).

Incident Injurious Falls (Necessitating Hospitalization)

Seventy-three men sustained injurious falls. The median time to the fall was 1551 days (interquartile range, 845-2073 days). The percentage of men with such falls was higher in the class with the lowest performance (18.7%) compared with the class with the highest performance (4%). In the final model, the risk of fall was higher in the poorest compared with the highest performance group (hazard ratio = 3.52; 95% CI, 1.57-7.90, $P < .05$). In a similar model, the risk of injurious fall was higher in the poorest performance class compared with the 3 upper classes jointly (hazard ratio = 2.60; 95% CI, 1.56-4.34, $P < .001$).

Incident Nonvertebral Fractures

Sixty-eight men had nonvertebral fragility fractures. Fracture incidence was similar in the second and the third quartiles and the proportional hazard risk was not observed between them (violation of the condition

Table 4. Annual changes in bone microarchitecture at distal tibia according to the score of physical performance at baseline

Score of physical performance	Q1 (0-7) (n = 206)	Q2 (8-10) (n = 231)	Q3 (11-12) (n = 176)	Q4 (ref) (13-16) (n = 200)
Change in bone microarchitectural variables as absolute values				
Tt.BMD, mg HA/cm^3/y	**–1.89 ± 0.14**[d]	**–0.75 ± 0.32**	**–0.86 ± 0.33**	**–0.71 ± 0.32**
Ct.Th^d, µm/y	**–16.63 ± 1.21**[d]	**–8.91 ± 2.69**	**–9.51 ± 2.74**	**–7.92 ± 2.70**
Ct.Ar, mm^2/y	**–1.98 ± 0.13**[d]	**–0.99 ± 0.29**	**–1.08 ± 0.29**	**–0.84 ± 0.29**
Ct.BMD, mg HA/cm^3/y	**–5.87 ± 0.33**[d]	**–3.56 ± 0.75**	**–3.88 ± 0.76**	**–3.33 ± 0.75**
Tb.Ar, mm^2/y	*1.41 ± 0.21*[d]	*0.65 ± 0.25*	*0.72 ± 0.25*	*0.53 ± 0.25*
Tb.BMD, mg HA/cm^3/y	0.03 ± 0.08[d]	*0.37 ± 0.17*	*0.38 ± 0.17*	*0.34 ± 0.17*
inn.Tb.BMD, mg HA/cm^3/y	**–0.18 ± 0.08**[d]	0.28 ± 0.19	0.31 ± 0.19	0.29 ± 0.19
s.e.Tb.BMD, mg HA/cm^3/y	*0.32 ± 0.08*	*0.50 ± 0.18*	*0.47 ± 0.19*	*0.40 ± 0.18*
Tb.N, 1/mm/y*10^3	*8.51 ± 2.18*[a]	*7.89 ± 3.30*	*8.37 ± 3.70*	*6.95 ± 3.31*
Tb.Th^d, µm/y	**–0.36 ± 0.10**[c]	–0.10 ± 0.22	0.02 ± 0.23	0.05 ± 0.23
Tb.Sp^d, µm/y	**–2.26 ± 0.62**	–2.10 ± 1.39	–1.20 ± 1.42	–0.90 ± 1.39
Tb.1/N.SD, µm/y	–0.55 ± 0.33	–0.39 ± 0.78	–0.11 ± 0.77	–0.77 ± 0.77
Reaction force, N/y	**–137.2 ± 12.6**[d]	**–72.0 ± 10.5**	**–60.4 ± 10.9**	**–53.6 ± 7.4**
Failure load, N/y	**–67.26 ± 5.63**[d]	**–35.67 ± 4.70**	**–32.43 ± 4.90**	**–27.37 ± 3.33**
Change in bone microarchitectural variables as percentage				
Tt.BMD, %/y	**–0.76 ± 0.06**[d]	**–0.28 ± 0.12**	**–0.33 ± 0.13**	**–0.26 ± 0.12**
Ct.Th^d, %/y	**–2.04 ± 0.15**[d]	**–0.90 ± 0.35**	**–1.03 ± 0.35**	**–0.83 ± 0.35**
Ct.Ar, %/y	**–2.13 ± 0.15**[d]	**–0.88 ± 0.34**	**–1.04 ± 0.35**	**–0.79 ± 0.34**
Ct.BMD, %/y	**–0.78 ± 0.05**[d]	**–0.45 ± 0.11**	**–0.49 ± 0.11**	**–0.42 ± 0.11**
Tb.Ar, %/y	*0.21 ± 0.05*[d]	*0.09 ± 0.04*	*0.11 ± 0.04*	*0.08 ± 0.04*
Tb.BMD, %/y	0.01 ± 0.05[c]	*0.22 ± 0.10*	*0.22 ± 0.10*	0.18 ± 0.10
inn.Tb.BMD, %/y	**–0.37 ± 0.08**[d]	0.23 ± 0.18	0.24 ± 0.19	0.20 ± 0.18
s.e.Tb.BMD, %/y	*0.15 ± 0.03*	*0.21 ± 0.08*	*0.20 ± 0.08*	*0.16 ± 0.08*
Tb.N, %/y	*0.46 ± 0.12*[a]	*0.40 ± 0.15*	0.18 ± 0.15	0.17 ± 0.15
Tb.Th^d, %/y	**–0.46 ± 0.12**[c]	–0.15 ± 0.27	0.03 ± 0.28	0.03 ± 0.27
Tb.Sp^d, %/y	**–0.48 ± 0.12**	–0.44 ± 0.27	–0.23 ± 0.28	–0.20 ± 0.27
Tb.1/N.SD, %/y	–0.20 ± 0.10	–0.22 ± 0.28	–0.16 ± 0.27	–0.40 ± 0.27
Reaction force, %/y	**–1.16 ± 0.07**[d]	**–0.54 ± 0.08**	**–0.46 ± 0.09**	**–0.39 ± 0.05**
Failure load, %/y	**–1.12 ± 0.09**[d]	**–0.53 ± 0.07**	**–0.49 ± 0.08**	**–0.40 ± 0.05**

