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Chevalley, Thierry; Bonjour, Jean-Philippe; van Rietbergen, Bert; Ferrari, Serge Livio; Rizzoli, René

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Fractures during Childhood and Adolescence in Healthy Boys: Relation with Bone Mass, Microstructure, and Strength

T. Chevalley, J. P. Bonjour, B. van Rietbergen, S. Ferrari, and R. Rizzoli

Division of Bone Diseases (T.C., J.P.B., S.F., R.R.), University Hospitals and Faculty of Medicine, CH-1211 Geneva 14, Switzerland; and Department of Biomedical Engineering (B.v.R.), Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands

Context: In healthy boys, fractures result from trauma of various severity, suggesting contribution of an intrinsic biomechanical fragility.

Objectives: Our objective was to characterize bone mineral mass, microstructure, and strength in boys with and without fractures.

Participants and Design: We followed 176 healthy boys from 7.4 ± 0.5 to 15.2 ± 0.5 (mean \pm sd) yr of age.

Outcomes: Areal (a) bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry at radius metaphysis and diaphysis, total hip, femoral neck and diaphysis, and L2–L4 vertebrae. Volumetric (v) BMD and microstructure were assessed by high-resolution peripheral computerized tomography at both distal tibia and radius. Bone strength was evaluated by micro-finite element analysis.

Results: A total of 156 fractures were recorded in 87 of 176 boys with peak incidence between 10 and 13 yr. At 7.4 yr, subjects with fractures had lower aBMD in all sites and at 15.2 yr in femoral and spinal, but not in radius, sites. At that age, boys with fractures displayed lower trabecular (Tb) vBMD ($P = 0.029$) and number ($P = 0.040$), stiffness ($P = 0.024$), and failure load ($P = 0.016$) at distal tibia, but not distal radius. Odds ratios of fracture risk per 1 sd decrease were 1.80 ($P = 0.006$) for femoral neck aBMD and 1.46 ($P = 0.038$) for distal tibia Tb vBMD, 1.59 ($P = 0.031$) for Tb number, 1.53 ($P = 0.072$) for stiffness, and 1.60 ($P = 0.056$) for failure load.

Conclusion: In a homogeneous cohort of healthy boys, fractures recorded until 15.2 ± 0.5 yr of age were associated with lower femoral neck aBMD and with lower distal tibia trabecular vBMD and number, stiffness and failure load. These deficits in bone mineral mass, microstructure and strength could contribute to the occurrence of fractures during growth. (*J Clin Endocrinol Metab* 96: 0000–0000, 2011)

Fractures resulting from trauma of various severity are frequently observed during childhood and adolescence in both genders. They constitute 10–25% of all pediatric trauma, with approximately 45–55% of all children breaking at least one bone before the age of 18 yr (1–5). Epidemiological studies have found an annual in-

cidence of fracture of 103–165 and 162–257 per 10,000 person-years in girls and boys, respectively (1–5).

The peak incidence of fracture occurs approximately between 11–12 and 13–14 yr in girls and boys, respectively (1–6). This period coincides to the age of peak height velocity (PHV) and precedes by nearly 1 yr the peak of

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Abbreviations: aBMD, Areal bone mineral density; BV/TV, trabecular bone volume fraction; CI, confidence interval; CSA, cross-sectional area; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; μ FE, micro-finite element; FEA, finite element analysis; HR-pQCT, high-resolution peripheral computerized tomography; OR, odds ratio; PHV, peak height velocity; vBMD, volumetric bone mineral density.

bone mineral accrual (6–8). In both genders, the maximal differences between PHV and bone mineral mass accrual corresponds to pubertal stages P2–P3 (7). Several studies strongly suggest that the higher incidence of fracture during PHV can result from a transient fragility condition due to a relative deficit in the amount of mineralized tissue within the skeletal pieces (6–9). As another but not mutually exclusive possibility, fracture may reflect an early prepubertal expression of reduced mechanical resistance that would outlast the period of sexual maturation and thus increase the risk of osteoporosis in later life. Evidence for this latter possibility has been documented in both girls (10) and boys (11). Although trauma can be an important determinant that may explain part of the gender difference in fracture incidence (1–5), an additional intrinsic bone mechanical fragility could therefore be involved (10, 11). We investigated this hypothesis in a prospective study carried out in a cohort of healthy boys, about half of whom had experienced a fracture until a mean age 15.2 yr. Several bone variables including areal bone mineral density (aBMD), microstructure, and strength were measured by dual-energy x-ray absorptiometry (DXA), high-resolution peripheral computerized tomography (HR-pQCT), and finite element analysis (FEA) to assess whether an intrinsic bone weakness is associated with a fracture history and to explore which bone traits could contribute to this mechanical deficit.

Subjects and Methods

Study subjects

The analysis presented in this report has been carried out on data obtained in 176 healthy adolescent boys with a mean age of 15.2 ± 0.5 (mean \pm SD) yr. These boys belonged to an 8-yr cohort study of healthy prepubertal Caucasian boys recruited at a mean age \pm SD of 7.4 ± 0.4 yr (range, 6.5–8.5 yr) through the Public Health Youth Service of the Geneva region from September 1999 to September 2000. These boys were then examined at mean ages 8.5 ± 0.4 and 9.6 ± 0.4 yr (12). Between 7.4 and 8.5 yr of age, half of the cohort received a calcium supplementation as previously reported in detail (12). Exclusion criteria were ratio of weight to height below the third or above the 97th percentile according to Geneva reference values, presence of physical signs of puberty, chronic disease, gastrointestinal disease with malabsorption, congenital or acquired bone disease, and regular use of medication. The protocol was approved by the Ethics Committee of the Department of Pediatrics of the University Hospitals of Geneva. Informed consent was obtained from the parents and their children.

