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Dichotomous location of 160 atypical femoral fractures.

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Abstract

Background and purpose

The risk of atypical fracture of the femur is associated with bisphosphonate use. While characterizing atypical fractures from a previous nationwide study in radiographic detail, we had the impression that the fractures were located either in the subtrochanteric region, or in the shaft. We now tested if there is a dichotomy in this respect.

Patients and methods

The distance between the atypical fractures and the lesser trochanter was measured on plain radiographs from 129 of 160 patients with atypical fractures occurring 2008 - 2010. Analysis of the measured distances showed 2 clusters, which were then analyzed with regard to bisphosphonate use and age.

Results

The distribution of the distances was best described as 2 clusters with a dichotomy at 8 cm. The proximal (subtrochanteric) cluster comprised 25 patients who were younger (71 years) compared to the 104 shaft fractures (80 years). The difference between the medians had a 95\% CI of 4 to 11 years). Of the patients with subtrochanteric fractures, 18/25 used bisphosphonates versus 89/104 for the shaft fractures.

Interpretation

The younger age and possibly smaller proportion of bisphosphonate users in the subtrochanteric region could be compatible with a greater influence of mechanical stress in the underlying pathophysiology of the proximal fractures.
Atypical fractures of the femur are often described as mainly located in the subtrochanteric region (Shane et al. 2010). When analyzing the radiographic features of 160 atypical femoral fractures of a nationwide study, we got the impression that the proportion of shaft fractures has been underestimated. However, the unclear definition of what constitutes the subtrochanteric region made it difficult to classify the atypical femoral fractures according to their location. Hence, we decided to actually measure where the fracture was located along the shaft, i.e. the distance from the lesser trochanter. By doing so, we noted a somewhat dichotomous distribution of the measured values. We therefore investigated whether the observed distribution of the values would be best described as a combination of two separate Gaussian distributions. This appeared to be the case.

Because the distance from the lesser trochanter showed a dichotomous distribution, the question came up if the 2 subgroups are different also in other aspects. Consequently we analyzed if there was a difference in age and bisphosphonate use between the subgroups.
Patients and methods

Study population

In a previous publication based on all women above 55 years of age in Sweden in 2008, we identified 51 patients with atypical femoral fractures out of 1,234 women with fractures of the subtrochanteric region or shaft (Schilcher et al. 2011). We now used the same data collection method for 2009 and 2010. Briefly, 3115 women, 55 years or older, who had a femoral subtrochanteric or shaft fracture (ICD 10 diagnosis codes S722, S723 and M84.3F with external cause code W, i.e. excluding transport accidents) were identified from the National Swedish Patient Register. Digitized radiographs from 3064 of the 3114 women (98 %) were obtained from the involved hospitals. These radiographs were reviewed together with a re-analysis of the 2008 radiographs. The criteria for atypical fracture were a lateral fracture angle of approximately 90 ± 15 degrees, and a visible callus reaction on the initial radiographs (Schilcher et al. 2013). Because these criteria have been refined, the reanalysis of the material from 2008 yielded slightly fewer fractures than the original publication (Schilcher et al. 2011). Altogether 160 atypical fractures were identified from 2008, 2009 and 2010.

After completion of fracture classification, data on bisphosphonate use were identified from the Swedish Prescribed Drug Register. Complete linkage between the registers is possible through the use of the personal identity number provided to all Swedish citizens. A full analysis of the fracture risks and their relation to drug use, treatment duration, comorbidities etc. is ongoing and will be published later.

Permission for the study was obtained from the Regional Ethics Committee without individual patient consent.
**Radiographical measurements**

All radiographic measurements and classifications were made by VK, blinded for all background information, including drug treatment. Digital DICOM files of plain radiographs of the pelvis, hip, femur and knee were imported into the database of SECTRA IDS7 Workstation, Version 14.1.0.503 and 12.5.0.264. Measurements were performed using the digital toolbox of this PACS software.