Bold indicates a decrease significantly different from zero. Italic indicates an increase significantly different from zero. Results presented as adjusted means ± SEM. Derived parameters (as opposed to measured) are denoted with a superscript "d." Models adjusted for age, body mass index, calcium intake, leisure and occupational physical activity, length of leg, apparent free testosterone ***or*** bioavailable 17β-estradiol, 25-hydroxycholecalciferol ***or*** parathyroid hormone, log-transformed high-sensitivity C-reactive protein, glomerular filtration rate, cancer, diabetes, prior stroke, ischemic heart disease, COPD, and Parkinson disease.

Abbreviations: BMD, bone mineral density; Ct.Ar^d, cortical area; Ct.BMD, cortical vBMD; Ct.Th^d, cortical thickness; inn.Tb.BMD, central trabecular vBMD; mg HA, mg hydroxyapatide; Q, quartile; Ref., reference; s.e.Tb.BMD, subendocortical vBMD; Tb.BMD, trabecular vBMD; Tb.N, trabecular number; Tb.1/N.SD, inhomogeneity of trabecular network; Tb.Sp^d, trabecular separation; Tb.Th^d, trabecular thickness; Tt.BMD, total volumetric bone mineral density (vBMD).

[a]Less than 0.05,

[b]less than 0.01,

[c]less than 0.005, and

[d]less than 0.001 for comparisons vs reference group (Q4).

for the test). Therefore, the second and the third quartile were combined to produce 3 classes according to the physical performance score: the poorest, the intermediate, and the highest category (Table 7). In the fully adjusted model, the nonvertebral fracture risk was significantly higher in the poorest performance category compared to the highest performance class (hazard ratio = 2.68; 95% CI, 1.08-6.66, $P < .05$) (Fig. 1). The risk of nonvertebral fractures increased across the categories (P for trend < .05).

Discussion

In older men followed up for 8 years, low RALM-LL and poor physical performance were associated with more rapid aging-related decline of distal tibia bone microarchitecture. Poor physical performance was associated with a higher risk of fall and of nonvertebral fracture.

Accelerated aging-related deterioration of distal tibia bone microarchitecture in men with low RALM-LL and poor physical performance suggests an interaction between muscle and bone in line with the "mechanostat" theory

Table 5. Aging-related changes in bone microarchitecture parameters according to the categories of physical performance and relative appendicular lean mass of the lower limbs

