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X-Ray–Verified Fractures Are Associated With Finite Element Analysis–Derived Bone Strength and Trabecular Microstructure in Young Adult Men

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ABSTRACT

It has been suggested that fracture during childhood could be a predictor of low peak bone mass and thereby a potential risk factor for osteoporosis and fragility fractures later in life. The aim of this cross-sectional, population-based study was to investigate whether prevalent fractures, occurring from birth to young adulthood, were related to high-resolution peripheral quantitative computed tomography (HR-pQCT)–derived trabecular and cortical microstructure, as well as bone strength estimated by finite element (FEA) analysis of the radius and tibia in 833 young adult men around the time of peak bone mass (ages 23 to 25 years). In total, 292 subjects with prevalent X-ray–verified fractures were found. Men with prevalent fractures had lower trabecular bone volume fraction (BV/TV) at the radius (5.5%, $p < 0.001$) and tibia (3.7%, $p < 0.001$), as well as lower cortical thickness (5.1%, $p < 0.01$) and cortical cross-sectional area (4.1%, $p < 0.01$) at the tibia. No significant differences were seen for the cortical porosity or mean pore diameter. Using a logistic regression model (including age, smoking, physical activity, calcium intake, height, and weight as covariates), every SD decrease of FEA-estimated failure load was associated with an increased prevalence of fractures at both the radius (odds ratio [OR] 1.22 [1.03–1.45]) and tibia (OR 1.32 [1.11–1.56]). Including dual-energy X-ray absorptiometry (DXA)–derived radius areal bone mineral density (aBMD), cortical thickness, and trabecular BV/TV simultaneously in a logistic regression model (with age, smoking, physical activity, calcium intake, height, and weight as covariates), BV/TV was inversely and independently associated with prevalent fractures (OR 1.28 [1.04–1.59]), whereas aBMD and cortical thickness were not (OR 1.19 [0.92–1.55] and OR 0.91 [0.73–1.12], respectively). In conclusion, prevalent fractures in young adult men were associated with impaired trabecular BV/TV at the radius, independently of aBMD and cortical thickness, indicating that primarily trabecular bone deficits are of greatest importance for prevalent fracture in this population. © 2013 American Society for Bone and Mineral Research.

KEY WORDS: TRABECULAR MICROSTRUCTURE; FRACTURE; HR-pQCT

Introduction

It has been suggested that fractures during childhood could be a predictor of low peak bone mass[1,2] and thereby a potential risk factor for osteoporosis and fragility fractures later in life.[3,4] Considering the increased incidence of forearm fractures in childhood and adolescence that has been observed over the last decades,[5] this could indicate a potentially increased fracture burden in the future.[3] To better predict individual fracture risk and facilitate the discovery of possible treatment targets, it is important to increase knowledge about the underlying bone features explaining fracture incidence in childhood and adolescence. The relationship between areal bone mineral density (aBMD) and prevalent fractures in childhood and adolescence is well studied, and it has been established that low aBMD, as measured by dual-energy X-ray absorptiometry (DXA), is associated with an increased rate of prevalent fractures.[6–9] The underlying properties (ie, affected volumetric BMD [vBMD] or bone size) of the bone corresponding to this lower areal density have been studied to some extent, but because of a relatively small number of studies on both males and females at different ages, no consensus has been reached. We have recently shown

that the vBMD of the trabecular compartment, as measured by peripheral quantitative computed tomography (pQCT) at the metaphysis of the radius and tibia, was more strongly associated with prevalent fractures from childhood to young adulthood than aBMD in 1068 18- to 20-year-old men, who had not yet reached their peak bone mass at some bone sites.[10,11] Both the cortical thickness and cortical vBMD of the diaphysis also showed associations with fracture history, although somewhat weaker.[10] Similar results were shown by Taes and colleagues in a study of older men (25 to 45 years), where the cortical thickness was more strongly associated with prevalent fractures than trabecular vBMD, and even more strongly associated with childhood fractures.[12] In a recent study of younger males (15.2 ± 0.5 years [mean ± SD]), only the trabecular vBMD at the tibia was associated with a fracture history.[13] Concerning females, Farr and colleagues reported that young females (8 to 13 years) with prevalent fractures had lower trabecular volumetric BMD than their nonfractured counterparts,[14] which was also shown in young adult females (20.4 ± 0.6 years) by Chevalley and colleagues.[15] With an increased resolution of the imaging techniques, it is now possible to get even more detailed information about the microstructure of the different compartments of the bone.[16,17] Using high-resolution pQCT (HR-pQCT) with a resolution of 82 μm, investigating the distal radius and tibia, the microstructure of the cancellous bone is measurable, and by also applying computed algorithms the cortical bone has recently been accessible for analysis of porosity.[18,19] A further step is to apply simulated forces in the scanned bone region by means of finite element analysis (FEA), and thereby obtain an estimation of the bones' resistance to fracture. FEA-estimated bone strength has been shown to be more strongly correlated to fracture load than DXA-derived measures in cadaver forearms.[20,21] As for prevalent fractures in childhood and their associations with microstructure and estimated failure load, only two studies have been published. In the first study, including 176 healthy adolescent boys (15.2 ± 0.5 years), subjects with at least one prevalent fracture were shown to have a lower trabecular bone volume fraction (BV/TV), a lesser amount of trabeculae, less stiffness, and a lower failure load at the tibia than boys with no previous fracture.[13] In the second study, including 124 healthy young adult women (20.4 ± 0.6 years), subjects with prevalent fractures had lower trabecular BV/TV, trabecular thickness, stiffness, and failure load than their nonfractured counterparts.[15] The aim of the present study was to investigate whether a prevalent fracture, occurring from birth to young adulthood, is related to impaired trabecular and cortical microstructure and FEA-estimated bone strength in young adult men around the time of peak bone mass (23 to 25 years).

Materials and Methods

The present study was performed at the time of the 5-year follow-up of the Gothenburg Osteoporosis and Obesity Determinants (GOOD) study cohort, which was initiated in 2003 with the aim of determining both environmental and genetic factors involved in the regulation of bone and fat mass. Subjects were randomly identified through national population registers and

contacted by letter and telephone. As the only criteria for inclusion, subjects had to be between 18 and 20 years of age and willing to participate in the study. In 2003, a total of 1068 subjects with a mean age of 18.9 ± 0.6 years were included in the study, corresponding to 48.6% of the initially approached study subjects. With respect to anthropometrics, the cohort was found to be representative of the general young male population in Gothenburg as described previously.[22] In 2008, a total of 833 subjects (78%) with a mean age of 24.1 ± 0.6 years were enrolled in the 5-year follow-up after being contacted by letter and telephone. Of the original GOOD subjects, 128 (12%) declined to participate and 107 (10%) could not be reached. The cohort of the 5-year follow-up was representative of the original cohort in 2003, as described elsewhere.[11] A standardized questionnaire was used to collect information about physical activity (hours/week), where questions from a validated physical activity questionnaire were used;[23] current smoking status (yes/no); calcium intake (mg/day), which was estimated from daily dairy product intake, according to the Swedish National Food Administration;[24] and self-reported fracture history. The GOOD study was approved by the local ethics committee at the University of Gothenburg. Written and oral informed consent was obtained from all study participants.

Anthropometric measurements

Height and weight were obtained using standardized equipment. The coefficients of variation values (CVs) were less than 1% for these measurements.