Clinical assessment

Participant's body weight and standing height using a stadiometer were measured, and body mass index (kilograms per square meter) was calculated. Tanner's pubertal stage was determined by a pediatrician at baseline, at the end of the inter-

vention study (12), and at each follow-up visit by self-assessment based on drawings and written description of Tanner's classification. Fracture history, including skeletal site, year of event, and type of treatment, was recorded from the children and their parents at each visit. During the 7.8-yr follow-up period, no other disorder susceptible to affect the skeleton was found in the participants.

Protein and calcium intakes assessment

Spontaneous calcium and protein intake was assessed by frequency questionnaire (13, 14) at each visit. The total animal protein intake was expressed either in grams per day or grams per kilogram body weight per day. It included dairy, meat, fish, and egg proteins. The calcium intake was essentially assessed from dairy sources.

Physical activity assessment

Physical activity was assessed by questionnaire based on self-reported time spent on physical education classes, organized sports, recreational activity, and usual walking and cycling (15). Subsequently, the collected data were converted and expressed as physical activity energy expenditure (kilocalories per day) using established conversion formulas (16).

Measurement of bone variables

The aBMD was determined by DXA using a Hologic QDR 4500 instrument (Waltham, MA) at radial metaphysis, radial diaphysis, femoral neck and total hip, femoral diaphysis, and L2–L4 lumbar spine in anteroposterior view as previously reported (12). The coefficient of variation (CV) of repeated measurements at these sites as determined in young healthy adults varied from 1.0–1.6% for BMD. Volumetric bone density (vBMD) and microstructure were determined at the distal radius and tibia by HR-pQCT with an XtremCT instrument (Scanco Medical AG, Brüttisellen, Switzerland) that acquires a stack of 110 parallel computerized tomography slices (9-mm length) with an isotropic voxel size of $82 \mu\text{m}$ as previously described (17). At the distal radius, four boys had no DXA and no HR-pQCT scans because wrist fractures could have interfered with data acquisition. At this site, HR-pQCT scans of four other boys were eliminated from the study because of obvious movement artifacts. The site of the HR-pQCT scans was precisely delineated by positioning a reference line at the proximal limit of the epiphyseal growth plate of the radius (18). For subjects whose radial epiphyseal plates had fused, the remnant of the plate was still visible, enabling us to set the reference line. Scans were started at a distance 1 mm proximal to the reference line. Such a technical process ensured that despite differences in radius length, the scanned anatomic site was selected to be as identical as possible in all subjects. For the distal tibia, the first CT slice was 22.5 mm proximal to the reference line as described in a previous adult study (17). The following variables were measured: total, cortical, and trabecular volumetric bone density expressed as milligrams hydroxyapatite per centimeter cubed; trabecular bone volume fraction (BV/TV); trabecular number, thickness (micrometers), and spacing (micrometers); mean cortical thickness (micrometers); and cross-sectional area (CSA) (square millimeters). The *in vivo* short-term reproducibility of HR-pQCT at the distal radius and distal tibia assessed in 15 subjects with repositioning varied from 0.6–1.0% and from 2.8–4.9% for bone density and for trabecular architecture, re-

spectively. These reproducibility ranges are similar to those previously published (19). DXA measurements were performed in nondominant forearm and the hip. HR-pQCT measurements in distal radius and tibia were likewise usually performed in the nondominant limb. Unless there was a fracture history on that side, the nonfractured limb was measured by both DXA and HR-pQCT techniques. One technician per device performed all the scans, as well as daily quality control phantom, to check for possible drifts in the x-ray sources.

Finite element analysis

Finite element models of the radius and the tibia were created directly from the segmented HR-pQCT images using a procedure similar to that used in earlier clinical studies (20–22). In summary, a voxel-conversion procedure was used to convert each voxel of bone tissue into an equally sized brick element (23), thus creating micro-finite element (μ FE) models that can represent the actual trabecular architecture in detail. The models contained approximately 2 million elements for the radius and 5 million elements for the tibia and could be solved in approximately 3 and 5 h, respectively. Material properties were chosen: isotropic and elastic. Both cortical and trabecular bone elements were assigned a Young's modulus of 10 and a Poisson's ratio of 0.3 (21, 24). A compression test was simulated to represent loading conditions during a fall from standing height (25). Bone failure load was calculated as the force for which 2% of the bone tissue would be loaded beyond 0.7% strain (24, 26). In addition to failure load (N), μ FEA-derived variables used in our study also included stiffness (kilo-Newtons per millimeter) and the percentage of load carried by the trabecular bone at the distal and proximal surface of the volume of interest (percent load trabecular distal and percent load trabecular proximal, respectively). All μ FEA were done using the FE solver integrated in the IPL software version 1.15 (Scanco Medical AG).

