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Atypical fractures are mainly subtrochanteric in Singapore and diaphyseal in Sweden. A cross-sectional study

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Abstract
We have previously noted a dichotomy in the location of atypical fractures along the femoral shaft in Swedish patients, and a mainly subtrochanteric location of atypical fractures in descriptions of patients from Singapore. These unexpected differences were now investigated by testing the following hypotheses in a cross-sectional study: First, that there is a dichotomy also in Singapore. Second, that the relation between subtrochanteric and diaphyseal location is different between the two countries. Third, that the location is related to femoral bow. The previously published Swedish sample (n = 151) was re-measured, and a new Singaporean sample (n = 75) was established. Both samples were based on radiographic classification of all femoral fractures in women above 55 years of age. The distance between the fracture line and the lesser trochanter was measured. Femoral bow was classified as present or absent on frontal radiographs. Frequency distribution of the measured distances was analyzed using the Bayesian information criterion to choose the best description of the observed variable distribution in terms of a compilation of normally distributed subgroups. This analysis showed a clear dichotomy of the fracture location: either subtrochanteric or diaphyseal. Subtrochanteric fractures comprised 48 percent of all fractures in Singapore, and 17 percent in Sweden (p=0.0001). In Singapore, femoral bow was associated with more fractures in the diaphyseal subgroup (P=0.0001). This was not seen in Sweden. A dichotomous location of atypical fractures was confirmed, as it was found also in Singapore. The fractures showed a different localization pattern in the two countries. This difference may be linked to anatomical variations, but might also be related to cultural differences between the two populations that influence physical activity. Keywords: Osteoporosis, Biomechanics, Antiresorptives. Radiology. Injury/fracture healing.
Introduction
Atypical femoral fractures, although first described in 2005, are now a well-defined clinical entity of insufficiency fractures with a strong association to bisphosphonate use. Early descriptions reported mainly a subtrochanteric fracture location,\(^1,2\) but in recent years it has become clear that atypical fractures may be located in the diaphysis as well.\(^3\)\(^-\)\(^5\) Atypical fractures show radiographic and clinical signs of insufficiency fractures.\(^1,6,7\) The occurrence of these fractures, from the subtrochanteric region to the supracondylar portion of the femur, has been shown to be related to the region of increased tensile stress in the femur. Classical papers and modern biomechanical analyses show that the lateral cortex of the femur is exposed to high tensile stress during each step. This stress is dependent on the activity performed and the musculoskeletal architecture of the individual.\(^8\)\(^-\)\(^10\) Therefore, the location of each fracture is likely to be influenced by the location of stresses and strains in the individual's femur.

In a nation-wide sample of Caucasian women, we found a dichotomous distribution in the location of atypical fractures with the majority of fractures occurring in the diaphysis.\(^5\) We have no explanation for this phenomenon. Surprisingly, in a similar sample from Singapore the majority of atypical femoral fractures appeared to be located in the subtrochanteric region.\(^1\) It remains uncertain if a dichotomy occurs in all geographic regions.\(^8\) In terms of mechanical stress, these differences are counterintuitive. Asian women are thought to have a stronger lateral bow in the femur compared to Caucasian women,\(^11\) which intuitively would be associated with a more distal fracture location, as bowing should shift the stress in the lateral cortex distally.\(^12\)

In this investigation we have tested three hypotheses regarding fracture location. First, that the dichotomy in fracture location detected in Sweden also exists in patients from Singapore. Second, that the relation between subtrochanteric and diaphyseal location is different between the two countries. Third, that location is related to femoral bow.

Material and Methods
Databases from Singapore and Sweden
Femur diaphyseal fractures captured in the databases of the Singapore General Hospital and the Swedish National Patient Register were analyzed (Figure 1). In Singapore, consecutive cases were included from March 2003 to May 2014. In Sweden, patients 55 years or older from January 1\(^{st}\) 2008 through December 31\(^{st}\) 2010 were included. In 2008, only women were considered. The ethical review board consented to the study at both study locations (Singapore: 2006/012/D, Sweden: DNR 2011/358-31).

The patients in Singapore comprised 75 females (74 Chinese and 1 Malay) with a median age of 69 years (47-88 years, SD 9.7 years). The Swedish sample comprised 151 females with a median age of 78 years (58-94 years, SD 7.8) and 11 males, median age 69 years (62-88 years, SD 10.9). Information on bisphosphonate use in the subgroups is shown in Table 1. All patients from Sweden and some patients from the Singapore sample have been reported on previously.\(^13\)\(^-\)\(^15\)

Inclusion criteria
Atypical femur fractures were defined according to the revised major criteria of the American Society for Bone and Mineral Research Taskforce.\(^16\) All 5 major criteria were required for the definition of atypical fracture. All fractures in Singapore and Sweden were associated
with low energy trauma such as a fall from standing height or less and were located in the femoral shaft below the lesser trochanter and above the supracondylar flare. The radiographic pattern consisted of a transverse fracture line on the lateral side with a focal thickening at the fracture line (callus reaction) and no or minimal comminution. To cross-evaluate the classification into atypical fractures between the two sites, a randomly selected sample of 10 atypical femoral fractures and 10 ordinary shaft fractures from each site was re-evaluated by two readers from each site. Complete agreement was achieved among all readers.

