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Atypical fractures do not have a thicker cortex

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Disclosure

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PA has a patent on a process for coating metal implants with bisphosphonates, and shares in a company (Addbio AB) trying to commercialize the principle. PA also has received consulting reimbursement and grants from Eli Lilly & Co.

VK and JS have no conflict of interest to declare.

Mini-abstract

An association between atypical fractures and general cortical thickness of the femoral shaft is often suggested in the literature. Our radiographic measurements of 59 atypical and 218 ordinary fractures now exclude a difference larger than 10 % in mean femoral cortical thickness (sum of lateral and medial) with 95% confidence.

Abstract

Purpose

An increased general cortical thickness in patients with fatigue fracture of the femoral shaft (atypical fractures) is commonly suggested. However, there is scarce data to support this.

Methods

In a published nationwide Swedish study, we identified by radiographic review 59 women with an atypical fracture during 2008. The femoral cortical thickness index (thickness / femoral diameter) of these women was now compared with the 218 ordinary fractures that occurred in the same region of the femur in a case - control design. The cortical thickness index 5 cm below the lesser trochanter was the primary variable.

Results

Patients with atypical fractures were younger. Without correction for age, they had a thicker cortex (i.e. higher index). However, the difference in cortical thickness disappeared after age correction. The 95% CI excludes a group mean difference exceeding 10% of total mean thickness. Similarly, there was no significant difference in cortical thickness between patients with or without bisphosphonate treatment, or between the ipsi- and contralateral femurs in patients with an atypical fracture.

Conclusion

The concept of a generally increased cortical thickness in patients with atypical fractures needs further assesment.

Keywords: Fractures, stress / bisphosphonates / osteoporosis / femoral fracture

Introduction

Fatigue fractures of the femoral shaft, so called atypical fractures, are strongly associated with bisphosphonates[1], yet they are uncommon..A search for other contributing risk factors is, therefore, warranted. As these patients are generally younger[2] than others with subtrochanteric or femoral shaft fractures, and because the fracture is related to material fatigue, a high physical activity could be an important predisposing factor. Unknown genetic factors might also play an important role. It has been suggested that patients with atypical fractures have a thicker cortex than others[1,3,4]. A thick cortex is here regarded as a general phenomenon, and should not be mixed up with focal thickening at the fracture. Focal thickening appears to be a periosteal or endosteal callus reaction, developing around the undisplaced fatigue crack before it becomes a complete fracture.

A thicker cortex should be expected to reduce the fracture risk[5]. If it is correct that patients with atypical fractures have a thicker cortex than others, a thick cortex could signal some kind of material deficit due to genetic or other predisposition. It would consequently be an important marker for an increased risk of atypical fracture. Another possibility would be that a thicker cortex is just an effect of bisphosphonate use. In either case, if a thick cortex is associated with an increased risk of atypical fracture, it could be a relative counter-indication for starting or continuing bisphosphonate use.

The cortical thickness of the femur decreases with age[5,6]. It is therefore necessary to have a sufficiently large patient material to allow correction for this confounding factor. Our previously published material of 277 femoral shaft fractures, from a nation-wide population-based study[7], seemed to enable this. We now tested the hypothesis that patients with atypical fractures have a thicker cortex than patients with other types of subtrochanteric or femoral shaft fractures, by re-evaluating the radiographs of this previous study.

Material and Methods

Study population

We measured the cortical thickness on radiographs, which were obtained for a previously published nationwide population-based study of atypical fractures. In that study, we investigated the radiographs of all 1234 women over 55 years of age in Sweden, who were registered as having sustained a femoral shaft fracture in the year 2008. We also obtained data from the National Swedish patient Register on the patients' drug use and comorbidities. Patients with high energy trauma were excluded. Of the 1234 radiographically reviewed cases, 277 met the criteria for inclusion, i.e. shaft fractures without major trochanteric involvement, implants or other skeletal pathology. 59 of these fractures were classified as atypical fractures in the previous study[7], where they were defined as fractures with a rather transverse orientation at the lateral cortex (fracture angle close to 90 degrees). 48 of them had focal thickening of the lateral cortex at the fracture site, and a few had a separate intermediate fragment. General cortical thickening was not used as a criterion to discern whether the fracture was atypical or not..