RALM-LL score of physical performance	< 5.27 kg/m^2 (4.91 ± 0.34) < 8 (7 [0; 7]) (n = 50)	> 5.27 kg/m^2 (5.77 ± 0.49) < 8 (7 [0; 7]) (n = 103)	< 5.27 kg/m^2 (4.98 ± 0.23) ≥ 8 (12 [8; 16]) (n = 155)	> 5.27 kg/m^2 (5.96 ± 0.49) ≥ 8 (12 [8; 16]) (Ref., n = 512)
Change in bone microarchitectural variables as absolute values				
Tt.BMD, mg HA/cm^3/y	**–2.26 ± 0.36**[d]	**–1.71 ± 0.32**[d]	**–1.02 ± 0.14**	**–0.78 ± 0.07**
Ct.Th[d], µm/y	**–2.41 ± 0.30**[d,e]	**–1.31 ± 0.10**[a]	**–1.10 ± 0.12**	**–0.87 ± 0.06**
Ct.Ar, mm^2/y	**–3.01 ± 0.33**[d,f]	**–1.52 ± 0.20**[c]	**–1.18 ± 0.13**	**–0.97 ± 0.06**
Ct.BMD, mg HA/cm^3/y	**–8.90 ± 0.84**[d,f]	**–4.09 ± 0.52**	**–4.18 ± 0.33**	**–3.59 ± 0.16**
Tb.Ar, mm^2/y	*2.36 ± 0.27*[d,f]	*1.12 ± 0.22*[c]	*0.80 ± 0.11*	*0.65 ± 0.05*
Tb.BMD, mg HA/cm^3/y)	*0.51 ± 0.19*	–0.24 ± 0.15[d]	*0.37 ± 0.08*	*0.34 ± 0.04*
inn.Tb.BMD, mg HA/cm^3/y	0.28 ± 0.21	**–0.46 ± 0.17**[d]	*0.26 ± 0.08*	*0.27 ± 0.04*
s.e.Tb.BMD, mg HA/cm^3/y	*0.84 ± 0.21*	0.09 ± 0.13[c]	*0.52 ± 0.08*	*0.44 ± 0.04*
Tb.N, 1/mm/y[e] 10^3	9.27 ± 5.39	7.17 ± 3.38	4.27 ± 2.16	*5.22 ± 1.02*
Tb.Th[d], µm/y	–0.11 ± 0.25	–0.41 ± 0.20[a]	–0.01 ± 0.10	–0.03 ± 0.05
Tb.Sp[d], µm/y	–1.94 ± 1.55	–1.93 ± 0.97	**–1.63 ± 0.62**	**–1.34 ± 0.29**
Tb.1/N.SD, µm/y	0.05 ± 0.09	**–0.41 ± 0.06**	**–0.76 ± 0.04**	**–0.42 ± 0.18**
Reaction force, N/y	**–173.1 ± 57.2**[d]	**–115.5 ± 16.2**[c]	**–75.2 ± 10.2**	**–64.1 ± 4.8**
Failure load, N/y	**-84.54 ± 26.53**[d]	**–57.29 ± 9.33**[d]	**–38.52 ± 4.59**	**–32.54 ± 2.17**
Change in bone microarchitectural variables as percentage				
Tt.BMD, %/y	**–0.86 ± 0.14**[d]	**–0.67 ± 0.09**[d]	**–0.39 ± 0.03**	**–0.30 ± 0.03**
Ct.Th[d], %/y	**–3.36 ± 0.39**[d,e]	**–1.40 ± 0.24**[a]	**–1.18 ± 0.15**	**–0.92 ± 0.07**
Ct.Ar, %/y	**–3.66 ± 0.38**[df]	**–1.41 ± 0.24**[c]	**–1.16 ± 0.15**	**–0.90 ± 0.07**
Ct.BMD, %/y	**–1.29 ± 0.12**[d,f]	**–0.52 ± 0.07**	**–0.53 ± 0.05**	**–0.45 ± 0.02**
Tb.Ar, %/y	*0.34 ± 0.04*[d,f]	*0.16 ± 0.02*[c]	*0.13 ± 0.02*	*0.09 ± 0.01*
Tb.BMD, %/y	*0.33 ± 0.11*	–0.10 ± 0.07[d]	*0.21 ± 0.04*	*0.19 ± 0.02*
inn.Tb.BMD, %/y	0.22 ± 0.21	**–0.51 ± 0.13**[d]	0.18 ± 0.08	*0.17 ± 0.04*
s.e.Tb.BMD, %/y	*0.37 ± 0.09*	0.08 ± 0.05	*0.22 ± 0.03*	*0.18 ± 0.02*
Tb.N, %/y	0.47 ± 0.30	0.41 ± 0.19	0.25 ± 0.12	*0.27 ± 0.06*
Tb.Th[d], %/y	–0.07 ± 0.30	**–0.49 ± 0.19**[a]	–0.04 ± 0.12	–0.06 ± 0.06
Tb.Sp[d], %/y	–0.49 ± 0.30	–0.37 ± 0.19	**–0.29 ± 0.12**	**–0.30 ± 0.06**
Tb.1/N.SD, %/y	–0.22 ± 0.34	–0.27 ± 0.22	0.19 ± 0.14	**–0.26 ± 0.07**
Reaction force, %/y	**–1.43 ± 0.19**[d]	**–0.93 ± 0.13**[c]	**–0.64 ± 0.08**	**–0.47 ± 0.04**
Failure load, %/y	**–1.40 ± 0.17**[d]	**–0.91 ± 0.12**[d]	**–0.64 ± 0.07**	**–0.47 ± 0.03**

Bold indicates a decrease significantly different from zero. Italic indicates an increase significantly different from zero. Results presented as adjusted means ± SEM. Derived parameters (as opposed to measured) are denoted with a superscript "d." Models adjusted for age, body mass index, calcium intake, leisure and occupational physical activity, length of leg, apparent free testosterone ***or*** bioavailable 17β-estradiol, 25-hydroxycholecalciferol ***or*** parathyroid hormone, log-transformed high-sensitivity C-reactive protein, glomerular filtration rate, cancer, diabetes, prior stroke, ischemic heart disease, and COPD, Parkinson disease.

Abbreviations: BMD, bone mineral density; Ct.Ar[d], cortical area; Ct.BMD, cortical vBMD; Ct.Th[d], cortical thickness; inn.Tb.BMD, central trabecular vBMD; mg HA, mg hydroxyapatide; Q, quartile; Ref., reference; s.e.Tb.BMD, subendocortical vBMD; Tb.BMD, trabecular vBMD; Tb.N, trabecular number; Tb.1/N.SD, inhomogeneity of trabecular network; Tb.Sp[d], trabecular separation; Tb.Th[d], trabecular thickness; Tt.BMD, total volumetric bone mineral density (vBMD).