Expression of the results and statistical analysis

The various anthropometric and osteodensitometric variables are given as mean \pm SD. The differences in density, microstructure, mechanical parameters, and clinical characteristics among healthy adolescent boys with or without a positive history of fracture were assessed by unpaired Student's *t* test or by Wilcoxon signed rank test whenever the variable was not normally distributed. For these differences in density, microstructure, and mechanical parameters, an analysis of covariance was used to control for the influence of age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between the age of 7.4 and 8.4 yr. Associations between density, microarchitecture, mechanical parameters, and fracture status were evaluated by logistic regression analysis with adjustment for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between the age of 7.4 and 8.4 yr and expressed as odds ratio (OR) [with 95% confidence intervals (CI)] per SD decrease. The significance level for two-sided *P* values was 0.05 for all tests. The data were analyzed using STATA software, version 7.0. (StataCorp LP, College Station, TX).

TABLE 1. Characteristics of the 176 boys at a mean age of 7.4 and 15.2 yr

	Age (yr)	
	7.4 \pm 0.4	15.2 \pm 0.5
Anthropometric variables		
Height (cm)	125.5 \pm 6.2	171.7 \pm 9.7
Weight (kg)	25.2 \pm 5.0	60.2 \pm 13.2
BMI (kg/m ²)	15.9 \pm 2.0	20.3 \pm 3.6
Pubertal stage (n) ^a	All P1	P2 (5), P3 (13), P4 (93), P5 (65)
Dietary intake		
Calcium (mg/d)	749 \pm 265	1029 \pm 538
Total proteins (g/d)	46.9 \pm 12.3	63.3 \pm 23.7
Total proteins (g/kg BW \cdot d)	1.78 \pm 0.46	1.08 \pm 0.41
Total physical activity (kcal/d)	241 \pm 93	720 \pm 386

All values are means \pm SD. BMI, Body mass index.

^a Pubertal maturity, with the number of boys at the corresponding Tanner stage shown within parentheses.

Results

The anthropometric characteristics of the cohort as assessed at 7.4 and 15.2 yr of age were within the normal values of the corresponding regional population (Table 1).

The total number of fracture was 156, occurring in 87 of the 176 boys followed up. Multiple fractures (two to five) were reported in 38 boys, accounting for two thirds of all fractures. Most common fractures were localized in forearm and wrist (39%), followed by hand/fingers (18%) and arm/shoulder (14%). Twenty percent of fractures occurred at the lower limb (including foot, ankle, tibia, and femur) and 8% at other sites. In boys having experienced more than one fracture, the upper limb was always affected. Peak fracture incidence occurred from 10–13 yr of age (Fig. 1).

Once the cohort was dichotomized according to the presence or absence of at least one fracture that occurred

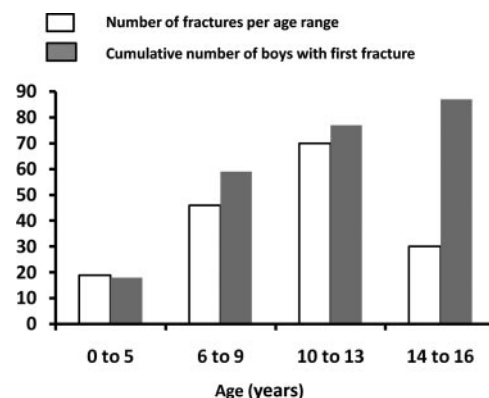


FIG. 1. Age-related distribution of total number of fractures and cumulative number of boys sustaining a first fracture. The histogram shows the age-related distribution of all fractures and cumulative number of the 87 of 176 healthy boys experiencing at least one fracture. The highest incidence is observed within the 10- to 13-yr age range.

TABLE 2. Characteristics of boys at 7.4 and 15.2 yr according to their fracture history at 15.2 yr

	Without fracture, n = 89	With fracture, n = 87	P	P ^a	Without fracture, n = 89	With fracture, n = 87	P	P ^b
Age (yr)	7.4 ± 0.4	7.4 ± 0.4			15.2 ± 0.5	15.2 ± 0.5		
Pubertal stage (n) ^c	All P1	All P1			P2 (1), P3 (7)	P2 (4), P3 (6)		
					P4 (49), P5 (32)	P4 (44), P5 (33)		
Height (cm)	126.1 ± 6.5	124.9 ± 5.7	0.173		172.2 ± 10.5	171.2 ± 8.8	0.484	
Weight (kg)	25.5 ± 5.0	25.0 ± 5.0	0.520		61.0 ± 13.0	59.4 ± 13.4	0.441	
BMI (kg/m ²)	15.9 ± 1.9	15.9 ± 2.1	0.884		20.5 ± 3.6	20.2 ± 3.6	0.579	
Calcium (mg/d)	767 ± 279	730 ± 250	0.359		1027 ± 526	1032 ± 554	0.949	
Total proteins (g/d)	48.5 ± 13.3	45.2 ± 11.1	0.082		65.4 ± 24.1	61.2 ± 23.1	0.241	
Total PA (kcal/d)	233 ± 96	249 ± 89	0.251		735 ± 449	705 ± 310	0.609	
Radial metaphysis BMD (mg/cm ²)	301 ± 28	290 ± 31	0.014	0.013	383 ± 54	379 ± 56	0.626	0.444
Radial diaphysis BMD (mg/cm ²)	481 ± 38	466 ± 37	0.010	0.034	660 ± 67	654 ± 70	0.583	0.716
Femoral neck BMD (mg/cm ²)	688 ± 70	663 ± 72	0.023	0.033	901 ± 133	847 ± 116	0.005	0.001
Total hip BMD (mg/cm ²)	690 ± 67	665 ± 72	0.017	0.032	992 ± 139	936 ± 133	0.007	0.002
Femoral diaphysis BMD (mg/cm ²)	1014 ± 85	982 ± 85	0.014	0.024	1682 ± 171	1623 ± 171	0.025	0.006
L2–L4 BMD (mg/cm ²)	568 ± 52	546 ± 57	0.010	0.017	918 ± 135	875 ± 133	0.032	0.010

All values are mean ± SD. BMI, Body mass index.