X-ray–verified fractures

It has previously been reported that there is a discrepancy between self-reported and X-ray–verified fractures.[10,25] To avoid this potential bias, we searched local X-ray records in hospitals in the greater Gothenburg area in 2009 to identify fractures in the study subjects. To further ensure no fractures were missed, we searched the National Patient Register, operated by the National Board of Health and Welfare, for orthopedic diagnostic ICD codes from both private and public outpatient clinics in all of Sweden. In total, 284 subjects reported a previous fracture in the questionnaire, of which only 212 could be verified in the X-ray records. The remaining 72 subjects were excluded from further analysis. In contrast, 81 subjects were found to have had a previous fracture, although they did not report that in the questionnaire. Of them, one subject had signs of an older fracture of unknown date and was therefore also excluded. This resulted in a total of 292 study subjects with datable X-ray–verified prevalent fractures and 468 subjects with no prevalent fractures. Thus, a total of 760 subjects were included for further analysis.

As the primary analysis, we investigated all men with prevalent fractures. However, to investigate whether it is fracture in childhood or fracture in young adulthood that is most associated with the skeletal phenotype in young adulthood, we also divided the subjects with prevalent fractures in two groups. Fractures occurring from birth to ≤16 years of age were considered childhood fractures, and fractures at 17 years or older were considered young adulthood fractures. This cut point was used in

a previous meta-analysis on bone density and fractures in children.[7] A total of 217 subjects had suffered at least one childhood fracture and 75 had their first fracture at 17 years or older. All subgroups were analyzed in relation to subjects with no prevalent fractures.

Dual-energy X-ray absorptiometry

Areal BMD (aBMD, g/cm^2) was obtained at the total body, lumbar spine (L$_2$ to L$_4$), total hip, femoral neck, and the nondominant radius using a Lunar Prodigy DXA scanner (GE Lunar Corp., Madison, WI, USA). The CVs for all aBMD measurements varied from 0.5% to 3.0%. Because of the weight restrictions of the Lunar Prodigy DXA, measurements of the total body, lumbar spine, total hip, and femoral neck were not performed in five subjects. In another subject, the measurement of the nondominant radius had to be excluded because of an incorrect positioning of the arm during the measuring procedure.

High-resolution pQCT

A high-resolution 3D peripheral quantitative computed tomography (HR-pQCT) device (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland) was used to scan the ultradistal radius and tibia of the nondominant arm and leg, respectively. The procedure of measuring the volume of interest (VOI) was executed according to a standardized protocol as described elsewhere.[16,26] Briefly, a reference line was manually placed at the center of the scan of the end plate of the distal radius and tibia. The first computed tomography slice started 9.5 and 22.5 mm proximal to the reference line for the radius and tibia, respectively. A total of 110 parallel computed tomography slices, with a nominal isotropic resolution (voxel size) of 82 μm, were obtained at each skeletal site, delivering a 3D representation of an approximately 9-mm section of both the radius and tibia in the proximal direction. According to previously described methods to process the data,[16] we obtained cortical thickness (μm), cortical cross-sectional area (CSA, mm^2), cortical volumetric BMD (vBMD, mg/cm^3), trabecular bone volume fraction (BV/TV, %), trabecular number (mm^{-1}), trabecular thickness (μm), and trabecular separation (μm). The CVs ranged from 0.3% to 3.9% of the radius and from 0.1% to 1.6% of the tibia. The same device, software, and operator were used throughout the study. Of the 833 subjects enrolled in the study, four subjects were not measured at all, and one subject was not measured at the radius because of technical problems with the equipment. All measurements were evaluated according to a five-item graded scale as recommended by the manufacturer (Scanco Medical AG), where 1 corresponded to highest quality, 2 to 3 to acceptable quality, and 4 to 5 to unacceptable quality. Measurements graded from 4 to 5 were excluded from the analysis. Of the measurements on the radius, 85 were considered unacceptable quality, leaving 743 subjects eligible for analysis of the radius. At the tibia, one measurement was considered to have unacceptable quality, leaving 828 subjects eligible for analysis of the tibia. Data from the maximum amount of included men available for each analysis was used, resulting in different sample sizes for many evaluated bone parameters. For details, see Table 1.

Ultradistal cortical evaluation

To assess cortical bone microstructure of the ultradistal radius and tibia, we used the cortical Autocontouring and Eval Crtx 6x softwares, provided by Scanco and incorporated in the manufacturer's Image Processing Language (IPL) software (μCT Evaluation Program v6, Scanco Medical AG).[18,19] In summary, endosteal and periosteal contours were automatically created to distinguish the boundaries of the cortical compartment in the VOI, excluding trabecular bone and extra-osseal soft tissue, respectively. Thereafter, all void voxels within the cortical compartment were identified, and by further processing, the Haversian canals were distinguished from artefacts owing to surface roughness and transcortical foramen or erosions. Finally, these images were digitally superimposed, generating a refined cortical compartment region in the VOI.[27] By using this method, we obtained cortical porosity (%) and mean cortical pore diameter (μm). The CVs for porosity were 15.9% at the radius and 5.5% at the tibia, and the CVs for mean cortical pore diameter were 6.0% at the radius and 3.9% at the tibia.

Finite element analysis

Biomechanical properties of the bone were derived by finite element analysis. The finite element (FE) models were created by a finite element software from Scanco (version V5.11/FE-V01.15), incorporated in the manufacturer's analysis software. To summarize, cortical and trabecular bone were first separated by a script provided in the software. The FE models were created by converting each voxel in the model to an equally sized brick element.[28] Both the cortical and trabecular elements were regarded as isotropic and linear elastic, and according to the method established by Pistoia and colleagues, a Young's modulus of 10 GPa and a Poisson ratio of 0.3 was used for all elements.[20] In the FE simulation, a uniaxial compression was applied in the longitudinal direction of the bone, at the radius corresponding to a fall from standing on an outstretched hand, representing the type of trauma involved in Colles fracture.[29] Following the failure criterion established by Pistoia and colleagues, failure load (N) was defined as the load at which at least 2% of the bone elements surpassed 7000 microstrain.[20] The same failure criterion has previously been used in a study on adolescent boys.[13] The FEA simulations were performed in the same manner at both the radius and tibia. FEA-derived stiffness (kN/mm) and percentage of load carried by the trabecular bone at the distal and proximal surface of the VOI (percent load trabecular distal and percent load trabecular proximal, respectively) were also reported. The CVs ranged from 0.8% to 3.9% at the radius and from 0.2% to 3.0% at the tibia for these measurements.