A line perpendicular to the femoral shaft axis was drawn through the most prominent tip of the lesser trochanter. A parallel line was drawn where the fracture met the lateral cortex. The distance between those 2 parallels determined the distance of the fracture from the lesser trochanter (Figure 1).

**Statistics**

Frequency distribution of the measured distances was analyzed using the R program for statistical computing, version 2.15.2, together with the mclust software package for model-based clustering, classification, and density estimation (Fraley and Raftery 2002, Fraley at al. 2012). It uses the Bayesian information criterion (BIC) to choose the best description of the observed variable distribution in terms of a compilation of subgroups.

We then tested if there was a difference in age and bisphosphonate use between the 2 subgroups that emerged from the above analysis, using IBM SPSS Statistics 19. For analysis of age differences, we used Mann-Whitney U Test and Hodges-Lehman’s confidence intervals for differences between medians. For analysis of bisphosphonate use we applied Fisher’s exact test.
Results

Measurements could not be performed in 31 patients, because the fracture was not displayed on the same radiograph as the lesser trochanter, or because flexion of the proximal fragment made it impossible to clearly identify the lesser trochanter. Thus, measurements from 129 of the 160 (81 %) patients with atypical femoral fracture were analyzed.

The density distribution for the measured distances showed 2 peaks. The BIC identified an unequal variance model with two components as the best description of the observed data (Figure 2). The proximal subgroup was located at 41 (SD 17) mm and the distal at 187 (SD 39) mm. The region of uncertainty between the subgroups was narrow, with its center at 80 mm (Supplementary material 1). In our material, no fracture occurred in that region. Thus, it seems that fractures closer than 8 cm to the lesser trochanter and those further away belong to 2 distinct subgroups.

The subgroup with fractures in the proximal region comprised 25 patients, and the mid-shaft subgroup comprised 104 patients. Patients with proximal fractures had a median age of 71 years (interquartile range 64 to 79), while the patients with shaft fractures were 80 years (interquartile range 74 to 84). The age difference between the group medians was 7 years (95 % CI from 4 to 11).

Bisphosphonate medication was slightly more common in the patients with distal fractures: 18 out of the 25 patients with proximal fractures were bisphosphonate users (72%), while 86 of the 104 patients with shaft fractures (89%) were treated with a bisphosphonate (p = 0.3), (Supplementary material 2).
Discussion

We found a dichotomous distribution of the values for distance between atypical fractures and the lesser trochanter. The proximal fractures were fewer, somewhat less related to bisphosphonate use, and occurred in younger patients. These findings possibly suggest a greater influence of mechanical stress in the underlying pathophysiology of the proximal fractures.

The ASMBR task force report describes atypical fractures as most commonly located in the proximal third of the shaft (Shane et al. 2010). Our findings suggest a different location. A study of 44 patients in Singapore also describes a predominantly proximal location of the fractures, without an apparent dichotomy (Koh et al. 2011). The discrepancy between the latter study and our findings might be partly explained by the different criteria for defining atypical femoral fractures. They included fractures with a short oblique configuration, while we abide by a transverse fracture line (Schilcher et al. 2013). Moreover, there might be genetic differences between the mainly Caucasian population in Sweden and the predominantly Asian population in Singapore. Asians are thought to have more curved femora, which might lead to a different mechanical stress distribution.

Atypical femoral fractures occur laterally, where the bone is exposed to tensional stress (Polgár et al. 2003, van der Meulen and Boskey 2012). However, a dichotomous distribution of the fractures along the shaft does not correspond to the distribution of this tensile stress. According to the classical analysis by Koch (1917), the highest tensile stress is located in the lateral side of the subtrochanteric region and remains on a rather high level further down into the mid-shaft, where it rapidly decreases (Supplementary material 3). These historic computations are confirmed by modern finite element models which show a maximum tensile strain in the subtrochanteric region under static conditions (Polgár et al. 2003, Phillips 2009),
as well as during walking or stair climbing (Speirs et al. 2007). The distribution of tensile strain suggests that fractures could be expected to be more proximal when mechanical factors dominate in the pathogenesis. This could be related to the slightly weaker relation to bisphosphonate use and younger age in the proximal fractures.