^a P value after adjustment for age, height, weight, pubertal stage, calcium and protein intake, and physical activity.

^b P value after adjustment for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr.

^c Pubertal maturity, with the number of boys at the corresponding Tanner stage shown within parentheses.

from infancy to the mean age of 15.2 yr, no significant difference in anthropometric values was noted, neither at 7.4 nor at 15.2 yr of age (Table 2). There was a slight but not statistically significant lower protein intake in the fractured group at both 7.4 (−7%) and 15.2 (−6%) yr of age (Table 2). This slight reduction was not abolished after body weight adjustment (data not shown). The fractured group was not more physically active than the nonfractured group (Table 2).

At the age of 7.4 yr, aBMD values were significantly reduced at the six scanned skeletal sites, even after adjustment for age, standing height, body weight, pubertal stage, calcium and protein intake, and physical activity (Table 2). As evaluated by logistic regression and expressed as OR (95%CI) per 1 SD decrease in aBMD, the risk of fracture was significantly increased, with the highest value obtained at the femoral diaphysis [1.64 (1.07–2.52)] and the lowest value at the femoral neck [1.46 (1.03–2.08)] (Fig. 2A).

At the age of 15.2 yr, significantly reduced aBMD values adjusted for age, standing height, body weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr were also measured at the femoral and spinal site levels, but no longer at the two radial sites (Table 2). Compared with the OR computed at the age of 7.4 yr, the corresponding OR at the femoral and spinal levels were greater, varying from 1.90 (1.15–3.14) for the femoral diaphysis to 1.62 (1.05–2.49) for the lumbar spine

(Fig. 2B). In contrast, the OR of the two radial sites were much lower, very close to the unit value (Fig. 2B).

At mean age 15.2 yr, microstructure measurements by HR-pQCT indicate that boys with a fracture history displayed significantly lower distal tibia trabecular vBMD (volumetric bone density or BV/TV) and number (Tb.N), and greater trabecular spacing (Tb.Sp) (Table 3). The statistical significance of these differences remained after adjustment for standing height, body weight, calcium and protein intake, physical activity, pubertal stage, and calcium supplement or placebo randomization between age 7.4 and 8.4 yr (Table 3). Total vBMD was also significantly lower in the fractured group after this adjustment (Table 3).

Bone strength evaluated by FEA at the age of 15.2 yr, showed that both stiffness and failure load at the distal tibia were 5.8% lower in fractured group (Table 3). There was no difference in the percentage of load carried by the trabecular or cortical bone at the distal and proximal surface between the fractured and nonfractured group (data not shown).

The risk of fracture as related to tibial microstructure measurements and strength estimates are depicted in Fig. 3. The OR was significantly higher than 1.0 for both trabecular volumetric density and number. A trend for significantly increased OR was computed for both stiffness and failure load estimates (Fig. 3).

In contrast, and in keeping with the DXA aBMD values monitored at the age of 15.2 yr, none of the distal radius

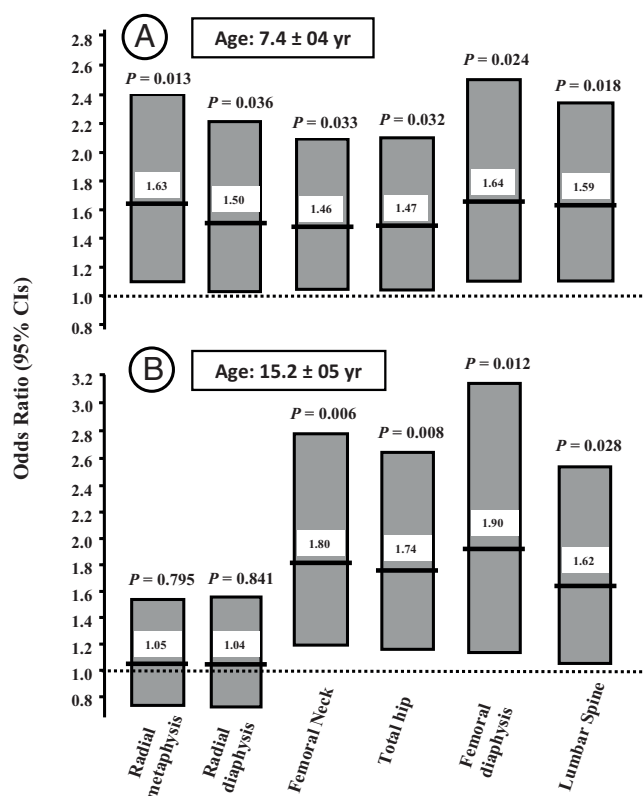


FIG. 2. Fracture risk in healthy boys: OR and 95% CI/sp decrease in aBMD measured by DXA at six skeletal sites. DXA scans were performed at mean age \pm sd of 7.4 ± 0.4 and 15.2 ± 0.5 yr in a cohort of 176 healthy boys of whom 87 experienced at least one fracture until mean age of 15.2 yr. OR were calculated using logistic regression analysis. The OR are depicted by the horizontal lines within the columns of which the upper and lower limits correspond to the 95% CI. The statistical significance is indicated above each column of the skeletal site examined. A, At 7.4 yr, OR were adjusted for age, height, weight, pubertal stage, calcium and protein intake, and physical activity; B, at 15.2 yr, OR were adjusted for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr.

