Fracture history of healthy premenopausal women is associated with a reduction of cortical microstructural components at the distal radius

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A B S T R A C T

Objectives: The objective of this study is to determine in healthy premenopausal women with a history of fracture which bone structural components of the distal radius are the most closely associated with a risk of fracture.

Methods and participants: The method was as follows: measurement of radial areal bone mineral density (aBMD) by DXA, microstructural components by high-resolution quantitative peripheral computerized tomography (HR-pQCT) and strength variables by micro Finite Element Analysis (μFEA) in 196 healthy premenopausal women aged 45.9 ± 3.7 (±SD) years with (FX, n = 96) and without (NO-FX, n = 100) a history of fracture. We evaluated differences in T-scores between FX and NO-FX and risk of fracture by Odds ratios (OR with 95% confidence intervals, CI) per one SD decrease, using logistic regression analysis after adjustment for age, height, weight, menarcheal age, calcium and protein intakes, and physical activity.

Results: In the whole group the mean radial metaphysis aBMD T-score was not significantly different from zero. In the FX as compared to the NO-FX group, the differences in T-scores were as follows: for radial metaphysis: aBMD, −0.24 (P = 0.005); for distal radius microstructure components: cortical volumetric BMD, −0.38 (P = 0.0009); cortical thickness, −0.37 (P = 0.0001); cross-sectional area (CSA), +0.24 (P = 0.034); and endosteal perimeter, +0.28 (P = 0.032); and for strength estimates: stiffness, −0.15 (P = 0.030); failure load, −0.14 (P = 0.044); and apparent modulus, −0.28 (P = 0.006). T-scores of trabecular volumetric BMD and thickness did not significantly differ between the FX and the NO-FX group. Accordingly, the risk of fracture (OR, 95% CI) for 1 SD decrease in radius bone parameters was as follows: radial metaphysis aBMD: 1.70 (1.18–2.44), P = 0.004; cortical volumetric BMD: 1.86 (1.28–2.71), P = 0.001; and cortical thickness: 2.36 (1.53–3.63), P = 0.0001. The corresponding fracture risk for the strength estimates was as follows: stiffness: 1.66 (1.06–2.61), P = 0.028; failure load: 1.59 (1.02–2.47), P = 0.041; and apparent modulus: 1.76 (1.17–2.64), P = 0.006.

Conclusions: In healthy premenopausal women, a history of fracture is associated with reduced T-scores in the distal radius, with the cortical components showing the greatest deficit. A reduction of one SD in cortical thickness is associated with a nearly three-fold increased risk of fracture. This finding strengthens the notion that, in healthy women, a certain degree of bone structural fragility contributes to fractures before the menopause and therefore should be taken into consideration in the individual prevention strategy of postmenopausal osteoporosis.

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Introduction

In postmenopausal women, low areal bone mineral density (aBMD) is a significant risk factor for fractures [1–4]. Likewise, it is established that low trauma fracture occurring after the menopause is a risk for further fragility fractures [5–8]. There is also evidence that, in women aged 65 years and older, fractures before menopause are independent risk factors for subsequent fractures after menopause [9]. This greater risk of about 30% of fracture after menopause is similar to a maternal history of about 30% of fracture after menopause is similar to a maternal history of fracture before menopause and therefore should be taken into consideration in the individual prevention strategy of postmenopausal osteoporosis.

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women with idiopathic osteoporosis [10–12]. Besides the pathological condition of premenopausal idiopathic osteoporosis, markedly reduced volumetric (v) BMD, as measured by peripheral quantitative computed tomography (pQCT) at the distal radius, is an important risk factor for low-energy or fragility fractures in premenopausal women [13]. In premenopausal women with fragility fracture, aBMD measured at the spine and proximal femur was markedly lower than that measured in postmenopausal women without a fracture history [13]. However, in healthy women without idiopathic osteoporosis, or substantially reduced vBMD due to secondary osteoporosis [14], whether a fracture history recorded before the menopause would be associated with subtle signs of defective bone integrity remains to be documented.

In the context of parent–offspring investigation we assessed several bone variables in healthy premenopausal women (mean age 46 years). These women were mothers of two cohorts of healthy girls [15,16] and boys [17,18] whose bone acquisition characteristics were studied over childhood and adolescence. Among them, about half had a history of fracture. In these healthy premenopausal women, we report which, among bone variables measured at the radial level by dual-energy X-ray absorptiometry (DXA), high-resolution peripheral quantitative computed tomography (HR-pQCT) and micro-finite element analysis (μFEA), differ in T-score and are significantly associated with an increased risk of fracture before the menopause.