Measurements

In the present study, we measured the cortical thickness on the radiographs of these 59 atypical fractures and the remaining 218 patients with other types of femoral subtrochanteric or shaft fractures. All measurements were undertaken by VK, blinded for any patient information, including medical background, drug history and former classification. Measurements were conducted on plain antero-posterior radiographs of the pelvis, hip or femur. In a few cases, because of outward rotation, the lateral radiographs were used because they gave a better frontal projection of the femur.

Measuring was carried out with the Sectra Workstation IDS7, Version 14.1.0.503, using the digital toolbox of this PACS software. We measured cortical thickness 5 and 10 cm below to the most prominent tip of the lesser trochanter. Cortical thickness was obtained by subtracting the medullary diameter from the shaft diameter .

First, two lines were drawn perpendicular to the femoral shaft axis 5 and 10 cm below the most prominent tip of the lesser trochanter. Along those lines we measured the width of the femoral shaft and the medullary cavity (Online Resource 1), the difference between these two being the cortical thickness. The ratio between cortical thickness and outer shaft diameter forms the cortical thickness index[8]. This unit-less index accounts for differences in radiographic magnification[1] and varying femoral size. A high index reflects greater cortical thickness and vice versa.

Apart from the periosteal, beak-like callus formation near an atypical fracture, sometimes also an endosteal callus can be seen, typically extending several centimeters from the fracture. Measurements were made only on those levels (5 or 10 cm below the lesser trochanter) where such callus was absent.

When measurement on the fractured femur was not possible, values were substituted with measurements from the contralateral femur, when available. Of the total 277 patients, there were 140 patients (4 atypical) in whom cortical thickness could not be measured on the fractured femur at 5 cm, mainly due to fracture characteristics, such as comminution. Of these 140 patients with missing ipsilateral data, 70 (no atypical) had contralateral values available (Table 1).

After these substitutions, 53 fractures remained (1 atypical) which could not be used in the analysis for any level. These were mainly cases with long spiral or comminuted fractures engaging both measuring levels, or cases with inappropriate projections or poor image quality. The number of appropriate measurements obtained at the different levels was 207 at 5 cm and 188 at 10 cm.

Statistical analysis

We used ANCOVA, with cortical thickness as dependent variable, atypical fracture or bisphosphonate use as independent variable and age as covariate. The measuring site with the highest number of appropriate measurements (5 cm) was used as the primary variable. The statistics program was IBM SPSS Statistics 19.

Results

Cortical thickness index of the fractured femur 5 cm below the lesser trochanter, decreased with age (r^2 0.17; p 0.000). Patients with atypical fractures were younger (75 SD 10 years, versus 84 SD 9). Without correction for age, patients with atypical fractures appeared to have a higher cortical thickness index (0.41 SD 0.09, versus 0.37 SD 0.08; p 0.003). However, after age correction the difference in cortical thickness index became statistically insignificant (95% CI -0.01 to $+0.04$; Table 1). Values for 10 cm were similar (95% CI -0.002 to $+0.07$). Patients using bisphosphonates had a higher cortical thickness index at 5 cm before (p 0.000), but not after age correction (95% CI -0.02 to $+0.03$).

In order to exclude that patients that were unfit for ipsilateral measurement had generally thinner cortices, we analyzed their contralateral values and compared them with data from patients ($n = 82$) who had both ipsi- and contralateral values available. With age correction there was no significant difference (95% CI -0.03 to $+0.02$), suggesting that substitution with contralateral measurements did not cause bias.

For the atypical fractures, a side comparison at 5 cm (by paired t-test) was possible in 29 patients. There was no significant difference (95% CI -0.006 to $+0.04$).

The mean cortical thickness at 5 cm was 13 mm, corresponding to a cortical thickness index of 0.38. The confidence limit of 0.04 (more exactly 0.039) for the difference in index between atypical and ordinary fractures (see above) therefore corresponds to approximately $0.039 \cdot 13 / 0.38 = 1.3$ mm, i.e. a 10% difference between the groups can be excluded.

Discussion

Our results show no association between atypical fractures and general cortical thickness of the femoral shaft, although an analysis without age-correction erroneously gives such an impression. The 95% confidence interval excludes that the medial and lateral cortex together are more than 1.3mm (10%) thicker than controls at 5 cm below the lesser trochanter. This is a small difference, considering the variation in cortical thickness in the population (Fig. 1). At 10 cm the confidence interval is wider, but still excludes a substantial difference between the groups.