microstructure measurements and strength estimates made by HR-pQCT and FEA, respectively (Table 3) were significantly different between the fractured and the non-fractured group.

Discussion

The reported prospective study carried out in a homogeneous cohort of healthy fractured boys shows deficiencies in bone mineral density, microstructure, and strength as assessed by three technical approaches using DXA, HR-pQCT, and FEA.

Over the last decades, several studies carried out in both healthy girls and boys have consistently reported an inverse relationship between the incidence or prevalence of fractures occurring during childhood and adolescence and aBMD as measured by DXA (10, 11, 27–33). Thus, like in

adults (34–36), low aBMD is associated with fractures in growing individuals. In adults, a site specificity for aBMD and fracture risk has been documented (34). In children and adolescents, some but not all studies support a site specificity for fracture prediction (10, 30, 31, 33, 37, 38). In a case control study of upper limb fractures in both girls and boys aged 9–17 yr, there was a trend for arm aBMD to be more predictive than other skeletal sites for wrist and forearm fractures in girls but not in boys (30). This apparent gender difference in site specificity of fracture prediction (30) would be, at least in part, consistent with our previous prospective study in girls showing significant lower bone mineral content in the radius diaphysis at 8.0 yr of age and still present 8.5 yr later (10) and the present investigation in boys in whom the fracture associated reduction in radial bone strength as measured before puberty was no longer observed at 15.2 yr of age.

The usual observation of reduced aBMD associated with fracture occurring during childhood and adolescence contrasts with diverse findings on the putative nature of the bone components that might explain this reduction. Particularly, it remains uncertain whether the mechanical weakness would be related to differences in bone size, geometry, and/or in vBMD of the cortical or trabecular compartments. Differences in the identification of the deficient bone components involved may be due to several factors including technical approaches, skeletal sites examined, and/or age at time of bone trait analysis. Our study illustrates two of these factors, *i.e.* age at time of bone assessment and the skeletal sites examined. At the age of 7.4 yr, aBMD at all skeletal sites was significantly lower in the group with than without fracture. Note that 74% of all fractures (115 of 156) occurred and 61% of boys (53 of 87) broke their bones after this first examination that clearly identified a relative weakness at both axial and appendicular sites, including radial metaphysis and diaphysis. This homogeneity among skeletal sites in the prediction of fracture risk at mean age of 7.4 yr as depicted in Fig. 2 was no longer present several years later. When reexamined at a mean age of 15.2 yr, aBMD remained lower in spinal and femoral sites but no longer in the radius. From 7.4–15.2 yr of age, the CV at the radial metaphysis level of the whole cohort ($n = 176$), increased from 10.1 to 14.4%. Such an age-dependent wider range of aBMD values could be expected to reduce the power for detecting a statistically significant difference in relation to the occurrence or not of fracture. However, an increase in aBMD CV of similar magnitude was observed in the femoral neck (from 10.7–14.5%) and spine (from 10.1–15.2%) levels, although the difference between boys with and without fracture remained highly significant (Table 2). Furthermore, bone microstructure and strength variables as as-

TABLE 3. Microstructure and FEA of distal tibia and distal radius in 15.2-yr-old boys according to their fracture history

	Distal tibia		<i>P</i>	<i>P^a</i>	Distal radius		<i>P</i>
	Without fracture, <i>n</i> = 89	With fracture, <i>n</i> = 87			Without fracture, <i>n</i> = 87	With fracture, <i>n</i> = 81	
D tot (mg HA/cm ³)	272 ± 45	262 ± 44	0.125	0.038	257 ± 38	255 ± 44	0.830
D cort (mg HA/cm ³)	730 ± 56	735 ± 52	0.551	0.766	637 ± 73	642 ± 72	0.688
D trab (mg HA/cm ³)	205 ± 27	196 ± 27	0.029	0.012	195 ± 27	192 ± 34	0.542
BV/TV (%)	17.1 ± 2.3	16.3 ± 2.2	0.030	0.012	16.2 ± 2.3	16.0 ± 2.8	0.544
Tb.N (mm ^{−1})	2.13 ± 0.31	2.04 ± 0.26	0.040	0.036	2.23 ± 0.20	2.20 ± 0.21	0.351
Tb.Th (μm)	81.1 ± 10.6	80.8 ± 10.7	0.875	0.252	72.6 ± 8.4	72.4 ± 10.9	0.872
Tb.Sp (μm)	398 ± 62	418 ± 60	0.028	0.020	379 ± 41	387 ± 53	0.404
Ct.Th (μm)	851 ± 336	807 ± 293	0.464	0.332	388 ± 219	383 ± 209	0.890
CSA (mm ²)	888 ± 151	858 ± 132	0.167	0.400	333 ± 61	322 ± 56	0.209
Stiffness (kN/mm)	259.6 ± 54.7	244.6 ± 48.6	0.060	0.024	87.2 ± 21.6	83.5 ± 19.3	0.249
Estimated failure load (N)	12430 ± 2559	11706 ± 2235	0.050	0.016	4239 ± 996	4044 ± 894	0.189

All values are mean ± SD. D tot, D cort, and D trab, total, cortical, and trabecular volumetric density, respectively, expressed in milligrams of hydroxyapatite (HA); Tb.N, Tb.Th, and Tb.Sp, trabecular number, thickness, and spacing, respectively; Ct.Th, cortical thickness.