Subjects and methods

Participants

Fracture history and bone mineral density, and cortical and trabecular microstructure including porosity as well as bone strength estimates assessed by HR-pQCT and μFEA, respectively, were studied in 196 healthy premenopausal women with a mean age of 45.9 ± 3.7 (mean ± SD) years. All subjects lived within the Geneva area. The persistence of regular menstruation at the time of examination was a prerequisite for inclusion in this study. The Ethics Committee of the University Hospitals of Geneva approved the protocol and written informed consent was obtained from the participants.

Clinical assessment

The participants were examined over a period of 1.5 years, from April 2006 to October 2007. Technical staff and instruments used for data acquisition did not change throughout the study. Weight, stadiometer measured standing height and body mass index (BMI, kg/m²) were determined in all subjects. Menarcheal age, as defined by the age of the first menstruation, was assessed retrospectively. Fracture history since birth was retrospectively self-reported, including skeletal site and year of event. After the age of 20 years, only low-trauma fractures defined as a fall from the standing height were recorded.

Calcium and protein intakes

Spontaneous calcium intake, essentially assessed from intake of dairy sources and protein intakes was estimated by frequency questionnaire [20]. It included organized sports, recreational activity and usual walking and cycling. Subsequently, the collected data were converted and expressed as physical activity energy expenditure (PAEE kcal/d) using established conversion formulas [21].

Measurement of bone variables

The aBMD was determined by DXA using a Hologic QDR 4500 instrument (Waltham, MA) at radial metaphysis and diaphysis in antero-posterior view as previously reported [22]. The coefficient of variation (CV, %) of repeated measurements at these sites, as determined in young healthy adults, varied from 1.0 to 1.6% for BMD.

Volumetric bone density and microstructure were determined at the distal radius by high resolution peripheral computerized tomography (HR-pQCT) with a XtremeCT instrument (Scanco medical AG®, Büttisellen, Switzerland) that acquires a stack of 110 parallel computerized tomography slices (9-mm length) with an isotropic voxel size of 82 μm as previously described [22,23]. Unless there was a history of fracture, DXA and HR-pQCT measurements were performed on the nondominant forearm. The following variables were measured: total, cortical and trabecular volumetric BMD bone densities expressed as milligrams hydroxyapatite (HA) per cubic centimeter, trabecular bone volume fraction (percent), trabecular number, thickness and spacing (micrometers), mean cortical thickness (micrometers) and cross-sectional area (square millimeters).

The HR-pQCT images were filtered and binarized using the standard manufacturer’s method [24]. The periosteal and endosteal boundaries were defined using an automated contouring method similar to the technique described previously by Buie and colleagues [25] as implemented in Image Processing Language (IPL V5.07, Scanco Medical). The automated segmentation used two threshold values and a series of morphologic operations (e.g., dilation and erosion operations) to extract the endosteal and periosteal surfaces of the cortex as well as the “apparent” cortical thickness after filling the pores, and was validated earlier [26,27]. Cortical porosity (Ct.Po, %) was calculated as the number of void voxels in each binary cortex image divided by the total number of voxels [27]. The in vivo short-term reproducibility of HR-pQCT at the distal radius assessed in 15 subjects with repositioning varied from 0.6 to 1.0% and from 2.8 to 4.9% for bone density and for trabecular structure, respectively. These reproducibility ranges are similar to those previously published [28]. 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

A finite element model of the radius was created directly from the segmented HR-pQCT images using a procedure similar to that used in earlier clinical studies [29–31]. In summary, a voxel-conversion procedure was used to convert each voxel of bone tissue into an equally sized brick element [32] thus creating micro-finite element (μFE) models that can represent the actual trabecular architecture in detail. The models contained approximately 2 million elements for the radius and could be solved in approximately 3 h. Material properties were chosen isotropic and elastic. Both cortical and trabecular bone elements were assigned a Young’s modulus of 10 GPa and a Poisson’s ratio of 0.3 [30,33]. A compression test was simulated to represent loading conditions during a fall from standing height [34]. Bone failure load was calculated as the force for which 2% of the bone tissue would be loaded beyond 0.7% strain [33,35]. In addition to failure load (N), μFE-derived variables used in our study also included stiffness (kilo–Newton per millimeter = kN/mm) and apparent modulus (N/mm²). This latter variable represents a measure of stiffness after correction for cross sectional area. All μFE analyses 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 ± SD. The differences in density, microstructure,
mechanical parameters and clinical characteristics among participants with or without a positive history of fracture were assessed by unpaired Student t-test or by Wilcoxon signed rank test whenever the variable was not normally distributed. For the differences in density, microstructural and mechanical parameters between fracture and non-fracture subjects, an analysis of covariance was used to control the influence of age, height, weight, menarcheal age, calcium and protein intakes, and physical activity. In order to test whether the deficits in cortical vBMD or in cortical thickness between the FX and NO-FX groups are greater than the deficit in metaphysis aBMD, we analyzed whether there was a significant interaction between the groups (FX and NO-FX) and the measured variables (cortical vBMD vs. metaphysis aBMD or cortical thickness vs. metaphysis aBMD) using two methods: A) a two way ANOVA with repeated measure design; and B) a mixed linear regression model.