Exclusion criteria
We excluded pathological fractures and those arising from metabolic disorders apart from osteoporosis and patients with any hardware in the femur prior to fracture. Male patients from the Swedish sample were also excluded, due to the exclusively female occurrence of atypical fractures in Singapore.

Ancillary data
In addition to demographic data, diabetes mellitus and the presence, type and duration of bisphosphonate use were recorded.

Radiological assessment
Digital DICOM files of plain radiographs of the hip, femur and knee were used to perform measurements using the respective PACS systems. No corrections for magnification were performed.

The lateral cortical fracture line was used as the reference point for fracture location.\[^{13,17}\] A best fit line was drawn along the periosteal surface of the lateral cortex of the proximal femur segment on a plain anteroposterior radiograph (ignoring the lateral cortical callus reaction). Perpendicular to the above, a line was drawn at the level of the most prominent point of the lesser trochanter and another at the level of the fracture. The distance between these 2 lines formed the main variable of this study (Figure 2A). The total length of the proximal segment was measured as above but from the tip of the greater trochanter to the fracture. The length of the distal segment was measured in a similar way. A best fit line was drawn along the periosteal surface of the lateral cortex of the distal femur segment on a plain anteroposterior radiograph. A perpendicular line was drawn at the roof of the inter-condylar notch and another perpendicular across the lateral cortical fracture line. The distance between these 2 lines was taken as the length of the distal femur segment (Figure 2B). Where severe rotational displacement precluded a proper assessment of proximal or distal segments on the anteroposterior radiograph, the lateral view of the distal segment was used. A best fit line was drawn along the periosteal surface of the anterior femur cortex. Perpendicular lines were drawn across the fracture site and the lowermost aspect of Blumensaat’s line, which corresponds to the roof of the inter-condylar notch. The distance between these two parallel lines was taken as the distal segment of the femur. The total femur length was derived by adding the total length of the proximal segment and the distal segment.

All radiographic measurements in Singapore were double-read and the average scores used. The Swedish measurements have been previously published \(^5\), but were now repeated by another investigator. Only the latter measurements were used. The measurement error within the sites (defined as the 95 % CI for a single measurement for measurements of the main variable) between readers in Singapore was 6.8 mm and the error between the current and the previous measurements from Sweden was 8.4 mm.
To cross-evaluate measurements between the two sites, the distance between the lesser trochanter and the fracture line was re-measured in 20 randomly selected patients with atypical fractures (10 from Singapore and 10 from Sweden) as above. Measurements were performed on printed copies of anteroposterior radiographs with a ruler and a pencil by investigators from both centers for all patients. The measurement error was calculated between readers from Singapore and Sweden and amounted to 6.8 mm and 8.4 mm.

Femoral bow assessment
Lateral femoral bow was independently categorized into “Nil”, “Mild” and “Moderate-Severe” based on anteroposterior radiographs of the femur. Discordant results were then adjudicated between the 2 readers and a final morphological classification documented. For statistical analysis the categories were simplified to absence (Nil) or presence (all others) of lateral bow. A randomly selected sample of 20 radiographs from Singaporean and Swedish patients was cross-evaluated for presence or absence of bow by readers from Singapore and Sweden without access to the previous classification. Inter-rater correlations (Kappa coefficient values) were calculated for Singapore patients (0.79) and patients from Sweden (0.68).

Statistical Analysis
This study analyzed whether the distribution of atypical fractures along the femoral shaft in Singapore shows a dichotomous pattern, as has previously been found in Sweden. We then tested the hypothesis that the relative frequency of a subtrochanteric location is different between the two countries. The main variable for testing was the distance from the lesser trochanter to the fracture.

The dichotomy analysis was performed as previously described. Frequency distribution of the measured distances was analyzed using the R program for statistical computing, version 3.1.1, together with the mclust software package for model-based clustering, classification, and density estimation. It uses the Bayesian information criterion to choose the best description of the observed variable distribution in terms of a compilation of normally distributed subgroups. The null hypothesis that the location had a unimodal distribution was tested using the diptest in R.

The number of patients in the two subgroups in the respective countries was analyzed with a chi2 test. The number of patients in the distal or proximal subgroups in the respective countries, and the association between subgroup and lateral femoral bow in each country were separately analyzed with a chi2 test. The influence of lateral femoral bow on the distance was tested by median test. Due to lack of radiographs comprising the whole femur in Sweden, the estimation of lateral femoral bow in the two countries could not be reliably merged to a combined material, and each country was analyzed separately.