^a *P* value after adjustment for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr.

sessed by HR-pQCT and FEA at 15.2 yr at the distal radius corroborated the absence of an aBMD difference measured by DXA at that age. It is quite possible that the lower radial aBMD values observed at 7.4 yr may have contributed to the increased fracture incidence, observed during the prepubertal years until the time of PHV, particularly those fractures localized in the upper limbs. The question whether the apparent favorable evolution of the radial bone mineral mass in the fractured group corresponds to a transient or lasting recovery remains open. Only new measurements of radius and other skeletal sites of this

cohort at the time of peak bone mass attainment will enable discrimination between these two possibilities. It might be argued that in some boys, the forearm fractures might have artifactually overestimated the radius bone measurements made at 15.2 yr. For instance, the fracture callus could have been included in the region of interest in 10 of 87 fractured boys. Alternatively, the side of the measurement could have been switched at the age 15.2 yr from the nondominant to the dominant arm in nine of 87 fractured boys. These two situations may thus have canceled out the forearm deficiency recorded at the age of 7.4 yr. Removing from the statistical analysis these few boys did not modify the nondifference of the radial measurements between the fractured and nonfractured group.

In our study, the measurements by HR-pQCT technique at the level of the distal tibia indicate that the bone mineral mass deficit detected by DXA in the femoral sites of the fractured group was associated with significant lower distal tibial trabecular vBMD (−4.4%). The magnitude of this fracture-associated reduction in trabecular vBMD was virtually identical with that reported (−4.6%) in a large group of young men aged 18.9 ± 0.6 yr in whom distal tibia was measured by pQCT (39). Using HR-pQCT in our study, we further documented that the lower vBMD in the fractured group was essentially due to a significant reduction in the number of trabeculae (−4.3%), without any decrease in their thickness. In our study, the lower, by 5.2 and 3.4%, respectively, cortical thickness and CSA were not statistically significant. The important interindividual variability of these two bone size components, as indicated by the large CV, about 36–40 and 15–17% in cortical thickness and CSA, respectively, suggest that in our study, the statistical power was insufficient to estab-

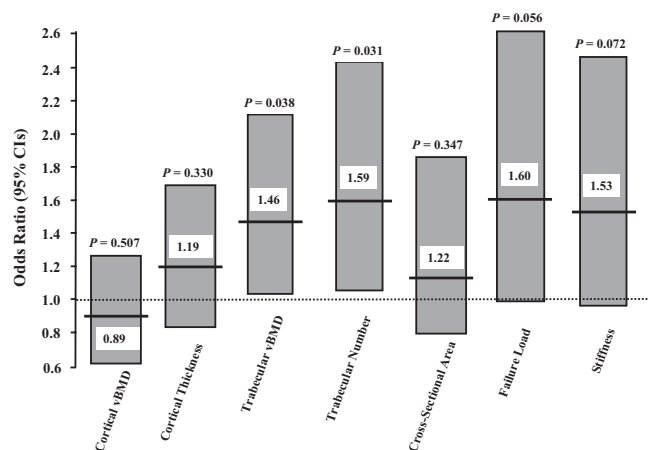


FIG. 3. Fracture risk in healthy boys: OR and 95% CI/SD decrease of several tibial bone microstructure and strength components. Measurements were performed at mean age ± SD of 15.2 ± 0.5 yr by HR-pQCT and FEA for the tibia microstructure and strength components, respectively. OR are depicted by the horizontal lines within the columns of which the upper and lower limits correspond the 95% CI. The statistical significance is indicated above each column of the skeletal site examined. OR were adjusted for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr.

lish possible significant contribution to the increased fracture risk.

The mechanical competence of the distal tibia as assessed by FEA was lower, but not statistically significantly so, in the fractured group. The relatively low stiffness and failure load suggest that the microstructural trabecular abnormality mainly characterized by reduced number and increased separation have compromised bone strength. Of note, both bone strength estimates at distal tibia were highly related to femoral neck aBMD with correlation coefficient r of 0.82 and 0.83 ($P < 0.001$) for stiffness and failure load, respectively. However, the correlation was less with trabecular number ($r = 0.56$), the main alteration observed at the level of the tibia microstructure. This suggests that other nontrabecular components could play a nonnegligible role in the mechanical competence deficit observed in the fractured group. Other studies have provided evidence that a transient cortical weakness could be implicated in the increased fragility occurring during the period of PHV (18, 40). This deficit may be due to a decreased cortical thickness associated with a putative increase in cortical porosity (18, 40). In our study, there was a lower, although not significant, value in cortical thickness in the distal tibia of the fractured group. Thus, in addition to the clearly detectable trabecular deficit, FEA (23) may have included this cortical component in the estimates of bone stiffness and failure load in relation to childhood and adolescent fracture.