The T-score values of radius aBMD by DXA and of microstructure and mechanical variables at the distal radius by HR-pQCT and µFEA were calculated from a homogenous cohort of healthy young adult women in their early twenties [36]. Associations between density, microstructure, mechanical parameters and fracture status were evaluated by logistic regression analysis with adjustment for age, height, weight, menarcheal age, calcium and protein intakes, and physical activity. They were expressed as Odds ratio (OR with 95% confidence interval) for a lower age-adjusted aBMD of 1 SD). The significance level for two-sided P-values was 0.05 for all tests. The data were analyzed using STATA software, version 9.2. (StataCorp LP, College Station, TX, USA).

Results

Fracture history

One hundred and forty-six fractures were reported by 49% of the 196 premenopausal women (Table 1). More than one fracture (2 to 5) was recorded in 34 of them, accounting for 84 fractures and 58% (84 of 146) of all fractures. Fractures occurred in 60 (62.5%) and 36 (37.5%) women up to and after 20 years of age, respectively. Fractures were localized in forearm/wrist (19.2%), hand/fingers (13%), arm/shoulder (10.3%), lower limb (29.5%) and 28.1% at other sites. Anthropometric, nutritional and physical activity did not significantly differ between women who fractured up to or later than 20 years of age (data not shown). Likewise, there was no significant difference between these two subgroups of fractured women for all measured bone variables adjusted or not for chronological and menarcheal age, height and weight, calcium and protein intakes and physical activity (data not shown).

Participants’ characteristics

Anthropometric data and reproductive life hallmarks did not differ between women with (FX) and those without (NO-FX) a history of fracture (Table 1). Likewise, dietary intakes of calcium and protein were very similar in the two groups (Table 1). The daily energy expenditure resulting from physical activity was ~18% higher in the FX than in the NO-FX group, a difference at the limit of statistical significance (Table 1).

Bone variables

The aBMD T-score of the whole cohort in the radial metaphysis was not significantly different from zero (P = 0.418) (Table 2). It was about one quarter SD above zero for the radial diaphysis (P = 0.023) (Table 2). The simultaneously measured aBMD T-scores of the whole cohort (mean ± SD) were, in femoral neck: −0.48 ± 0.98 (P < 0.001); in total hip: −0.28 ± 1.07 (P = 0.018); and in L2–L4 vertebrae: −0.34 ± 1.17 (P = 0.006). Based on aBMD values used in the clinical unit dedicated to the diagnosis of osteoporosis at the University Hospital in Geneva [16], 14.6% were osteopenic and 85.4% had normal BMD at the radial metaphysis in the FX group. At the femoral neck, these percentages were 35.4% and 64.6%, respectively. In the FX group, as compared to the NO-FX group, a small but significant reduction in aBMD by about 2.5% was recorded in the radial metaphysis but not in the radial diaphysis (Table 2).

Among the microstructural components, total volumetric bone mineral density (vBMD) was significantly lower in the FX than in the NO-FX group (Table 2). This reduced vBMD was essentially due to a thinner cortex (−7.2%) as well as “apparent” (−7.0%) cortical thickness and, to a smaller extent, to a lower cortical density (−1.9%) (Table 2). By a two way ANOVA analysis as well as a mixed linear regression model, the deficits in the FX group, as compared to the NO-FX group, were greater in cortical vBMD (P = 0.004 and P = 0.003, respectively) and cortical thickness (P = 0.030 and P = 0.005, respectively) than the deficits in radial metaphysis aBMD. In contrast, there was no significant difference between the FX and NO-FX groups in the trabecular components: vBMD or BV/TV, Tb.N, Tb.Th, Tb.Sp and Tb.Sp SD (Table 2). The thinner cortex was associated with a significantly greater CSA and endosteal perimeter (Table 2). Cortical porosity was low and did not differ between the FX and NO-FX groups (Table 2). The strength estimates, stiffness (−2.9%), failure load (−2.6%) and apparent modulus (−6.0%) were significantly lower in the FX than in the NO-FX group (Table 2).