Statistical analysis

Differences in anthropometrics, environmental factors, and bone parameters between subjects with and without fractures were investigated by means of independent samples t test. The distribution of smokers in the different subgroups was determined by chi-square test. Adjusted odds ratios for evaluation of associations between bone parameters and fracture prevalence were calculated with logistic regression models, at all times

Table 1. Number of Subjects Included in Each Subgroup Analysis

	No fracture	Any fracture	Fracture ≤16 years	Fracture >16 years	Forearm fracture	Lower extremity fracture
Total body aBMD (g/cm^2)	465	290	216	74	95	63
Lumbar spine aBMD (g/cm^2)	465	290	216	74	95	63
Total hip aBMD (g/cm^2)	465	290	216	74	95	63
Femoral neck aBMD (g/cm^2)	465	290	216	74	95	63
Radius nondominant aBMD (g/cm^2)	468	292	217	75	95	63
Radius						
Cortical thickness (μm)	415	263	194	69	87	
Cortical CSA (mm^2)	415	263	194	69	87	
Cortical vBMD (mg/cm^3)	415	263	194	69	87	
Cortical porosity (%)	413	263	194	69	87	
Cortical pore diameter (μm)	413	263	194	69	87	
Trabecular BV/TV (%)	415	263	194	69	87	
Trabecular number (mm^{-1})	415	263	194	69	87	
Trabecular thickness (μm)	415	263	194	69	87	
Trabecular separation (μm)	415	263	194	69	87	
Stiffness (kN/mm)	414	263	194	69	87	
Failure load (N)	414	263	194	69	87	
Percent load trabecular distal (%)	414	263	194	69	87	
Percent load trabecular proximal (%)	414	263	194	69	87	
Tibia						
Cortical thickness (μm)	466	289	215	74		63
Cortical CSA (mm^2)	466	289	215	74		63
Cortical vBMD (mg/cm^3)	466	289	215	74		63
Cortical porosity (%)	466	289	215	74		63
Cortical pore diameter (μm)	466	289	215	74		63
Trabecular BV/TV (%)	466	289	215	74		63
Trabecular number (mm^{-1})	466	289	215	74		63
Trabecular thickness (μm)	466	289	215	74		63
Trabecular separation (μm)	466	289	215	74		63
Stiffness (kN/mm)	465	289	215	74		63
Failure load (N)	465	289	215	74		63
Percent load trabecular distal (%)	465	289	215	74		63
Percent load trabecular proximal (%)	465	289	215	74		63

including anthropometric and environmental factors (age, smoking status, physical activity, calcium intake, height, and weight). Weight was not normally distributed, and therefore log-transformed before inclusion in the statistical models. For predictors of estimated failure load, stepwise linear regression equations were used, where R^2 and R^2 change were calculated to evaluate the role of each independent variable. Any p values less than 0.05 were considered significant. All analyses were performed using SPSS (Version 20, SPSS, Inc., Chicago, IL, USA).

Results

A total of 292 study subjects had experienced at least one prevalent fracture, whereas 468 had no previous fractures. Of the fractured study participants, 209 had sustained a single fracture, 65 had two fractures, 13 had three fractures, three had four fractures, and two subjects had sustained five fractures. In total, there were 400 fractures, and the most common fracture sites were the distal forearm (27.3%, 109/400), followed by phalanges

of the hand (15.3%, 61/400), carpals and metacarpals (13.3%, 53/400), clavicula (6.8%, 27/400), tibia/fibula (6.5%, 26/400), foot, including toes, tarsals, metatarsals, and calcaneus (6.3%, 25/400), and the facial cranium (5.8%, 23/400). The mean age of the first fracture was 13.3 ± 5.3 years. The median time from fracture to the time of the bone measurements was 10.7 years (range 0.2 to 24.3 years).

Anthropometrics and environmental factors

There were no differences in age, smoking status, amount of physical activity per week, calcium intake, or weight. Men with a prevalent fracture, any fracture, and fracture age 17 years and older were slightly taller than their nonfractured peers (Table 2).

Areal BMD

Men with prevalent fractures or childhood fractures had slightly lower aBMD of the total body and the nondominant radius than men with no fracture (Table 3). Using a logistic regression model

Table 2. Anthropometrics and Environmental Factors in Young Adult Men With and Without Prevalent Fractures

	No fracture (n = 468)	Any fracture (n = 292)	Fracture ≤16 years (n = 217)	Fracture >16 years (n = 75)
Age (years)	24.1 ± 0.6	24.1 ± 0.6	24.1 ± 0.6	24.0 ± 0.6
Smoking (%)	6.4	8.6	8.3	9.3
Physical activity (hours/week)	3.6 ± 6.0	3.6 ± 4.5	3.4 ± 4.4	4.1 ± 4.7
Calcium intake (mg/day)	787 ± 500	761 ± 485	767 ± 500	745 ± 443
Height (cm)	181.6 ± 6.8	182.8 ± 6.4[a]	182.6 ± 6.5	183.5 ± 6.2[a]
Weight (kg)	78.2 ± 12.1	78.7 ± 12.9	78.3 ± 13.1	79.7 ± 12.4

Values are given as mean ± SD. Columns 2, 3, and 4 compared with column 1 by independent samples t test.
The distribution of smokers in the different subgroups was determined by chi-square test.
[a] $p < 0.05$.

Table 3. Areal BMD, Bone Geometry, Microstructure, and Parameters of Finite Element Analysis in Young Adult Men With and Without Prevalent Fractures

	No fracture (n = 468)	Any fracture (n = 292)	Fracture ≤16 years (n = 217)	Fracture >16 years (n = 75)
Total body aBMD (g/cm^2)	1.30 ± 0.10	1.28 ± 0.10[a]	1.28 ± 0.10[a]	1.29 ± 0.09
Lumbar spine aBMD (g/cm^2)	1.29 ± 0.16	1.28 ± 0.16	1.27 ± 0.16	1.29 ± 0.15
Total hip aBMD (g/cm^2)	1.15 ± 0.16	1.13 ± 0.16	1.13 ± 0.16	1.14 ± 0.17
Femoral neck aBMD (g/cm^2)	1.13 ± 0.16	1.12 ± 0.17	1.11 ± 0.16	1.13 ± 0.18
Radius nondominant aBMD (g/cm^2)	0.63 ± 0.05	0.62 ± 0.05[b]	0.62 ± 0.05[c]	0.63 ± 0.05
Radius				
Cortical thickness (μm)	873 ± 176	846 ± 182	833 ± 182[b]	881 ± 176
Cortical CSA (mm^2)	70.5 ± 13.7	68.9 ± 13.9	67.8 ± 13.8[a]	72.2 ± 13.7
Cortical vBMD (mg/cm^3)	849 ± 39	844 ± 43	842 ± 45	849 ± 34
Cortical porosity (%)	1.12 ± 0.49	1.09 ± 0.44	1.06 ± 0.43	1.17 ± 0.44
Cortical pore diameter (μm)	146 ± 14	145 ± 13	144 ± 12[a]	147 ± 17
Trabecular BV/TV (%)	17.1 ± 3.0	16.1 ± 2.8[c]	16.1 ± 2.7[c]	16.3 ± 2.8
Trabecular number (mm^{-1})	2.12 ± 0.26	2.08 ± 0.25[a]	2.07 ± 0.25[a]	2.08 ± 0.25
Trabecular thickness (μm)	80.9 ± 12.7	78.1 ± 12.2[b]	77.9 ± 12.6[b]	78.5 ± 11.0
Trabecular separation (μm)	399 ± 61	411 ± 60[a]	412 ± 61[a]	408 ± 57
Stiffness (kN/mm)	113 ± 20	110 ± 20[a]	109 ± 20[a]	113 ± 19
Failure load (N)	5727 ± 983	5573 ± 953[a]	5517 ± 969[a]	5730 ± 897
Percent load trabecular distal (%)	62.3 ± 7.0	61.2 ± 7.5[a]	61.2 ± 7.7	61.0 ± 6.9
Percent load trabecular proximal (%)	27.5 ± 6.3	27.0 ± 6.3	27.1 ± 6.4	26.7 ± 6.1
Tibia				
Cortical thickness (μm)	1332 ± 305	1264 ± 282[b]	1255 ± 290[b]	1291 ± 259
Cortical CSA (mm^2)	155 ± 32	148 ± 31[b]	147 ± 31[b]	153 ± 29
Cortical vBMD (mg/cm^3)	874 ± 33	870 ± 32	870 ± 32	871 ± 30
Cortical porosity (%)	3.03 ± 1.18	2.91 ± 1.12	2.92 ± 1.14	2.90 ± 1.07
Cortical pore diameter (μm)	168 ± 20	167 ± 20	168 ± 21	164 ± 18
Trabecular BV/TV (%)	18.5 ± 2.7	17.8 ± 2.7[c]	17.7 ± 2.7[c]	18.1 ± 2.7
Trabecular number (mm^{-1})	2.09 ± 0.26	2.06 ± 0.30	2.06 ± 0.30	2.07 ± 0.29
Trabecular thickness (μm)	89.1 ± 11.1	87.0 ± 11.1[a]	86.7 ± 11.4[b]	87.9 ± 10.2
Trabecular separation (μm)	397 ± 59	408 ± 72 [a]	409 ± 70[a]	406 ± 76
Stiffness (kN/mm)	304 ± 48	296 ± 46[a]	294 ± 47[a]	301 ± 43
Failure load (N)	15,146 ± 2330	14,780 ± 2268[a]	14,701 ± 2316[a]	15,009 ± 2121
Percent load trabecular distal (%)	66.3 ± 6.3	66.6 ± 5.5	66.6 ± 5.7	66.9 ± 5.2
Percent load trabecular proximal (%)	45.0 ± 7.1	45.5 ± 6.5	45.5 ± 6.7	45.5 ± 6.0