This study has some limitations. The reported fractures by the parents were not confirmed by a direct radiological examination by the investigators. However, taken into account both the prospective study design and the parental concern of the event affecting the health of their children and requiring urgent medical care, it is unlikely that the number of recorded fractures substantially differs from the reality. The magnitude of the trauma was not categorized; therefore, any fractures resulting from some severe trauma were included in our analysis. Such inclusion may have attenuated some of the bone trait observed differences. In this respect, a previous study has documented that bone fragility contributes to the risk of fracture in children even after severe trauma (41). Still, the relative small number of subjects may have limited the statistical power of our study for ascertaining a statistically significant contribution of either cortical thickness or CSA to the increased fracture risk.

One can only speculate on the role of genetic and/or environmental factors that might explain the bone deficit observed in the fractured group. The fact of detecting the deficit at mean age 7.4 yr, which is before the peripubertal period during which the fracture risk culminates as shown in Fig. 1, could speak in favor of a role for a genetic com-

ponent. From birth to maturity, bone development of each healthy individual follows a given trajectory that can be moderately modified by environmental factors (42). The genes responsible for the large interindividual variability of aBMD, as measured once peak bone mass is attained in early adulthood, still remain to be clearly identified (42). A previous study in girls indicated that fractures during growth are associated with relatively low bone mass from the beginning to the end of pubertal maturation (10), which suggested that the increased fracture risk was predetermined very early in life and remained unabated until the end of the skeletal development period (10). Regarding the role of environmental factors, physical activity as well as both calcium and protein consumptions as surveyed at 7.4 or 15.2 yr (Table 2) did not show any significant differences between the fracture and the non fracture group.

Our study has some strengths compared with other cross-sectional reports comparing children of both genders with wide age and pubertal maturation ranges. Boys were prospectively followed up for a period of 7.8 yr, starting from prepuberty and covering for most of them the PHV years during which the greatest incidence of fractures was recorded in previous studies as in the present study. Finally, the fact that bone investigation methods including DXA and HR-pQCT were applied in each subject during the same visit by a single technician also provides a certain strength to our study.

In conclusion, in a homogeneous cohort of healthy boys, fractures recorded until 15.2 ± 0.5 yr of age were associated with lower femoral neck aBMD measured by DXA and with a lower distal tibia trabecular vBMD and number as assessed by HR-pQCT, whereas FEA indicated a decrease in stiffness and failure load. These deficits in bone mineral mass, microstructure, and strength could contribute to the occurrence of fractures during growth.

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Address all correspondence and requests for reprints to: Thierry Chevalley, M.D., Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4. CH-1211 Geneva 14, Switzerland. E-mail: Thierry.Chevalley@hcuge.ch.