Cortical thickness of the shaft decreases with age (Koeppen et al. 2012). This might be related to the higher age of the patients with distal fractures in our study.

The definition of “subtrochanteric” is problematic: There are at least 15 different classification methods for subtrochanteric femoral fractures in the literature (Loizou et al. 2010). The positive predictive value to identify a subtrochanteric or diaphyseal femoral fracture through the medical record coding may be as low as 36% (Spangler et al. 2011). According to the AO classification system, subtrochanteric fractures are a subcategory of diaphyseal fractures, occurring within 3 cm below the lesser trochanter (Müller et al. 1990). Nevertheless, in the literature, subtrochanteric fractures are often defined as occurring within 5 cm below the lesser trochanter. The dichotomy we found suggests that for atypical fractures there may be a natural border of some kind as far down as 8 cm.

Our study has several limitations. Our findings are observational, and can only hint at possible causative relations. It might be harder to identify an atypical femoral fracture in the subtrochanteric region than in the shaft. Because of the shape of the cortical contour, it becomes difficult to distinguish a small callus reaction there. Furthermore, when the proximal fragment is small, the hip is often flexed on the initial radiographs, making the typical appearance of atypical fractures less obvious. Therefore it is possible that the atypical femoral fractures of the subtrochanteric region are underrepresented. Our study is restricted to a female Caucasian population from a Nordic country. Also we did not assess the duration of
bisphosphonate therapy in the patients. The measurements were performed on non-calibrated plain radiographs, leading to decreased comparability among the cases and disregarding the complex three-dimensional architecture.

Due to the algorithm used to identify patients in the National Register, only the first femoral fracture occurring during 2008 – 2010 was studied. Thus, we lack information about bilateral fractures. On the other hand, this means that we avoid the statistical problem of having dependent data points.

In conclusion, atypical femoral fractures show a dichotomous distribution that might represent 2 different subgroups: atypical shaft fractures and the less common atypical subtrochanteric fractures. The differences in age and possibly bisphosphonate use imply that the subtrochanteric fractures might be more related to mechanical loading.
References


Figure 1 The distance was measured along the axis of the shaft, from where the fracture meets the lateral cortex to the most prominent tip of the lesser trochanter.

A) Fracture of the subtrochanteric region

B) Fracture of the shaft region
**Figure 2** Density plot of the distribution of atypical fractures along the shaft (thick grey line). The distribution can be best described as two separate Gaussian distributions. Each fracture is indicated as a vertical line above the distance axis.
Contribution of authors

VK contributed to the evaluation of radiographs, analysis, and interpretation of data, and drafting the article. JS contributed to collecting all radiographs and revising the article.
PA contributed to the interpretation of data, drafting and revising the article.

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Conflict of interest

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.

Supplementary material 1 – 3, see www.actaorthop.org, identification number 6660.
Supplementary material 1

The degree of uncertainty of group affiliation of atypical fractures along the shaft. Each fracture indicated as a vertical line above the distance axis.
Supplementary material 2

Scatter plot of the atypical femoral shaft fractures with reference to their distance from the lesser trochanter, patient age at fracture occurrence, and Bisphosphonate medication.
Supplementary material 3

Koch’s classical analysis of the distribution of stress along the shaft.

The highest tensile stress is located in the lateral side of the subtrochanteric region and remains on a rather high level further down into the mid-shaft, where it rapidly decreases.

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LAW OF BONE ARCHITECTURE

Fig. 18. Diagram illustrating the computed lines of maximum stress in the normal femur. The section numbers correspond to the sections indicated in figure 14 and succeeding figures. The amounts of the maximum tensile and compressive stress at the standing position (at attention) are to be multiplied by 1.6, and for running these stresses are to be multiplied by 2.2.