Whether the bone size (CSA) greater in the FX than in the NO-FX group could account for the statistically significant differences described above was also analyzed. After further adjustment to CSA, all bone variables (total vBMD, cortical vBMD, cortical thickness and “apparent” cortical thickness, cortical area, trabecular area, stiffness, estimated failure load and apparent modulus) remained significantly lower in the FX group as compared to those in the NO-FX group, with the exception of the endosteal perimeter (Table 2). The possibility that the differences in cortical microstructural components between the FX and NO-FX groups might entirely depend on the difference in radial metaphysis aBMD was analyzed too. After adjustment to usual confounding factors and further adjustment to radial metaphysis aBMD, the deficits in cortical vBMD (P = 0.035) and cortical thickness (P = 0.003) remained significant in premenopausal women with a fracture history.

Forearm fractures were recorded in 26 out of the 96 women with a fracture history. In this subgroup, cortical vBMD (P = 0.019) and cortical thickness (P = 0.014) were also significantly lower in the FX as compared to the NO-FX group. After further adjustment to CSA, cortical

Table 1
Characteristics of healthy middle-aged premenopausal women according to their fracture history.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 196)</th>
<th>NO-FX (n = 100)</th>
<th>FX (n = 96)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.9 ± 3.7</td>
<td>45.9 ± 3.7</td>
<td>46.0 ± 3.7</td>
<td>0.850</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.6 ± 6.1</td>
<td>164.8 ± 6.4</td>
<td>164.6 ± 5.9</td>
<td>0.851</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.6 ± 11.8</td>
<td>64.5 ± 10.3</td>
<td>66.8 ± 13.1</td>
<td>0.422</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2 ± 4.2</td>
<td>23.8 ± 3.6</td>
<td>24.7 ± 4.7</td>
<td>0.218</td>
</tr>
<tr>
<td>Menarcheal age (years)</td>
<td>13.2 ± 1.6</td>
<td>13.4 ± 1.5</td>
<td>13.0 ± 1.8</td>
<td>0.198</td>
</tr>
<tr>
<td>Pregnancies (n)*</td>
<td>2.98 ± 1.23</td>
<td>2.96 ± 1.12</td>
<td>3.01 ± 1.33</td>
<td>0.774</td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>869 ± 408</td>
<td>846 ± 442</td>
<td>892 ± 369</td>
<td>0.153</td>
</tr>
<tr>
<td>Protein intake (g/d)</td>
<td>48.0 ± 16.6</td>
<td>48.0 ± 18.4</td>
<td>48.0 ± 14.6</td>
<td>0.409</td>
</tr>
<tr>
<td>Protein intake (g/kg BW·d⁻¹)</td>
<td>0.75 ± 0.28</td>
<td>0.76 ± 0.32</td>
<td>0.74 ± 0.23</td>
<td>0.981</td>
</tr>
<tr>
<td>Physical activity (kcal/d)</td>
<td>329 ± 195</td>
<td>302 ± 174</td>
<td>356 ± 212</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Values are means ± SD.

* P difference between women with (FX) and without (NO-FX) fracture.

# The corresponding number of life birth pregnancies was in all: 2.38 ± 0.73. In NO-FX 2.38 ± 0.79 and FX 2.39 ± 0.67, P = 0.959.
thickness remained significantly lower ($P = 0.042$) and cortical vBMD was at the limit of significance ($P = 0.060$).

The significant differences in the T-score bone variables between the FX and NO-FX groups are illustrated in Fig. 1. The highest likelihood of fracture was associated with one standard deviation drop in cortical thickness (Odds ratio: 2.36, 95% CI 1.53–3.63) (Fig. 2). This probability was somewhat smaller for radial metaphysis aBMD and cortical vBMD (Fig. 2). In contrast, the trabecular variables of the distal radius were not significantly associated with the risk of fracture (Fig. 2). A drop of one standard deviation in the apparent modulus was the strength estimate most closely associated with an increased fracture risk (Fig. 2).