[a]Less than 0.05,

[b]less than 0.01,

[c]less than 0.005, and

[d]less than 0.001 for comparisons vs reference group,

[e]Less than 0.05 and

[f]less than 0.005 for the comparisons Q1 vs Q2.

(38). This interaction drives bone gain during growth and in young athletes. In older individuals, mechanical strain may prevent bone loss and preserve bone mass. Clinical data are consistent with regard to this "mechanostat" concept. In older individuals physical activity preserves BMD (39, 40). The studies using pQCT showed that older men with low muscle strength had lower cross-sectional area, Ct.Ar, and estimated bone strength at the distal

Table 6. Association of physical performance of the lower legs with risk of fall

Quartiles of performance score	Men with incident falls, %	Adjusted for age HR (95% CI)	Adjusted for age, prior falls, RALM-LL	Adjusted for age, prior falls, RALM-LL, systolic blood pressure, hsCRP, AFTC
Incident multiple falls, ≥ 1 fall/y				
Best, 13-16	24.4	1.00	1.00	1.00
11-12	23.7	0.95 (0.63-1.44)	0.90 (0.60-1.37)	0.94 (0.62-1.43)
8-10	28.0	1.17 (0.81-1.70)	1.11 (0.76-1.61)	1.14 (0.78-1.67)
Poorest, < 8	41.6	1.69 (1.16-2.46)[a]	1.68 (1.15-2.46)[a]	1.72 (1.17-2.54)[a]
Ref., 8-16	25.	1.00	1.00	1.00
Poorest, < 8	41.6%	1.60 (1.20-2.13)[b]	1.67 (1.25-2.22)[c]	1.67 (1.24-2.23)[c]
Incident falls necessitating hospitalization (injurious fall)				
Best, 13-16	4.0	1.00	1.00	1.00
11-12	7.9	1.86 (0.78-4.43)	1.87 (0.78-4.47)	1.88 (0.78-4.51)
8-0	5.2	1.17 (0.48-2.87)	1.18 (0.48-2.89)	1.22 (0.49-2.99)
Poorest, < 8	18.7	3.48 (1.57-7.74)[a]	3.61 (1.62-8.04)[a]	3.52 (1.57-7.90)[a]
Ref., 8-16	5.6	1.00	1.00	1.00
Poorest, < 8	18.7	2.64 (1.59-4.37)[b]	2.72 (1.64-4.49)[b]	2.60 (1.56-4.34)[b]

Abbreviations: AFTC, apparent free testosterone concentration; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; RALM-LL, relative appendicular lean mass of the lower limbs; Ref., reference.
[a]*P* less than .05.
[b]*P* less than .005.
[c]*P* less than .001.

Table 7. Association between physical performance of the lower legs and risk of incident nonvertebral fracture

Performance score	Men with fractures	Adjusted for age HR (95% CI)	Adjusted for age, weight, hip aBMD HR (95% CI)	Adjusted for age, weight, hip aBMD, prior fractures and falls, RALM-LL, IHD, and 25OHD HR (95% CI)
Best score (13-16)	3.5%	1.00	1.00	1.00
Intermediate score (8-12)	8.8%	2.44 (1.09-5.51)[a]	2.20 (0.97-4.97)	2.27 (0.99-5.14)
Poorest score (< 8)	11.9%	3.11 (1.29-7.47)[a]	2.43 (1.00-5.93)[a]	2.68 (1.08-6.66)[a]
P for trend		< .05	.07	< .05

Abbreviations: 25OHD, 25-hydroxycholecalciferol; aBMD, areal bone mineral density; HR, hazard ratio; IHD, ischemic heart disease; RALM-LL, relative appendicular lean mass of the lower limbs.
[a]*P* less than .05.

tibia and radius (41, 42). Men with low ALM of upper limbs and low grip strength had poorer bone microarchitecture and its faster decline at the non–load-bearing distal radius (14, 15).

Mechanical stress exerts direct, local strain on osteocytes and activates bone metabolism (10, 11). It may affect bone microarchitecture, its internal structure, and its strength (43). Our cross-sectional data showed that men with poor physical function of the lower limbs had poorer bone microarchitecture at the tibia compared with the radius (17). However, cross-sectional data do not assess the temporal order. In this prospective study of the distal tibia, poor physical performance and low RALM-LL were associated with more rapid loss of cortical bone and of bone strength compared with the reference group. Men with the lowest physical performance had more rapid endocortical expansion compared with those with the highest one. Endocortical resorption results in bone loss of the internal layer of the cortex leading to cortical thinning and medullary expansion. However, it also produces cortical remnants resembling trabeculae (trabecularization). Cortical remnants, mistaken by the software for trabecular bone, are subtracted from cortical bone and added to trabecular bone. It leads to the overestimation of cortical bone loss and to the underestimation of trabecular bone loss. The inclusion of cortical remnants in trabecular bone results in an apparent stability of Tb.N and Tb.BMD (even an increase in s.e.Tb.BMD) (44). Endocortical bone loss may also result in cortical pore perforation, which may promote crack propagation during mechanical loading and aggravate the loss of failure load (45).

To overcome the effect of trabecularization, we assessed bone status in the central zone, which undergoes aging-related decline but does not comprise cortical remnants.