Values are given as mean ± SD. Columns 2, 3, and 4 compared with column 1 by independent samples t test.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

Table 4. Adjusted Odds Ratios (OR) and Confidence Intervals (95% CI) for Prevalent Fractures in Young Adult Men

	Any fracture OR (CI)[a]	Fracture ≤16 years OR (CI)[a]	Fracture >16 years OR (CI)[a]
Total body aBMD (g/cm^2)	**1.3 (1.1–1.5)**	**1.3 (1.1–1.6)**	1.2 (0.9–1.7)
Lumbar spine aBMD (g/cm^2)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	1.1 (0.8–1.4)
Total hip aBMD (g/cm^2)	1.1 (1.0–1.3)	1.1 (0.9–1.4)	1.1 (0.8–1.5)
Femoral neck aBMD (g/cm^2)	1.1 (1.0–1.3)	1.1 (0.9–1.4)	1.1 (0.8–1.4)
Radius nondominant aBMD (g/cm^2)	**1.3 (1.1–1.5)**	**1.4 (1.1–1.6)**	1.1 (0.8–1.4)
Radius			
Cortical thickness (μm)	1.1 (0.9–1.3)	**1.2 (1.0–1.4)**	0.9 (0.7–1.2)
Cortical CSA (mm^2)	1.1 (0.9–1.3)	**1.2 (1.0–1.4)**	0.9 (0.7–1.2)
Cortical vBMD (mg/cm^3)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.9 (0.7–1.2)
Cortical porosity (%)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.0 (0.7–1.2)
Cortical pore diameter (μm)	1.1 (1.0–1.3)	**1.2 (1.0–1.4)**	0.9 (0.7–1.2)
Trabecular BV/TV (%)	**1.4 (1.2–1.6)**	**1.4 (1.2–1.7)**	1.3 (1.0–1.7)
Trabecular number (mm^{-1})	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (0.9–1.5)
Trabecular thickness (μm)	**1.2 (1.0–1.5)**	**1.3 (1.0–1.5)**	1.2 (0.9–1.6)
Trabecular separation (μm)	**0.8 (0.7–1.0)**	**0.8 (0.7–1.0)**	0.8 (0.6–1.1)
Stiffness (kN/mm)	**1.2 (1.0–1.4)**	**1.3 (1.1–1.5)**	1.1 (0.8–1.4)
Failure load (N)	**1.2 (1.0–1.4)**	**1.3 (1.1–1.5)**	1.1 (0.8–1.5)
Percent load trabecular distal (%)	**1.2 (1.0–1.4)**	**1.2 (1.0–1.4)**	**1.3 (1.0–1.7)**
Percent load trabecular proximal (%)	1.1 (1.0–1.4)	1.1 (0.9–1.3)	1.3 (1.0–1.7)
Tibia			
Cortical thickness (μm)	**1.2 (1.0–1.4)**	**1.3 (1.1–1.5)**	1.0 (0.8–1.4)
Cortical CSA (mm^2)	**1.2 (1.0–1.4)**	**1.3 (1.1–1.5)**	1.0 (0.8–1.4)
Cortical vBMD (mg/cm^3)	1.0 (0.9–1.2)	1.1 (0.9–1.3)	0.9 (0.7–1.2)
Cortical porosity (%)	**1.2 (1.0–1.4)**	1.2 (1.0–1.4)	1.3 (1.0–1.8)
Cortical pore diameter (μm)	1.2 (0.9–1.2)	1.0 (0.9–1.2)	1.2 (0.9–1.6)
Trabecular BV/TV (%)	**1.3 (1.1–1.5)**	**1.3 (1.1–1.6)**	1.2 (0.9–1.6)
Trabecular number (mm^{-1})	1.2 (1.0–1.4)	1.1 (1.0–1.4)	1.2 (0.9–1.6)
Trabecular thickness (μm)	**1.2 (1.0–1.4)**	**1.2 (1.0–1.5)**	1.0 (0.8–1.4)
Trabecular separation (μm)	**0.8 (0.7–0.9)**	**0.8 (0.7–1.0)**	0.8 (0.6–1.0)
Stiffness (kN/mm)	**1.3 (1.1–1.6)**	**1.3 (1.1–1.6)**	1.2 (0.9–1.6)
Failure load (N)	**1.3 (1.1–1.6)**	**1.3 (1.1–1.6)**	1.3 (1.0–1.7)
Percent load trabecular distal (%)	1.1 (0.9–1.3)	1.0 (0.9–1.3)	1.1 (0.8–1.5)
Percent load trabecular proximal (%)	1.0 (0.9–1.3)	1.0 (0.8–1.2)	1.2 (0.9–1.6)

Values are given as odds ratios (OR) and 95% confidence intervals (CI) per standard deviation (SD) decrease. Associations tested by logistic regression. Bold ORs indicate statistical significance ($p < 0.05$).

[a]Adjusted odds ratio (including age, smoking, physical activity, calcium intake, height, and weight as covariates).

(including age, smoking, physical activity, calcium intake, height, and weight as covariates), every SD decrease of total body and nondominant radius aBMD was associated with an increased prevalence of fracture, and even more strongly with childhood fracture prevalence, whereas no association was found between aBMD and fractures in young adulthood (Table 4).

Cortical bone geometry, vBMD, and microstructure

The cortical thickness and cross-sectional area of the tibia, but not the radius, were significantly lower in men with prevalent fractures than in men with no fractures (5.1% and 4.1%, respectively). Men with childhood fractures displayed even lower cortical thickness (5.8%) and CSA (5.1%) at the tibia, and also had affected corresponding bone traits at the radius (4.6% and 3.9% lower, respectively). There were no differences in cortical vBMD. Investigating the microstructural features of the cortex revealed no differences in porosity, at either the radius or tibia, whereas men with a childhood fracture had a smaller mean cortical pore diameter at the radius than men without prevalent fractures (Table 3). Using the same covariates as above in a logistic regression model, prevalent fractures were inversely associated with cortical thickness, cross-sectional area, and porosity of the tibia but not of the radius. Childhood fractures were inversely associated with cortical thickness and CSA at both the radius and tibia, and with mean cortical pore diameter at the radius (Table 4).