### Table 2

<table>
<thead>
<tr>
<th>Areal BMD, microstructure, porosity and FEA of the distal radius in 196 middle-aged premenopausal women according to their fracture history.</th>
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<tr>
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<td>---------------------------------</td>
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<tr>
<td>aBMD (mg/cm²)</td>
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<tr>
<td>Radial metaphysis</td>
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<tr>
<td>Radial diaphysis</td>
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<tr>
<td>vBMD (mg HA/cm³)</td>
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<tr>
<td>Total</td>
</tr>
<tr>
<td>Cortical</td>
</tr>
<tr>
<td>Trabecular</td>
</tr>
<tr>
<td>BV/TV (%)</td>
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<tr>
<td>Tb.N (mm⁻¹)</td>
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<tr>
<td>Tb.Th (μm)</td>
</tr>
<tr>
<td>Tb.Sp (μm)</td>
</tr>
<tr>
<td>Tb.Sp SD (μm)</td>
</tr>
<tr>
<td>Ct.Th (μm)</td>
</tr>
<tr>
<td>Apparent Ct.Th (μm)</td>
</tr>
<tr>
<td>CSA (mm²)</td>
</tr>
<tr>
<td>Cortical area (mm²)</td>
</tr>
<tr>
<td>Trabecular area (mm²)</td>
</tr>
<tr>
<td>Cortical porosity (%)</td>
</tr>
<tr>
<td>Endosteal perimeter (mm)</td>
</tr>
<tr>
<td>Periosteal perimeter (mm)</td>
</tr>
<tr>
<td>Stiffness (kN/mm)</td>
</tr>
<tr>
<td>Estimated failure load (N)</td>
</tr>
<tr>
<td>Apparent modulus (N/mm²)</td>
</tr>
</tbody>
</table>

Values are means ± SD. NA: not available. BV/TV, trabecular bone volume fraction; Tb.N, trabecular number; Tb.Sp, trabecular spacing; Tb.Th, trabecular thickness; Ct.Th, cortical thickness; CSA, cross sectional area.

- $P$ difference between women with (FX) and without (NO-FX) fracture.
- Bold values indicate significance at $p < 0.05$.
- * $P$ after adjustment to age, menarcheal age, height, weight, calcium and protein intakes, and physical activity.
- # $P$ after adjustment to age, menarcheal age, height, weight, calcium and protein intakes, physical activity and CSA.

Fig. 1. Difference in bone variable T-scores between healthy premenopausal women with (FX) and without (NO-FX) a history of fracture. The absolute differences and the probability ($P$) of statistical significance are indicated within each and above each column, respectively. These differences were adjusted for age, menarcheal age, height, weight, calcium and protein intakes, and physical activity. The corresponding absolute values for each group are given in Table 2.
for all fractures [37]. Note that this meta-analysis published about 16 years ago remains the key reference for the World Health Organization [38] regarding the performance of bone mineral measurement for assessing the risk of fracture. The similar magnitude of the risk of fracture observed at the distal radius may have contributed to weaker bones in the mid-forty cohort of women reported in our cohort of premenopausal women with a history of fracture, the reduced cortical thickness observed at the distal radius may have contributed to weaker bones despite a larger cross sectional area which is likely a compensatory response to either less endocortical deposition in adolescent girls with later menarche [16] and increased endocortical resorption with aging [42].

Discussion

Relation between bone deficit and fracture risk

Our study shows that fractures occurring before the menopause in healthy middle-aged women are associated with alterations in several bone variables measurable at the distal radius. As calculated from the radial metaphysis aBMD, the increased risk of fractures (OR: 1.7, 95% CI 1.18–2.44) is very close to that obtained in postmenopausal women in the important meta-analysis including eleven separate populations with about 90,000 person years of observation time and over 2000 fractures by Marshall et al. [37]. For measurement at the level of the distal radius, the relative risk (OR, 95% CI) for a lower age-adjusted mean aBMD of 1 SD was 1.7 (1.4–2.0) for forearm fractures and 1.4 (1.3–1.6) for all fractures [37]. Note that this meta-analysis published about 16 years ago remains the key reference for the World Health Organization [38] regarding the performance of bone mineral measurement for assessing the risk of fracture. The similar magnitude of the risk of fracture between the classical study by Marshall et al. [37] in postmenopausal women and our results strongly suggests that fracture before the menopause should potentially be flagged for osteoporosis prevention at the time of menopause. The ability of a technique to predict fracture is traditionally expressed as the increase in relative risk per standard deviation unit decrease in the selected bone measurement [38]. This gradient of risk appears to be similar when measuring distal forearm BMD in healthy premenopausal and in postmenopausal women. Furthermore, the possibility that a fracture occurring during childhood and adolescence [15,36], and now also during the third to the fifth decade, could be a marker of bone fragility in postmenopausal life as previously proposed [9], is corroborated by the results above described.