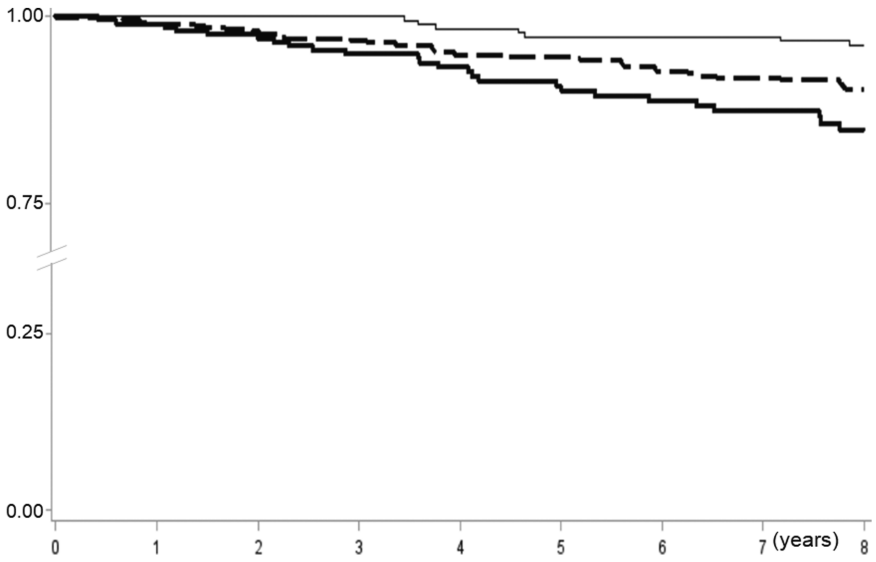

Figure 1. Survival without nonvertebral fractures according to the score of physical performance: thin, highest quartile (13-16, best performance, reference group); dashed, intermediate group (8-12); bold, lowest quartile (< 8, worst performance).

In our study, poor physical performance is associated with greater inn.Tb.BMD loss and trabecular thinning. This suggests that the mechanical strain is transferred inside bone to the trabeculae. Bone reaction to mechanical strain and its resistance to fracture are partly determined by cortical and trabecular microarchitecture (46). From the mechanical point of view, both trabecular and cortical bone transfer the load from the articular surface and work as a unit to prevent the fracture (46). In our study, the greatest declines in bone microarchitecture and strength were found in men with the lowest RALM-LL and in those with the poorest physical performance. It shows that leg disability contributes to the greater loss of bone strength at the distal tibia in older men.

In our cohort, bone microarchitecture decline was associated with poor physical performance more strongly than with muscle mass. This finding is in line with other studies (47). However, having both low RALM-LL and low physical performance score was associated with a 2-fold faster deterioration of Ct.Ar, Ct.BMD and greater Tb.Ar expansion compared with men having low physical performance but high RALM-LL. Thus, this residual muscle mass and strength may play a protective role in individuals with poor physical performance.

Our previous research (15) and these data show similar patterns of the link of muscle mass and force (or performance) with bone microarchitecture decline at the non–weight-bearing distal radius and at the weight-bearing distal tibia. Jointly, they show the importance of muscle status for bone microarchitecture and its decline regardless of the impact of body weight. Thus, they are another argument in favor of the link between sarcopenia and bone loss.

In our study, poor physical performance was associated with a high risk of fall, in line with prior data (16, 48, 49). The ability to prevent a fall requires not only muscle strength, but also power (acceleration) and sense of balance (50, 51). Thus, better physical performance can lower the risk of fall and fracture. However, in our study, men with the poorest physical performance had not only a higher risk of fall but also a greater decline in bone microarchitecture compared with the reference group. Thus, physical performance may increase the fracture risk of fracture both via its effect on the risk of falling and on bone itself. However, numerous factors may influence bone and muscle in parallel but independently of each other. Previous studies of the relationships of bone, muscle, and fracture did not consider all potential confounders and could not assess the role of the link between bone and muscle as determinants of the fracture risk (2, 3, 52-54).

The study of the muscle and bone crosstalk has to account for shared risk factors to better assess their interaction with fall, bone structure, and fracture. Sex steroids regulate bone metabolism and influence bone status (22, 55, 56). Aging men with lower testosterone have faster loss of lean mass and of physical performance (56). Thus, bone microarchitecture decline and muscle loss could be parallel but independent consequences of low testosterone secretion. T2DM is associated with greater cortical bone deterioration and more rapid muscle loss (21, 24, 57). Thus, the higher risk of fracture in patients with diabetes may be due to the independent effects on bone and muscle (58). Vitamin D deficit is associated with poor physical performance and poor bone microarchitecture (23, 59). Thus, muscle loss

and bone loss may be 2 parallel pathways increasing the fracture risk in vitamin D-deplete individuals (60). However, in our study, adjustment for these confounders had no effect on the results.