The term cortical thickening sometimes refers to focal cortical thickening, caused by the callus reaction at the site of a fatigue fracture, and sometimes to a general cortical thickness of the diaphyseal femoral shaft, seen as reflecting a premorbid condition. Unfortunately, the distinction between these two is often unclear in the literature. This paper only refers to the latter definition, i. e. general cortical thickness.

There are two hypotheses often mentioned regarding cortical thickness in the context of atypical fractures. First, that it is caused by bisphosphonates. This hypothesis has no support in our data, and has been refuted previously[6,9]. Secondly, that increased cortical thickness is a risk factor for atypical fracture[3,4]. This is an interesting thought, because if an independent risk factor could be identified, it could alter indications for bisphosphonate use. Moreover, it could have a bearing on the pathophysiology of atypical fractures. However, our data do not support this hypothesis, since a substantial difference was excluded.

Several case reports[10,11] about atypical fractures have mentioned that the cortices seem generally thick, nourishing the concern that an increased cortical thickness might be a risk factor. Atypical fractures have been defined as “simple with thick cortices” according to Lenart et al.[1], who found that patients on bisphosphonates with atypical fractures were younger and seemed to have thicker cortices. However, the authors did not connect cortical thickness with age, and it is unclear if they refer to focal or general thickening.

Although most authors only report their visual impression, Giusti et al. [6] actually measured cortical thickness. At 5 cm below the lesser trochanter, they found a significantly higher cortical thickness index in 10 atypical fractures (mean value of 0.49) compared to 53 controls (0.39). Their atypical fractures had thicker cortices than ours. This difference is hard to explain, but a thick cortex might have been part of their definition of atypical fracture (“fracture in an area of thickened cortices”), or they inadvertently included an endosteal callus in the measurement. Sometimes an endosteal callus reaction can extend several cm from an atypical fracture. In our study, this was avoided by measuring at another level when necessary.

A prospective multicenter cohort study[5] showed that women with thicker cortices were at a lower risk of suffering from any kind of fracture of the femur, including subtrochanteric or shaft fractures. It makes sense that thicker cortices are less likely to fracture.

A comprehensive review on atypical femoral fractures by the American Society for Bone and Mineral Research[3] summarized the features of those fractures in a chart with 5 major and 7 minor criteria. Increased general cortical thickening is one of those minor criteria. Our results suggest that this minor criterion should be reassessed.

The strength of the present study is mainly the fact that it is based on the entire Swedish population, which excludes selection bias, and that the material is sufficiently large to produce narrow confidence intervals for the difference between atypical and ordinary fractures. Another advantage is that we compared cases which all had subtrochanteric femoral fractures. A comparison of atypical fracture cases with controls without fractures, or with hip fractures, could have been prone to selection bias. A further strength is the bilateral measurements at two different levels of the femur with consistent findings. The weaknesses include that the radiographs of 19 % of the patients did not permit measurement on any level of the fractured side. Almost all these immeasurable cases belonged to the non-atypical group, and many of them had long, spiral fractures. However, the cortical thickness of the contralateral side of these cases was not different from the measurable ones, suggesting that the immeasurable cases did not cause bias due to a thinner cortex. A further weakness is that only women were studied, which does not take gender differences in cortical thickness into account. Finally, we did not differentiate between the medial and lateral cortices, as we regarded the sum of their thickness as the best measure of cortex thickness in general.

The absence of a substantial difference in cortical thickness between atypical and ordinary fractures suggests that we have to reconsider the idea that, an increased general cortical thickness indicates the presence of unknown factors, increasing the susceptibility for atypical fractures.

Table**Table 1** Differences in cortical thickness index between atypical fractures and controls, after age correction