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References

- Landin LA 1983 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* 202:1–109
- Tiderius CJ, Landin L, D  ppe H 1999 Decreasing incidence of fractures in children: an epidemiological analysis of 1,673 fractures in Malmö, Sweden, 1993–1994. *Acta Orthop Scand* 70:622–626
- Jones IE, Williams SM, Dow N, Goulding A 2002 How many children remain fracture-free during growth? a longitudinal study of children and adolescents participating in the Dunedin Multidisciplinary Health and Development Study. *Osteoporos Int* 13:990–995
- Khosla S, Melton 3rd LJ, Dekutoski MB, Achenbach SJ, Oberg AL, Riggs BL 2003 Incidence of childhood distal forearm fractures over 30 years: a population-based study. *Jama* 290:1479–1485
- Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP 2004 Epidemiology of childhood fractures in Britain: a study using the general practice research database. *J Bone Miner Res* 19:1976–1981
- Bailey DA, Wedge JH, McCulloch RG, Martin AD, Bernhardtson SC 1989 Epidemiology of fractures of the distal end of the radius in children as associated with growth. *J Bone Joint Surg Am* 71:1225–1231
- Fournier PE, Rizzoli R, Slosman DO, Theintz G, Bonjour JP 1997 Asynchrony between the rates of standing height gain and bone mass accumulation during puberty. *Osteoporos Int* 7:525–532
- McKay HA, Bailey DA, Mirwald RL, Davison KS, Faulkner RA 1998 Peak bone mineral accrual and age at menarche in adolescent girls: a 6-year longitudinal study. *J Pediatr* 133:682–687
- Faulkner RA, Davison KS, Bailey DA, Mirwald RL, Baxter-Jones AD 2006 Size-corrected BMD decreases during peak linear growth: implications for fracture incidence during adolescence. *J Bone Miner Res* 21:1864–1870
- Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R 2006 Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? *J Bone Miner Res* 21:501–507
- Kindblom JM, Lorentzon M, Norjavaara E, Hellqvist A, Nilsson S, Mellstr  m D, Ohlsson C 2006 Pubertal timing predicts previous fractures and BMD in young adult men: the GOOD study. *J Bone Miner Res* 21:790–795
- Chevalley T, Bonjour JP, Ferrari S, Hans D, Rizzoli R 2005 Skeletal site selectivity in the effects of calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys. *J Clin Endocrinol Metab* 90:3342–3349
- Fardellone P, Sebert JL, Bouraya M, Bonidan O, Leclercq G, Doutrelot C, Bellony R, Dubreuil A 1991 [Evaluation of the calcium content of diet by frequential self-questionnaire]. *Rev Rhum Mal Osteoartic* 58:99–103 (French)
- Morin P, Herrmann F, Ammann P, Uebelhart B, Rizzoli R 2005 A rapid self-administered food frequency questionnaire for the evaluation of dietary protein intake. *Clin Nutr* 24:768–774
- Boot AM, de Ridder MA, Pols HA, Krenning EP, de Muinck Keizer-Schrama SM 1997 Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity. *J Clin Endocrinol Metab* 82:57–62
- Ainsworth BE, Haskell WL, Leon AS, Jacobs Jr DR, Montoye HJ, Sallis JF, Paffenbarger Jr RS 1993 Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 25:71–80
- Boutroy S, Buxsein ML, Munoz F, Delmas PD 2005 In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 90:6508–6515
- Kirmani S, Christen D, van Lenthe GH, Fischer PR, Buxsein ML, McCready LK, Melton 3rd LJ, Riggs BL, Amin S, M  ller R, Khosla S 2009 Bone structure at the distal radius during adolescent growth. *J Bone Miner Res* 24:1033–1042
- MacNeil JA, Boyd SK 2007 Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys* 29:1096–1105
- Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Buxsein ML, Delmas PD 2008 Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res* 23:392–399
- Dalzell N, Kaptoge S, Morris N, Berthier A, Koller B, Braak L, van Rietbergen B, Reeve J 2009 Bone micro-architecture and determinants of strength in the radius and tibia: age-related changes in a population-based study of normal adults measured with high-resolution pQCT. *Osteoporos Int* 20:1683–1694
- Vilaythiou N, Boutroy S, Sornay-Rendu E, Van Rietbergen B, Munoz F, Delmas PD, Chapurlat R 2010 Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in postmenopausal women. *Bone* 46:1030–1037
- van Rietbergen B, Weinans H, Huiskes R, Odgaard A 1995 A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. *J Biomech* 28:69–81
- Pistoia W, van Rietbergen B, Lochm  ller EM, Lill CA, Eckstein F, R  egsegger P 2002 Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone* 30:842–848
- Chiu J, Robinovitch SN 1998 Prediction of upper extremity impact forces during falls on the outstretched hand. *J Biomech* 31:1169–1176
- Mueller TL, Christen D, Sandercott S, Boyd SK, van Rietbergen B, Eckstein F, Lochm  ller EM, M  ller R, van Lenthe GH 2011 Computational finite element bone mechanics accurately predicts mechanical competence in the human radius of an elderly population. *Bone* 48:1232–1238
- Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Barned NJ 1998 Bone mineral density in girls with forearm fractures. *J Bone Miner Res* 13:143–148
- Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ 2001 Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. *J Pediatr* 139:509–515
- Clark EM, Ness AR, Bishop NJ, Tobias JH 2006 Association between bone mass and fractures in children: a prospective cohort study. *J Bone Miner Res* 21:1489–1495
- Jones G, Ma D, Cameron F 2006 Bone density interpretation and relevance in Caucasian children aged 9–17 years of age: insights from a population-based fracture study. *J Clin Densitom* 9:202–209
- Jones G, Boon P 2008 Which bone mass measures discriminate adolescents who have fractured from those who have not? *Osteoporos Int* 19:251–255
- Flynn J, Foley S, Jones G 2007 Can BMD assessed by DXA at age 8 predict fracture risk in boys and girls during puberty? An eight-year prospective study. *J Bone Miner Res* 22:1463–1467
- Kalkwarf HJ, Laor T, Bean JA 2011 Fracture risk in children with a forearm injury is associated with volumetric bone density and cortical area (by peripheral QCT) and areal bone density (by DXA). *Osteoporos Int* 22:607–616
- Marshall D, Johnell O, Wedel H 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 312:1254–1259
- Cummings SR, Melton LJ 2002 Epidemiology and outcomes of osteoporotic fractures. *Lancet* 359:1761–1767

36. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A 2005 Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20:1185–1194
37. Goulding A, Jones IE, Taylor RW, Manning PJ, Williams SM 2000 More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. *J Bone Miner Res* 15:2011–2018
38. Clark EM, Tobias JH, Ness AR 2006 Association between bone density and fractures in children: a systematic review and meta-analysis. *Pediatrics* 117:e291–297
39. Darelid A, Ohlsson C, Rudäng R, Kindblom JM, Mellström D, Lorentzon M 2010 Trabecular volumetric bone mineral density is associated with previous fracture during childhood and adolescence in males: the GOOD study. *J Bone Miner Res* 25:537–544
40. Wang Q, Wang XF, Iuliano-Burns S, Ghasem-Zadeh A, Zebaze R, Seeman E 2010 Rapid growth produces transient cortical weakness: a risk factor for metaphyseal fractures during puberty. *J Bone Miner Res* 25:1521–1526
41. Clark EM, Ness AR, Tobias JH 2008 Bone fragility contributes to the risk of fracture in children, even after moderate and severe trauma. *J Bone Miner Res* 23:173–179
42. Bonjour JP, Chevalley T, Rizzoli R, Ferrari S 2007 Gene-environment interactions in the skeletal response to nutrition and exercise during growth. *Med Sport Sci* 51:64–80