Our study has limitations. It is a single-center cohort composed of home-dwelling White (98%) older men. Our results may not be extrapolated to women and other ethnic groups. Prior nonspine fractures and comorbidities were self-reported and not checked. We did not measure muscle force of lower limbs directly (eg, bench press). However, our score is similar to the Short Physical Performance Battery, the results of which are correlated with knee extensor strength (61). Although our physical performance score was validated in previous studies, it does not fully assess lower limb function. The attrition rate was 46% at 8 years. Men who were lost to follow-up could have poorer physical performance and more rapid bone loss. Thus, we may underestimate the associations between the variables. Self-reported incident nonvertebral fractures were checked, but false negatives are possible. There were only 68 incident fractures; however, the post hoc calculation showed that we had 89% statistical power to find the significantly higher fracture risk in men with poor physical performance. Incident falls were not ascertained. We assessed muscle mass and force, lifestyle, and health status only at baseline, but their changes during the follow-up may influence the rate of bone loss. Tb.Th^{d} and Ct.Th^{d} were calculated, not measured. Bone microarchitecture assessment may be inaccurate because of partial volume effect. HR-pQCT does not reflect the age-related intrinsic bone deterioration (microdamage, posttranslational modification of proteins, mineral imperfection). Currently, RIA is not the gold standard for the assessment of 25OHD and sex hormones.

Overall, our prospective study shows the importance of lower-limb physical performance for the aging-related decline of bone microarchitecture and estimated strength at the distal tibia, and for the risk of fall and nonvertebral fracture. The associations remained significant after adjustment for shared risk factors. Thus, poor physical performance may increase the fracture risk not only via its impact on the risk of falling but also via the direct effect on bone. Further studies are needed to better understand the mechanisms underlying this association. From the clinical point of view, efforts to maintain physical performance of the lower limbs are needed to prevent injurious falls and fractures in older populations.

Acknowledgments

Financial Support: This work was supported by Roche Pharmaceutical Company, Basel, Switzerland, Agence nationale de la recherche (grant Nos. ANR-07-PHYSIO-023 and ANR-10-BLAN-1137), Abondement ANVAR (grant No. E1482.042), and Hospices Civils de Lyon (grant No. 50564). The funding sponsors had no role in the study.

Additional Information

Correspondence: Pawel Szulc, MD, PhD, Department of Rheumatology, Hospices Civils de Lyon, INSERM UMR 1033, Hôpital Edouard Herriot, Pavillon F, Place d'Arsonval, 69437 Lyon, France. Email: pawel.szulc@inserm.fr.

Disclosures: The authors have nothing to disclose.

Data Availability: Data may be available on reasonable request as a part of collaboration project. Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Locquet M, Beaudart C, Bruyère O, Kanis JA, Delandsheere L, Reginster JY. Bone health assessment in older people with or without muscle health impairment. *Osteoporos Int*. 2018;**29**(5):1057-1067.
2. Yu R, Leung J, Woo J. Incremental predictive value of sarcopenia for incident fracture in an elderly Chinese cohort: results from the Osteoporotic Fractures in Men (MrOs) Study. *J Am Med Dir Assoc*. 2014;**15**(8):551-558.
3. Scott D, Seibel M, Cumming R, et al. Does combined osteopenia/osteoporosis and sarcopenia confer greater risk of falls and fracture than either condition alone in older men? The Concord Health and Ageing in Men Project. *J Gerontol A Biol Sci Med Sci*. 2019;**74**(6):827-834.
4. Lundin H, Sääf M, Strender LE, Nyren S, Johansson SE, Salminen H. Gait speed and one-leg standing time each add to the predictive ability of FRAX. *Osteoporos Int*. 2017;**28**(1):179-187.
5. Drey M, Sieber CC, Bertsch T, Bauer JM, Schmidmaier R; FiAT Intervention Group. Osteosarcopenia is more than sarcopenia and osteopenia alone. *Aging Clin Exp Res*. 2015;**28**(5):895-899.
6. Huo YR, Suriyaarachchi P, Gomez F, et al. Phenotype of osteosarcopenia in older individuals with a history of falling. *J Am Med Dir Assoc*. 2015;**16**(4):290-295.
7. Frost HM. From Wolff's law to the mechanostat: a new "face" of physiology. *J Orthop Sci*. 1998;**3**(5):282-286.
8. Locquet M, Beaudart C, Reginster JY, et al. Prevalence of concomitant bone and muscle waisting in elderly women from the SarcoPhAGE cohort: preliminary results. *J Frailty Aging*. 2017;**6**(1):18-23.
9. Locquet M, Beaudart C, Reginster JY, Bruyère O. Association between the decline in muscle health and the decline in bone health in older individuals from the SarcoPhAge cohort. *Calcif Tissue Int*. 2019;**104**(3):273-284.
10. Klein-Nulend J, Bakker AD, Bacabac RG, Vatsa A, Weinbaum S. Mechanosensation and transduction in osteocytes. *Bone*. 2013;**54**(2):182-190.
11. Bonewald LF. Mechanosensation and transduction in osteocytes. *Bonekey Osteovision*. 2006;**3**(10):7-15.