Trabecular bone microstructure

Men with any prevalent fracture and men with a childhood fracture had lower trabecular bone volume fraction (BV/TV) at both the radius (5.5% and 5.9%, respectively) and tibia (3.7% and 4.2%, respectively). This was mainly owing to a smaller trabecular

thickness but also an increased separation between trabeculae and at the radius a reduced trabecular number (Table 3). In a logistic regression model (including the same covariates as previously), every SD decrease of trabecular BV/TV and thickness, as well as increase of trabecular separation, of both the radius and tibia were associated with an increased prevalence of fracture and childhood fracture (Table 4). Including radius aBMD, cortical thickness, and trabecular BV/TV simultaneously in a logistic regression model (with age, smoking, physical activity, calcium intake, height, and weight as covariates), BV/TV was inversely and independently associated with prevalent fractures (OR 1.28 [1.04–1.59]), whereas aBMD and cortical thickness were not (OR 1.19 [0.92–1.55] and OR 0.91 [0.73–1.12], respectively).

Biomechanical features and fracture prevalence

Study participants with at least one prevalent fracture had reduced stiffness and estimated failure load at the metaphysis of both the radius (3.0% and 2.7%, respectively) and tibia (2.6% and 2.4%, respectively) than nonfractured subjects (Table 3). An even lower stiffness and estimated failure load was seen in subjects with childhood fractures (radius 4.0% and 3.7%, respectively, and tibia 3.2% and 2.9%, respectively). In men with prevalent fractures, the trabecular bone at the distal end of the VOI at the radius carried a smaller fraction of the load than in men without fractures, whereas there was no difference at the tibia (Table 3). Both low stiffness and reduced estimated failure load of the radius and tibia were associated with an increased prevalence of fractures and childhood fractures, using a logistic regression model, including covariates as previously. There was also an association between low trabecular load fraction at the distal scanned region of the radius but not tibia and increased fracture prevalence. This association was seen for all prevalent fractures, childhood fractures, and fractures in young adulthood (Table 4).

Predictors of estimated failure load

To investigate the predictors of estimated failure load at the radius, we used a stepwise linear regression model, with estimated failure load as dependent variable and cortical CSA, cortical thickness, cortical vBMD, and trabecular BV/TV as independent variables. All of these variables together explained a total of 86.8% (R^2, $p < 0.001$) of the variation in estimated failure load at the radius. The cortical CSA alone explained 53.4% (R^2 change, $p < 0.001$), cortical thickness 18.2% ($p < 0.001$), cortical vBMD 0.3% ($p < 0.001$), and trabecular BV/TV 14.9% ($p < 0.001$).

Forearm fractures

A total of 109 prevalent forearm fractures were distributed among 95 study participants. There were no differences between subjects with at least one prevalent forearm fracture and the 468 men without prevalent fractures regarding age, smoking habits, amount of physical activity, calcium intake, height, and weight (Table 5). Areal BMD of the total body, lumbar spine, and the nondominant radius were lower in men with forearm fractures. There were no differences in cortical thickness, cross-sectional area, vBMD, porosity, or mean pore diameter of the radius between men with and without prevalent forearm fractures (Table 5). The trabecular BV/TV of the radius was, however,

markedly lower (6.7%) in men with a prevalent forearm fracture than in men without a fracture. This was because of a lower trabecular number and higher trabecular separation. Of biomechanical parameters, study participants with a prevalent forearm fracture had lower stiffness and estimated failure load of the radius than men without fractures. The fraction of load distributed in the trabecular bone at the distal part of the VOI of the radius, but not the proximal, was also lower in subjects with a prevalent forearm fracture. Including covariates (age, smoking habits, amount of physical activity, calcium intake, height, and weight) in a logistic regression model, only parameters of trabecular microstructure and percentage of trabecular load fraction of the distal VOI were inversely associated with prevalent forearm fractures. Stiffness and estimated failure load were, however, of borderline significance inversely associated with prevalent forearm fractures ($p = 0.06$ and $p = 0.06$, respectively) (Table 5). Including both radius aBMD and trabecular BV/TV simultaneously in a logistic regression model (with age, smoking habits, amount of physical activity, calcium intake, height, and weight as covariates), the trabecular BV/TV was inversely associated with prevalent forearm fractures (OR 1.56 [1.13–2.14]) independently of radius aBMD (OR 0.88 [0.64–1.21]).

Lower extremity fracture

A total of 63 men had at least one fracture in their lower extremity, here defined as fracture in the foot (including toes, tarsals, metatarsals, and calcaneus), tibia/fibula, patella, and femur. There were no differences in age, smoking status, physical activity, calcium intake, height, or weight between men with a prevalent lower extremity fracture and subjects with no previous fracture (data not shown). Men with a prevalent fracture in the lower extremity had substantially lower cortical thickness (8.3%) and cross-sectional area (7.0%) at the tibia than nonfractured subjects (1221 mm $\pm$ 266 versus 1332 mm $\pm$ 305, $p < 0.01$, and 144 mm$^2 \pm$ 30 versus 155 mm$^2 \pm$ 32, $p < 0.05$, respectively). There were no differences in cortical vBMD, porosity, or pore size of the tibia (data not shown). BV/TV of the tibia was 6.1% lower (17.4% $\pm$ 2.5 versus 18.5 $\pm$ 2.7, $p < 0.01$), reflected in a higher trabecular separation (415 μm $\pm$ 72 versus 397 μm $\pm$ 59, $p < 0.05$), whereas trabecular thickness and number was not significantly lower (86.2 μm $\pm$ 12.1 versus 89.1 $\pm$ 11.1, $p = 0.053$, and 2.04 mm$^{-1} \pm$ 0.31 versus 2.09 mm$^{-1} \pm$ 0.26, $p = 0.18$, respectively). Both stiffness and estimated failure load of the tibia were lower in subjects with a prevalent lower extremity fracture (289 kN/mm $\pm$ 50 versus 304 $\pm$ 48, $p < 0.05$, and 14498 N $\pm$ 2480 versus 15146 N $\pm$ 2330, $p < 0.05$, respectively).

Subjects with fractures only on the contralateral side of the measured arm

A total of 107 subjects had a fracture or fractures only on the right side, and 113 only on the left side. Bilateral fractures were found in 37 subjects, and 23 subjects had fractures in the skull or vertebral column, ie, no side determinable. In a total of 12 subjects, no side was reported in the archives.

Of the 263 subjects with prevalent fractures and HR-pQCT measurements of acceptable quality at the radius, a total of 117

Table 5. Areal BMD, Geometry, Microstructure, and Parameters of Finite Element Analysis in Young Adult Men With Prevalent Forearm Fractures Versus No Fracture