Bone component contributing to the risk of fracture

The greatest deficit and therefore highest risk was for cortical thickness followed by cortical volumetric mineral density. The reduced cortical thickness of the distal radius was associated with higher risk of fracture not only in the forearm and wrist but also in other sites such as upper arm and shoulder and also in lower limbs. This is in keeping with studies showing that microstructural and strength alterations detected by HR-pQCT and μFEA in the distal radius were associated with higher risk of all types of fragility fractures in both postmenopausal women [31,39,40] and men [41]. In our cohort of premenopausal women with a history of fracture, the reduced cortical thickness observed at the distal radius may have contributed to weaker bones despite a larger cross sectional area which is likely a compensatory response to either less endocortical deposition in adolescent girls with later menarche [16] and increased endocortical resorption with aging [42].

Origin of the fracture-associated distal radius deficits measured in premenopausal women

About two thirds of the recorded fractures occurred ≤20 years of age. This suggests that for a substantial number of fractures, the deficit was already present during bone development. In a recent study we have documented that in healthy young adult women (mean age: 20.4 years), fractures occurring during childhood and adolescence were also associated with alterations in some distal radius variables [36]. However, the microstructural characteristics associated with the higher fracture risk differed from those reported here in healthy premenopausal women (mean age: 45.9 years). In the cohort in their early twenties [36], the higher risk of prior fractures was rather associated with a deficit in the trabecular [36] than in the cortical compartment as reported here in the mid-forty women cohort. Despite this difference in the affected bone compartment of the distal radius, the excess risk of fracture for 1 SD drop in the μFEA-estimated strength variables – stiffness, failure load and apparent modulus – was of similar magnitude, varying from 1.79 to 2.02 in women in their early twenties [36], and from 1.59 to 1.76 in the mid-forty cohort of women reported in the foregoing analysis. The reason why the structural deficit involved more cortical than trabecular components in the midforty than in women in their early twenties with a history of fracture can only be a matter of speculation. The HR-pQCT slices proximal to the endplate of the distal radius selected in order to define the measured volume of...
interest might not have been localized at the same site. Related to this possibility, the proportion of load carried by the cortical versus the trabecular bone might change from the early twenties to the mid-fourties, and thus might shift the fracture risk from one to the other compartment. Furthermore, the use of a new method of segmentation for quantifying porosity [43] might reveal a subtle difference in cortical porosity between premenopausal women with or without a history of fracture.

Strengths of the study

The two groups of participants with and without a history of fracture were very homogenous in terms of demographic, reproductive life and nutritional variables. Their bone measurements were not made in relation with knowledge of a fracture history. Therefore, the subjects of this study cannot be considered as having been recruited for a typical case-control study, but rather as a randomized sample of healthy women with and without a fracture history.

Limitations

Fractures were not prospectively recorded, and based on self-questionnaire. There was a trend to higher physical activity which might have increased the number of participants included in the fracture group. Nevertheless, the significance of the difference in the bone variables and fractures risk was not attenuated after adjustment by the degree of physical activity. Our study cannot ascertain whether the deficits observed were already present by the end of the growth period and thus resulted essentially from a lower peak bone mass, even in those women whose fractures occurred after twenty years of age. Alternatively, we cannot rule out that some metabolic disturbance, acquired after the attainment of peak bone mass, would have been causally related to the greater bone cortical fragility measured in the fracture group. However, a vitamin D insufficiency severe enough to induce secondary hyperparathyroidism and cortical thinning appears to be unlikely in these healthy premenopausal, physically active and in good nutritional state women.

Conclusions

This study shows that, at the distal radius, a history of fracture in healthy premenopausal women is associated with a significantly lower T-score with a predominant deficit in the cortical components. A reduction of one standard deviation in the distal radius cortical thickness nearly triples the risk of fracture occurring before the menopause. This finding strengthens the notion that in healthy women a subtle degree of bone structural fragility contributes to premenopausal fractures and therefore should be taken into consideration in the individual prevention strategy of postmenopausal osteoporosis.

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