12. Proctor DN, Melton LJ, Khosla S, Crowson CS, O'Connor MK, Riggs BL. Relative influence of physical activity, muscle mass and strength on bone density. *Osteoporos Int*. 2000;**11**(11):944-952.
13. Matsui Y, Takemura M, Harada A, Ando F, Shimokata H. Effects of knee extensor muscle strength on the incidence of osteopenia and osteoporosis after 6 years. *J Bone Miner Metab*. 2014;**32**(5):550-555.
14. Szulc P, Blaizot S, Boutroy S, Vilayphiou N, Boonen S, Chapurlat R. Impaired bone microarchitecture at the distal radius in older men with low muscle mass and grip strength: the STRAMBO study. *J Bone Miner Res*. 2013;**28**(1):169-178.
15. Wagner P, Chapurlat R, Ecochard R, Szulc P. Low muscle strength and mass is associated with the accelerated decline of bone microarchitecture at the distal radius in older men: the prospective STRAMBO study. *J Bone Miner Res*. 2018;**33**(9):1630-1640.
16. Shigematsu R, Rantanen T, Saari P, et al. Motor speed and lower extremity strength as predictors of fall-related bone fractures in elderly individuals. *Aging Clin Exp Res*. 2006;**18**(4):320-324.
17. Blaizot S, Boutroy S, Vilayphiou N, Boonen S, Chapurlat R, Szulc P. Poor bone microarchitecture in older men with impaired physical performance—the STRAMBO study. *Osteoporos Int*. 2012;**23**(12):2785-2796.
18. Vilayphiou N, Boutroy S, Szulc P, et al. Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in men. *J Bone Miner Res*. 2011;**26**(5):965-973.
19. Vandenput L, Mellström D, Laughlin GA, et al. Low testosterone, but not estradiol, is associated with incident falls in older men: the international MrOS Study. *J Bone Min Res*. 2017;**32**(6):1174-1181.
20. Barrett-Connor E, Laughlin GA, Li H, et al; Osteoporotic Fractures in Men (MrOS) Research Group. The association of concurrent vitamin D and sex hormone deficiency with bone loss and fracture risk in older men: the Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res*. 2012;**27**(11):2306-2313.
21. Renoud A, Ecochard R, Marchand F, Chapurlat R, Szulc P. Predictive parameters of accelerated muscle loss in men—MINOS study. *Am J Med*. 2014;**127**(6):554-561.
22. Argoud T, Boutroy S, Claustrat B, Chapurlat R, Szulc P. Association between sex steroid levels and bone microarchitecture in men: the STRAMBO study. *J Clin Endocrinol Metab*. 2014;**99**(4):1400-1410.
23. Chaitou A, Boutroy S, Vilayphiou N, et al. Association of bone microarchitecture with parathyroid hormone concentration and calcium intake in men: the STRAMBO study. *Eur J Endocrinol*. 2011;**165**(1):151-159.
24. Samelson EJ, Demissie S, Cupples LA, et al. Diabetes and deficits in cortical bone density, microarchitecture, and bone size: Framingham HR-pQCT Study. *J Bone Miner Res*. 2018;**33**(1):54-62.
25. Szulc P, Feyt C, Chapurlat R. High risk of fall, poor physical function, and low grip strength in men with fracture—the STRAMBO study. *J Cachexia Sarcopenia Muscle*. 2016;**7**(3):299-311.
26. Szulc P, Maurice C, Delmas PD. Increased bone resorption is associated with higher mortality in community-dwelling men > or = 50 years of age: the MINOS study. *J Bone Min Res*. 2009;**24**(6):1116-1124.
27. Szulc P, Delmas PD. Bone width is correlated positively with the upper to the lower segment ratio in elderly men—the MINOS study. *Bone*. 2007;**40**(1):194-199.
28. Whittier DE, Boyd SK, Burghardt AJ, et al. Guidelines for the assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography. *Osteoporos Int*. 2020;**31**(9):1607-1627.
29. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab*. 2005;**90**(12):6508-6515.
30. Pauchard Y, Liphardt AM, Macdonald HM, Hanley DA, Boyd SK. Quality control for bone quality parameters affected by subject motion in high-resolution peripheral quantitative computed tomography. *Bone*. 2012;**50**(6):1304-1310.
31. Engelke K, van Rietbergen B, Zysset P. FEA to measure bone strength: a review. *Clin Rev Bone MinerMetab*. 2016;**14**:26-37.
32. Macneil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. *Bone*. 2008;**42**(6):1203-1213.
33. Pistoia W, van Rietbergen B, Lochmüller EM, Lill CA, Eckstein F, Rüegsegger P. Image-based micro-finite-element modeling for improved distal radius strength diagnosis: moving from bench to bedside. *J Clin Densitom*. 2004;**7**(2):153-160.
34. Fardellone P, Sebert JL, Bouraya M, et al. Evaluation of the calcium content of diet by frequential self-questionnaire [article in French]. *Rev Rhum Mal Osteoartic*. 1991;**58**(2):99-103.
35. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*. 1999;**84**(10):3666-3672.
36. Schoppet M, Rauner M, Benner J, Chapurlat R, Hofbauer LC, Szulc P. Serum fetuin-A levels and abdominal aortic calcification in healthy men—the STRAMBO study. *Bone*. 2015;**79**:196-202.
37. Wagner PP, Whittier DE, Foesser D, Boyd SK, Chapurlat R, Szulc P. Zenodo. Uploaded June 4, 2021. https://zenodo.org/record/4895390#.YLfhFqGxVPY
38. Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec A Discov Mol Cell Evol Biol*. 2003;**275**(2):1081-1101.
39. Segal NA, Torner JC, Yang M, Curtis JR, Felson DT, Nevitt MC; Multicenter Osteoarthritis Study Group. Muscle mass is more strongly related to hip bone mineral density than is quadriceps strength or lower activity level in adults over age 50 year. *J Clin Densitom*. 2008;**11**(4):503-510.
40. Blain H, Vuillemin A, Teissier A, Hanesse B, Guillemin F, Jeandel C. Influence of muscle strength and body weight and composition on regional bone mineral density in healthy women aged 60 years and over. *Gerontology*. 2001;**47**(4):207-212.
41. Cousins JM, Petit MA, Paudel ML, et al; Osteoporotic Fractures in Men (MrOS) Study Group. Muscle power and physical activity are associated with bone strength in older men: the Osteoporotic Fractures in Men Study. *Bone*. 2010;**47**(2):205-211.
42. Zengin A, Pye SR, Cook MJ, et al. Associations of muscle force, power, cross-sectional muscle area and bone geometry in older UK men. *J Cachexia Sarcopenia Muscle*. 2017;**8**(4):598-606.
43. Cointry GR, Capozza RF, Negri AL, Roldán EJA, Ferretti JL. Biomechanical background for a noninvasive assessment of bone strength and muscle-bone interactions. *J Musculoskelet Neuronal Interact*. 2004;**4**(1):1-11.