	No fracture ($n = 468$)	Forearm fracture ($n = 95$)	Forearm fracture OR (CI)[a]
Age (years)	24.1 ± 0.6	24.1 ± 0.6	
Smoking (%)	6.4	8.4	
Physical activity (hours/week)	3.6 ± 6.0	3.0 ± 3.5	
Calcium intake (mg/day)	787 ± 500	718 ± 483	
Height (cm)	181.6 ± 6.8	182.4 ± 7.0	
Weight (kg)	78.2 ± 12.1	77.0 ± 12.8	
DXA			
Total body aBMD (g/cm^2)	1.30 ± 0.10	1.27 ± 0.09[b]	1.3 (1.0–1.7)
Lumbar spine aBMD (g/cm^2)	1.29 ± 0.16	1.25 ± 0.14[b]	1.3 (1.0–1.6)
Total hip aBMD (g/cm^2)	1.15 ± 0.16	1.12 ± 0.14	1.1 (0.9–1.4)
Femoral neck aBMD (g/cm^2)	1.13 ± 0.16	1.11 ± 0.16	1.0 (0.8–1.3)
Radius non-dom aBMD (g/cm^2)	0.63 ± 0.05	0.62 ± 0.05[b]	1.2 (1.0–1.6)
Radius			
Cortical thickness (μm)	873 ± 176	844 ± 187	1.1 (0.9–1.4)
Cortical CSA (mm^2)	70.5 ± 13.7	68.2 ± 14.1	1.1 (0.9–1.4)
Cortical vBMD (mg/cm^3)	849 ± 39	843 ± 50	1.1 (0.9–1.4)
Cortical porosity (%)	1.12 ± 0.5	1.06 ± 0.5	1.1 (0.9–1.4)
Cortical pore diameter (μm)	146 ± 14	146 ± 16	1.1 (0.8–1.4)
Trabecular BV/TV (%)	17.1 ± 3.0	15.9 ± 2.6[d]	**1.4 (1.1–1.9)**
Trabecular number (mm^{-1})	2.12 ± 0.26	2.04 ± 0.25[c]	**1.3 (1.0–1.7)**
Trabecular thickness (μm)	80.9 ± 12.7	78.7 ± 12.7	1.2 (0.9–1.5)
Trabecular separation (μm)	399 ± 61	420 ± 62[c]	**0.8 (0.6–0.9)**
Stiffness (kN/mm)	113 ± 20	108 ± 19[b]	1.3 (1.0–1.6)
Failure load (N)	5727 ± 983	5487 ± 955[b]	1.3 (1.0–1.7)
Percent load trab. distal (%)	62.3 ± 7.0	60.7 ± 7.3[b]	**1.3 (1.0–1.6)**
Percent load trab. proximal (%)	27.5 ± 6.3	26.8 ± 6.8	1.1 (0.9–1.4)

Values in the first and second columns are given as mean $\pm$ SD. Differences between the groups tested by independent samples t test. In the far right column, values are given as odds ratios (OR) and 95% confidence intervals (CI) per standard deviation (SD) decrease. Associations tested by logistic regression. Bold ORs indicate statistical significance ($p < 0.05$).

[a]Adjusted odds ratio (including age, smoking, physical activity, calcium intake, height, and weight as covariates).
[b]$p < 0.05$.
[c]$p < 0.01$.
[d]$p < 0.001$.

had suffered at least one fracture of the upper extremity on the same side as the measurement (including clavicula and scapula), and 73 subjects had a fracture or fractures only on the contralateral side. In six subjects with fractures of the upper extremity, no side was reported. We compared the 73 subjects with fracture or fractures of the upper extremity only on the contralateral side of the measured arm with the 415 subjects with no fracture (Table 1), using independent samples t test. Radius trabecular BV/TV and thickness were lower (16.0% $\pm$ 2.9 versus 17.1 $\pm$ 3.0, $p < 0.01$, and 77.7 μm $\pm$ 11.0 versus 80.9 $\pm$ 12.7, $p < 0.05$, respectively), whereas trabecular separation (415 μm $\pm$ 65 versus 399 $\pm$ 61, $p < 0.05$) was higher in men with upper extremity fractures on the contralateral side of the measurement than in men with no fracture. There were no significant differences in cortical thickness (840 μm $\pm$ 171 versus 873 μm $\pm$ 176, $p = 0.12$), cortical CSA (68.6 mm^2 $\pm$ 12.7 versus 70.5 mm^2 $\pm$ 13.7, $p = 0.26$), or estimated failure load (5540 N $\pm$ 896 versus 5727 N $\pm$ 983, $p = 0.13$).

At the tibia, a total of 23 subjects had fractures on their measured side, whereas 35 had fractures only at the contralateral side of the measured side. In five subjects, no side was reported. The 35 subjects with lower extremity fractures only on the contralateral side of the measured side had lower cortical thickness and CSA of the tibia (1199 μm $\pm$ 256 versus 1332 μm $\pm$ 305, $p < 0.05$, and 143 mm^2 $\pm$ 31 versus 155 mm^2 $\pm$ 32, $p < 0.05$, respectively) than the 466 subjects without prevalent fractures (Table 1). The trabecular BV/TV and thickness of the radius were also lower (17.5% $\pm$ 2.8 versus 18.5 $\pm$ 2.7, $p < 0.05$, and 83.8 $\pm$ 11.7 versus 89.1 μm $\pm$ 11.1, $p < 0.01$, respectively), whereas there was no difference in estimated failure load (14694 N $\pm$ 2687 versus 15146 N $\pm$ 2330, $p = 0.3$).

Discussion

In the present study, we demonstrated that a prevalent fracture, occurring from birth to young adulthood, was associated with trabecular bone volume fraction, independently of aBMD and

cortical thickness, in a larger cohort of young adult men around the age of peak bone mass.

Moreover, fractures occurring in childhood before the age of 17 years were even more strongly linked to a less advantageous trabecular microstructure as well as a reduced cortical bone size, resulting in reduced failure load, as estimated using finite element analysis, in the investigated bone.

There are no previous studies on this subject with such homogeneity in aspect of age at this stage of skeletal maturity. However, similar findings have been published in a smaller study on boys aged 15.2 years (SD ± 0.5), where fracture cases had lower trabecular BV/TV at the tibia as a result of decreased trabecular number and increased separation.[13] In the present study, men with prevalent childhood fractures had a smaller cortical thickness and cross-sectional area at both the radius and tibia. This has also been demonstrated previously by Taes and colleagues, but only at the radius, and in that study the men were somewhat older with a greater variance in age (25 to 45 years), and thereby also in skeletal age.[12] In contrast to the present study, the latter study and our previously reported findings (in men 18 to 20 years)[10] have also indicated associations with low cortical density and prevalent fractures, however, not shown for childhood fractures. In these studies, cortical parameters were assessed at the diaphyseal region, in contrast to the present study where the metaphyseal region was investigated. In a recent observational cross-sectional study on boys and girls (5 to 18 years) by Wang and colleagues, boys displayed a decline in cortical density as well as thickness and CSA at the metaphyseal region during puberty, in timing with peak height velocity (PHV). The authors suggest that this is likely caused by a transient increase in cortical porosity, which was also demonstrated by Kirmani and colleagues.[30,31] Wang and colleagues propose that this in turn is caused by the rapid increase in height during PHV, which because of the rapidity precedes the normal corticalization of trabecular bone, with its origin from the periphery of the growth plate, that takes place on the endocortical surface of the metaphysis.[30] This hypothesis is mainly applicable to the radius where the growth in length to 90% is achieved from the distal growth plate during puberty and thereby presents a higher velocity of growth than at the tibia, where the distal growth plate only accounts for 30% of the growth over the same period.[32,33] Porosity has previously been shown to be negatively associated with bone strength,[34] and both of the above mentioned studies suggest that this could be part of the explanation to the peak in forearm fractures during PHV observed in previous studies.[35,36] It has also previously been suggested that the increased incidence of fractures in general observed around PHV could be because of a lag in mineralization owing to an increased gain in stature.[37]

In the present study, where the participants were measured up to a decade after PHV, we found no associations between high porosity and forearm fractures, childhood fractures, or all prevalent fractures. Rather, the opposite: We found adjusted porosity to be inversely associated with any prevalent fracture at the tibia but not at the radius. Thus men without fractures had tibias with larger cortices and higher porosity than fractured men. As for the interpretation of porosity, some caution must be taken because of the high CV values of this variable for measurements at the radius in the present cohort.