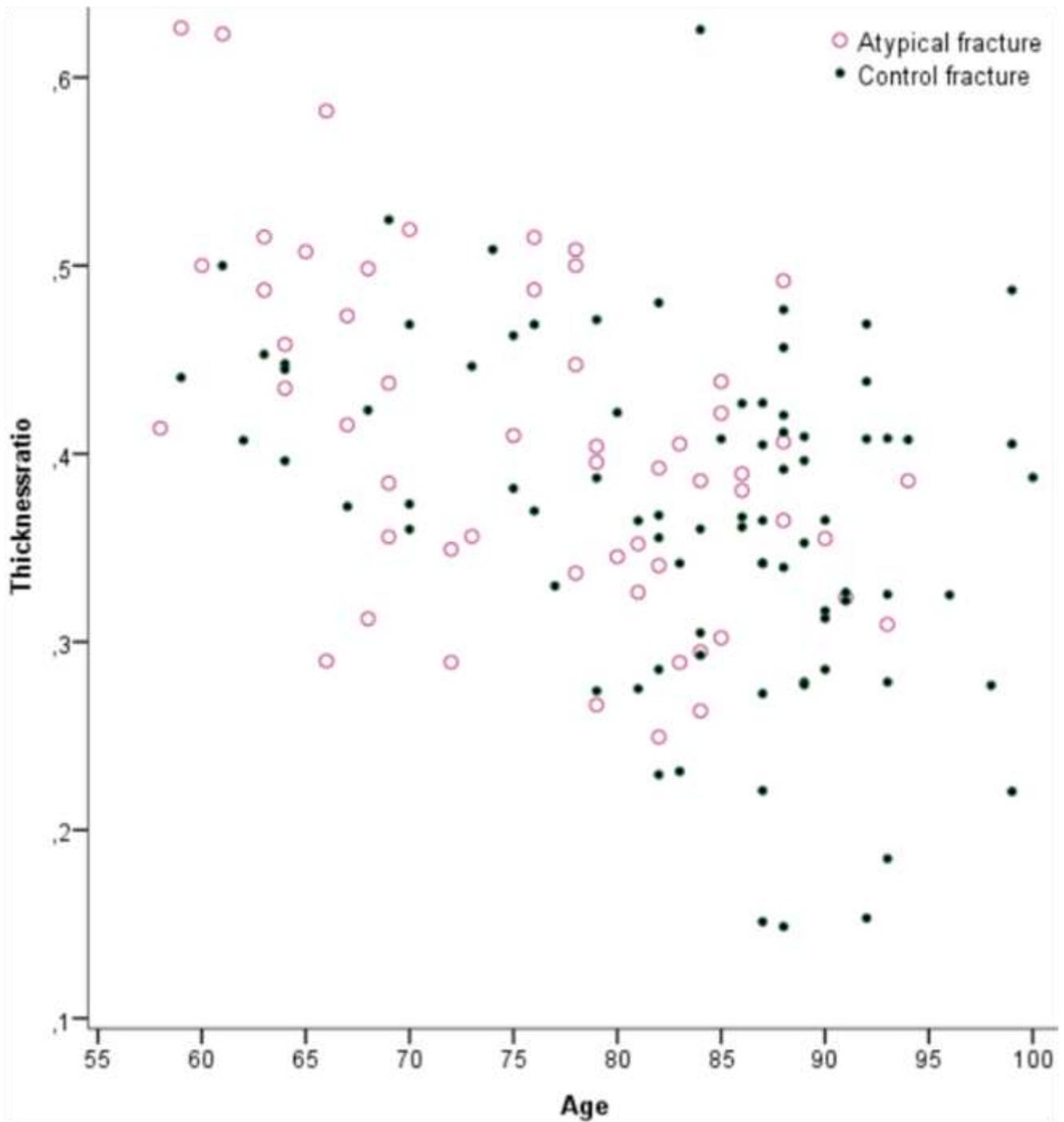
	Total	Atypical Fractures			Control Fractures			Difference			
	n	n	Mean	SE	n	Mean	SE	Mean	Sig.	CI low	CI high
<i>5cm</i>											
combined ¹	207	55	.39	.011	152	.37	.011	.014	.291	-.012	.039
ipsilateral	137	55	.39	.011	82	.38	.009	.010	.520	-.020	.040
<i>10cm</i>											
combined ¹	188	55	.46	.014	133	.43	.009	.032	.067	-.002	.066
ipsilateral	148	52	.46	.014	96	.44	.010	.021	.233	-.014	.055

¹ i.e. lacking ipsilateral values substituted with contralateral measurements.

Figure

Fig. 1 Correlation of cortical thickness ratio with age in atypical and control fractures:

The scatter-plot shows a decrease in cortical thickness index with age. Atypical fractures tend to occur at a younger age.



Online Resource

ESP 1 Measurement of cortical thickness at 5cm. The fracture is considered atypical. The endosteal contour is often somewhat blurred, and the measuring point was chosen at the border of the compact bone, as seen in higher magnification.



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