44. Zebaze RMD, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. *Lancet*. 2010;**375**(9727):1729-1736.
45. Vilayphiou N, Boutroy S, Sornay-Rendu E, Van Rietbergen B, Chapurlat R. Age-related changes in bone strength from HR-pQCT derived microarchitectural parameters with an emphasis on the role of cortical porosity. *Bone*. 2015;**83**:233-240.
46. Oftadeh R, Perez-Viloria M, Villa-Camacho JC, Vaziri A, Nazarian A. Biomechanics and mechanobiology of trabecular bone: a review. *J Biomech Eng*. 2015;**137**(1):010802.
47. Visser M, Deeg DJ, Lips P, Harris TB, Bouter LM. Skeletal muscle mass and muscle strength in relation to lower-extremity performance in older men and women. *J Am Geriatr Soc*. 2000;**48**(4):381-386.
48. Pavasini R, Guralnik J, Brown JC, et al. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. *BMC Med*. 2016;**14**(1):215.
49. Zhang F, Ferrucci L, Culham E, Metter EJ, Guralnik J, Deshpande N. Performance on five times sit-to-stand task as a predictor of subsequent falls and disability in older persons. *J Aging Health*. 2013;**25**(3):478-492.
50. Watt A, Clark C, Williams JM. Differences in sit-to-stand, standing sway and stairs between community-dwelling fallers and non-fallers: a review of the literature. *Phys Ther Rev*. 2018;**23**(4-5):273-290.
51. Cianferotti L, Brandi ML. Muscle-bone interactions: basic and clinical aspects. *Endocrine*. 2014;**45**(2):165-177.
52. Rolland T, Boutroy S, Vilayphiou N, Blaizot S, Chapurlat R, Szulc P. Poor trabecular microarchitecture at the distal radius in older men with increased concentration of high-sensitivity C-reactive protein—the STRAMBO study. *Calcif Tissue Int*. 2012;**90**(6):496-506.
53. Rosengren BE, Ribom EL, Nilsson JÅ, et al. Inferior physical performance test results of 10,998 men in the MrOS Study is associated with high fracture risk. *Age Ageing*. 2012;**41**(3):339-344.
54. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;**319**(26):1701-1707.
55. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab*. 1998;**83**(7):2266-2274.
56. LeBlanc ES, Wang PY, Lee CG, et al. Higher testosterone levels are associated with less loss of lean body mass in older men. *J Clin Endocrinol Metab*. 2011;**96**(12):3855-3863.
57. Patsch JM, Burghardt AJ, Yap SP, et al. Increased cortical porosity in type 2 diabetic postmenopausal women with fragility fractures. *J Bone Min Res*. 2013;**28**(2):313-324.
58. Bai J, Gao Q, Wang C, Dai J. Diabetes mellitus and risk of low-energy fracture: a meta-analysis. *Aging Clin Exp Res*. 2020;**32**(11):2173-2186.
59. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab*. 2007;**92**(6):2058-2065.
60. Tamaki J, Iki M, Sato Y, et al; JPOS Study Group. Total 25-hydroxyvitamin D levels predict fracture risk: results from the 15-year follow-up of the Japanese Population-based Osteoporosis (JPOS) Cohort Study. *Osteoporos Int*. 2017;**28**(6):1903-1913.
61. Kim KE, Jang SN, Lim S, et al. Relationship between muscle mass and physical performance: is it the same in older adults with weak muscle strength? *Age Ageing*. 2012;**41**(6):799-803.