We found that bone parameters were also associated with childhood fractures, in addition to all prevalent fractures, indicating that, eg, low trabecular bone volume fraction and reduced cortical thickness was present already at childhood in men with early fractures. In agreement with this hypothesis, Ferrari and colleagues previously demonstrated that a low BMC of the diaphysis of the radius in young prepubertal girls predicted incident fractures, and that this low BMC persisted into pubertal maturity. Furthermore, the BMC gain across puberty was also decreased at both the spine and hip in fracture cases compared with nonfracture controls, indicating that a childhood fracture could be a predictor of a low peak bone mass.[1] One recently published 27-year prospective case-control study demonstrated that young men with a fracture in childhood had lower BMD as measured with single photon absorptiometry at both the time of the fracture as well as many years later.[2]

Regarding biomechanical parameters, stiffness and estimated failure load at both the radius and tibia were negatively associated with prevalent fractures. This was mostly driven by fractures occurring in childhood, a finding in line with the results from the only study on prevalent fractures in young male subjects using biomechanical estimates derived by finite element analysis, where 15.2-year-old boys with a fracture had both lower stiffness and failure load than nonfractured boys, however, only at the tibia.[13] In the present cohort, the majority of estimated failure load at the radius was explained by cortical geometrical parameters (cortical CSA and thickness, 71.6%). Altogether, the results we present indicate that except for the cortical geometrical parameters, the trabecular BV/TV also has an important role for estimated failure load because the fraction of load distributed in the trabecular bone of the radius was lower in previously fractured study subjects, which could possibly be because of a markedly lower trabecular bone volume fraction.

The failure load in the present study was estimated using linear FE models based on 3D HR-pQCT measurements with a homogenous Young's modulus, which has been demonstrated to correlate well to experimentally determined bone strength at the radius in cadaver studies.[20,21] MacNeil and colleagues previously compared linear to nonlinear FE models in a cadaver study on human radii and concluded that a linear approach can provide a good estimate of strength with less computational effort than nonlinear models, which can estimate the strength behavior of the tissue but could be computationally demanding.[38] The estimation of failure load in the present study was performed as originally demonstrated by Pistoia and colleagues, using a failure criterion where 2% of the bone volume is strained over 7000 microstrain.[20] It is, however, important to address that this failure criterion was established with a lower resolution (165 μm) than the equipment used in the present study (82 μm). The location of the VOI at the radius was also different, not in full concordance with the VOI recommended by the manufacturer of the used HR-pQCT (Scanco).[20] In a later study from the same research group though, the data were reanalyzed, using a more distal and smaller VOI, which also showed good correlations with experimentally determined bone strength. This VOI was, however, in full concordance with the VOI currently recommended by the manufacturer.[21] Partly because of these issues,

the validity of the method has been questioned. Mueller and colleagues demonstrated in a cadaver study that estimated failure load was more strongly and accurately correlated to bone strength when using a VOI more distally located, just below the subcondral plate.[39] They also present data supporting the use of a higher critical bone volume (7.5%) for the estimation of failure load when using the VOI recommended by Scanco. Mueller and colleagues recommend that future studies adapt to their method for better accuracy on estimated failure load but also point out that the method established by Pistoia and colleagues will mainly affect the accuracy of absolute strength estimates and that correlations within studies will be less affected.[39] In the only previous study on young males, Chevalley and colleagues[13] assessed failure load in a similar manner to the present study, including the chosen Young's modulus, which facilitates comparison between these two studies.

Investigating forearm fractures, these were exclusively associated with the microstructure of the trabecular compartment of the radius, and even though the cortical bone size parameters tended to be lower in subjects with forearm fractures, the differences were not significant. This association with trabecular bone was also reflected in a lower percentage of load distributed in the trabecular compartment. Interestingly, we found large differences between fracture cases and controls in cortical geometrical parameters of the tibia when investigating prevalent lower extremity fractures. Also at this site, the trabecular BV/TV was associated with fracture, but the large differences in cortical geometry indicate that at weight-bearing sites, the dimensions of the cortex are of greater importance for fracture resistance than at non-weight-bearing sites.

A fracture in an extremity is likely to cause a period of immobility, which theoretically could affect the BMD negatively on the side of the fracture with possibly long-lasting residual effects. In the present study, the participants were measured on their nondominant side regardless of whether they had previously suffered a fracture on that side. To adjust for the possibility that this may have confounded the associations reported in this study, we performed subanalyses on HR-pQCT measurements on the radius and tibia where subjects with a prevalent fracture involving the upper and lower extremity on the measured side, respectively, were excluded. In these analyses, a prevalent fracture in the upper extremity was primarily associated with trabecular microstructure at the radius, and a prevalent fracture in the lower extremity to both trabecular microstructure but also cortical geometry at the tibia. Thus, essentially the same results as in the original analysis were obtained. No associations were, however, found for estimated failure load, which could be because of insufficient statistical power owing to the small groups included in these analyses.

The limitations of this study are, first, the cross-sectional retrospective design, obstructing any further inferences than merely to report observed associations. We have, however, attempted to control for anthropometric and environmental factors known to influence bone mass in young men. The use of X-ray–verified fractures and the large sample size constitute strengths of the study, although all fractures, irrespective of amount of trauma, were included, which could potentially mean that several fractures would have occurred irrespective of bone

quality. There are, however, reports suggesting that fractures after moderate and severe trauma are also contributed to by bone fragility in children,[6] as well as in adults.[40,41] The chosen cut point to define childhood fractures (16 years or younger) resulted in a rather small group of subjects with young adulthood fractures ($n = 75$). This has decreased the statistical power in that analysis, making it unlikely to trace possibly true differences of smaller magnitude. However, in our opinion, the main finding was that the associations with both cortical geometrical and trabecular microstructural parameters as well as estimated bone strength variables with childhood fracture were generally more pronounced than in the analysis including all fractures, indicating that childhood fractures contribute to the highest extent to the associations found between all fractures and these bone traits.

Prevalent fractures in childhood have previously been suggested to predict low peak bone mass,[1] a hypothesis recently supported in a 27-year prospective study on men.[2] To better predict individual fracture risk and find possible treatment targets, it is important to increase knowledge about the underlying bone features explaining the increasing fracture incidence in childhood and adolescence we are facing today. In the current study, we present clear associations between childhood fractures and especially trabecular microstructural parameters, geometrical properties of the cortical bone, and estimated biomechanical parameters derived by finite element analysis in young adult men around the time of peak bone mass.

In our cohort of young adult men, the trabecular bone volume fraction was independently associated with prevalent fractures occurring from birth to young adulthood, suggesting that trabecular bone is of importance for fracture prevalence in this population. Thus, men with prevalent fractures develop impaired trabecular bone microstructure, but whether this leads to increased future fracture incidence in later adulthood or at old age remains to be studied.

Disclosures

Acknowledgments

References

1. Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R. Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility?. J Bone Miner Res. Apr 2006; 21(4):501–7.

2. Buttazzoni C, Rosengren EB, Tveit M, Landin L, Nilsson JA, Karlsson KM. Does a childhood fracture predict low bone mass in young adulthood? A 27-year prospective controlled study. J Bone Miner Res. Feb 2013;28(2):351–9.

3. Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporos Int. Oct 2003;14(10):843–7.

4. Hui SL, Slemenda CW, Johnston CC Jr. The contribution of bone loss to postmenopausal osteoporosis. Osteoporos Int. Oct 1990;1(1): 30–4.

5. Khosla S, Melton LJ 3rd, Dekutoski MB, Achenbach SJ, Oberg AL, Riggs BL. Incidence of childhood distal forearm fractures over 30 years: a population-based study. JAMA. Sep 17 2003;290(11):1479–85.

6. Clark EM, Ness AR, Tobias JH. Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma. J Bone Miner Res. Feb 2008;23(2):173–9.

7. Clark EM, Tobias JH, Ness AR. Association between bone density and fractures in children: a systematic review and meta-analysis. Pediatrics. Feb 2006;117(2):e291–7.

8. Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Barned NJ. Bone mineral density in girls with forearm fractures. J Bone Miner Res. Jan 1998;13(1):143–8.

9. Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. J Pediatr. Oct 2001;139(4):509–15.

10. Darelid A, Ohlsson C, Rudang R, Kindblom JM, Mellstrom D, Lorentzon M. Trabecular volumetric bone mineral density is associated with previous fracture during childhood and adolescence in males: the GOOD study. J Bone Miner Res. Mar 2010; 25(3): 537–44.

11. Ohlsson C, Darelid A, Nilsson M, Melin J, Mellstrom D, Lorentzon M. Cortical consolidation due to increased mineralization and endosteal contraction in young adult men: a five-year longitudinal study. J Clin Endocrinol Metab. Jul 2011;96(7):2262–9.

12. Taes Y, Lapauw B, Griet V, De Bacquer D, Goemaere S, Zmierczak H, Kaufman JM. Prevalent fractures are related to cortical bone geometry in young healthy men at age of peak bone mass. J Bone Miner Res. Jun 2010;25(6):1433–40.

13. Chevalley T, Bonjour JP, van Rietbergen B, Ferrari S, Rizzoli R. Fractures during childhood and adolescence in healthy boys: relation with bone mass, microstructure, and strength. J Clin Endocrinol Metab. Oct 2011;96(10):3134–42.

14. Farr JN, Tomas R, Chen Z, Lisse JR, Lohman TG, Going SB. Lower trabecular volumetric BMD at metaphyseal regions of weight-bearing bones is associated with prior fracture in young girls. J Bone Miner Res. Feb 2011;26(2):380–7.

15. Chevalley T, Bonjour JP, van Rietbergen B, Rizzoli R, Ferrari S. Fractures in healthy females followed from childhood to early adulthood are associated with later menarcheal age and with impaired bone microstructure at peak bone mass. J Clin Endocrinol Metab. Nov 2012;97(11):4174–81.

16. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. Technol Health Care. Dec 1998; 6(5–6):329–37.

17. Majumdar S, Genant HK. Assessment of trabecular structure using high resolution magnetic resonance imaging. Stud Health Technol Inform. 1997;40:81–96.

18. Burghardt AJ, Kazakia GJ, Ramachandran S, Link TM, Majumdar S. Age- and gender-related differences in the geometric properties and biomechanical significance of intracortical porosity in the distal radius and tibia. J Bone Miner Res. May 2010;25(5):983–93.

19. Nishiyama KK, Macdonald HM, Buie HR, Hanley DA, Boyd SK. Postmenopausal women with osteopenia have higher cortical porosity and thinner cortices at the distal radius and tibia than women with normal aBMD: an in vivo HR-pQCT study. J Bone Miner Res. Apr 2010;25(4):882–90.

20. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. Bone. Jun 2002;30(6):842–8.

21. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P. Image-based micro-finite-element modeling for improved distal radius strength diagnosis: moving from bench to bedside. J Clin Densitom. Summer. 2004;7(2):153–60.

22. Lorentzon M, Mellstrom D, Ohlsson C. Age of attainment of peak bone mass is site specific in Swedish men—The GOOD study. J Bone Miner Res. Jul 2005;20(7):1223–7.

23. Kemper HC, Bakker I, Twisk JW, van Mechelen W. Validation of a physical activity questionnaire to measure the effect of mechanical strain on bone mass. Bone. May 2002;30(5):799–804.

24. The National Food Administration Food Database (Sweden). National Food Administration, Uppsala, Sweden; 2012. Cited 2012 November 7. Available from: http://www.slv.se/en-gb/Group1/Food-and-Nutrition/The-Food-Database/.

25. Nevitt MC, Cummings SR, Browner WS, Seeley DG, Cauley JA, Vogt TM, Black DM. The accuracy of self-report of fractures in elderly women: evidence from a prospective study. Am J Epidemiol. Mar 1 1992;135(5):490–9.

26. MacNeil JA, Boyd SK. Load distribution and the predictive power of morphological indices in the distal radius and tibia by high resolution peripheral quantitative computed tomography. Bone. Jul 2007;41(1):129–37.

27. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. Bone. Sep 2010;47(3):519–28.

28. van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. J Biomechan. Jan 1995;28(1):69–81.

29. Chiu J, Robinovitch SN. Prediction of upper extremity impact forces during falls on the outstretched hand. J Biomech. Dec 1998;31(12):1169–76.

30. Wang Q, Wang XF, Iuliano-Burns S, Ghasem-Zadeh A, Zebaze R, Seeman E. Rapid growth produces transient cortical weakness: a risk factor for metaphyseal fractures during puberty. J Bone Miner Res. Jul 2010;25(7):1521–6.

31. Kirmani S, Christen D, van Lenthe GH, Fischer PR, Bouxsein ML, McCready LK, Melton LJ 3rd, Riggs BL, Amin S, Muller R, Khosla S. Bone structure at the distal radius during adolescent growth. J Bone Miner Res. Jun 2009;24(6):1033–42.

32. Pritchett JW. Growth plate activity in the upper extremity. Clin Orthopaed Rel Res. Jul 1991; (268):235–42.

33. Pritchett JW. Longitudinal growth and growth-plate activity in the lower extremity. Clin Orthopaed Rel Res. Feb 1992; (275):274–9.

34. Yeni YN, Brown CU, Wang Z, Norman TL. The influence of bone morphology on fracture toughness of the human femur and tibia. Bone. Nov 1997;21(5):453–9.

35. Bailey DA, Wedge JH, McCulloch RG, Martin AD, Bernhardson SC. Epidemiology of fractures of the distal end of the radius in children as associated with growth. J Bone Joint Surg. American volume. Sep 1989;71(8):1225–31.

36. Landin LA. Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950-1979. Acta Orthop Scand Suppl. 1983;202:1–109.

37. Bonjour JP, Theintz G, Law F, Slosman D, Rizzoli R. Peak bone mass. Osteoporos Int. 1994;4(Suppl 1):7–13.

38. 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. Jun 2008;42(6):1203–13.

39. Mueller TL, Christen D, Sandercott S, Boyd SK, van Rietbergen B, Eckstein F, Lochmuller EM, Muller R, van Lenthe GH. Computational finite element bone mechanics accurately predicts mechanical competence in the human radius of an elderly population. Bone. Jun 1 2011;48(6):1232–8.

40. Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, Hillier TA, Lewis CE, Barrett-Connor E, Cummings SR. High-trauma fractures and low bone mineral density in older women and men. JAMA. Nov 28 2007;298(20):2381–8.

41. Sanders KM, Pasco JA, Ugoni AM, Nicholson GC, Seeman E, Martin TJ, Skoric B, Panahi S, Kotowicz MA. The exclusion of high trauma fractures may underestimate the prevalence of bone fragility fractures in the community: the Geelong Osteoporosis Study. J Bone Miner Res. Aug 1998;13(8):1337–42.