Results
Frequency distribution analysis of all patients from both countries showed a clear dichotomy, both when analyzed together or separately, meaning that in both countries, fractures tended to be either subtrochanteric or diaphyseal (Figure 3). Notably, we here use the term subtrochanteric as defined by our frequency analysis, and not according to any previous classification. The probability density for both countries analyzed together showed peaks at 40 and 180 mm below the lesser trochanter. The degree of uncertainty, as to whether a fracture should be classified as subtrochanteric or shaft, was above 5% only in a small region...
between 60 and 90 mm, with a peak at 80 mm. The patients in Sweden had their peak probability for shaft fracture at 195 mm, and those in Singapore at 124 mm (Table 2). This difference seems to be due to on average 106 mm (26 %) longer femurs in Swedish women compared to women from Singapore (Figure 4). Swedish women had a femoral length of 519 mm (SD 67 mm; measurements missing due to insufficient radiographs in 27 patients) and Singaporean had femurs of 413 mm (SD 20 mm). Unimodality was rejected for both Swedish (p = 0.036) and Singaporean women (p = 0.034).

In spite of the similar dichotomous pattern, the number of patients in the two subgroups was different in Sweden and Singapore. In Singapore, 48 % of the fractures were subtrochanteric, whereas in Sweden only 17 % were subtrochanteric (Table 1). This difference was statistically significant (p<0.0001).

Presence of lateral femoral bow was seen in 45% of women from the Singapore sample and 19% of women from Sweden (Table 1). In Singapore, lateral femoral bow was associated with fracture location in the distal subgroup (p<0.0001). No such association could be shown in Sweden. Within the diaphyseal subgroup (analyzed separately) the distance from the lesser trochanter was higher in patients with lateral femoral bow (Median test p=0.002 for Sweden, 0.0001 for Singapore). In contrast, the subtrochanteric fractures showed no association between distance and bow.

Discussion
In a previous nation-wide cohort of Swedish women, we found a dichotomous distribution in the location of atypical fractures with the majority of fractures occurring in the diaphysis.\(^5\) The existence of 2 subcategories was now also found in Singapore, but here the fractures were equally distributed between the subtrochanteric and diaphyseal subgroups.

Within the diaphyseal subgroup, presence of femoral bow was associated with a more distal fracture. Paradoxically, more subtrochanteric fractures occurred in Singapore, the sample with more femoral bowing. This seems to further stress the difference between the two types of atypical fracture, suggesting a different mechanical contribution to pathogenesis.

The predominance of subtrochanteric fractures in Singaporean, mainly Chinese, women versus shaft fractures in Sweden might possibly be related to anatomical differences, such as alignment of the lower limb, offset or femoral version. This may lead to differences in the localization of increased tensile stress. However, it is hard to conceive a dichotomy of such factors. For example, it is unlikely that a genetically rather homogenous population, such as Swedish women above 55 years of age would show a dichotomy in femoral bow. Another possibility would be a dichotomy in vitamin D status causing a dichotomy in femoral bowing. However, when our patients were growing up, vitamin D supplementation for children was compulsory in Sweden, and vitamin D levels in the population are normally distributed.\(^{20,21}\)

In contrast, it seems likely that separate types of loading events could cause distinctly different areas of stress maximum, explaining a dichotomy. Rising from a chair, or climbing stairs, causes rotatory stress of the proximal femoral shaft, which might concentrate proximally. Walking on plain ground instead causes valgus stress, possibly with a more distal location. The stress fracture will occur at the site where the stress first reaches the insufficiency level. Rather subtle differences in physical behavior could then conceivably cause that the fracture occurs at radically different locations. Moreover, the urban life-style in Singapore versus the more rural environment of many elderly Swedish women could then
possibly cause differences in physical behavior that manifest themselves as different proportions of subtrochanteric versus shaft stress fractures under the influence of bisphosphonates.

The relationship of femoral geometry and bowing to the occurrence of atypical femoral fractures has recently been described in the literature and complies with our results. Several studies have shown an increase in the risk of atypical femoral fracture in patients with smaller femoral neck-shaft angles.\(^{(22,23)}\) Other geometrical parameters likely to increase the risk of atypical femoral fracture include shorter hip axis length, narrowed center-edge angle,\(^{(22)}\) shorter lower limbs, wider hip-knee shaft angle and increased femoral torsion.\(^{(24)}\) Also increased femoral curvature might be associated with increased risk of atypical femoral fracture and a diaphyseal fracture location.\(^{(12,25)}\)

The bimodal distribution of the location has possible implications for surgical management of atypical fractures. Plating may be relatively contra-indicated as it might cause stress concentration in the adjacent region: plating of a diaphyseal fracture would have the implant terminating at the subtrochanteric region and vice versa. A long, cephalomedullary nail would appear the treatment of choice.

This study has several weaknesses. Values for distance from the lesser trochanter were not compensated for total femoral length. We would have preferred to express all distances as the fraction of total femoral length, but because there were many Swedish patients in which length measurements could not be performed with sufficient accuracy, we decided to use absolute values. Men were excluded from the analysis and we have no control group. We required all 5 major criteria of the revised American Society for Bone and Mineral Research Taskforce report to define the stress fracture pattern of atypical fractures.\(^{(16)}\) According to the ASBMR only 4 criteria are required. This might preclude generalization of our results. Lateral femoral bow was not measured, just estimated from general appearance. For regulatory reasons, lateral bow had to be estimated separately in the two countries, and a direct comparison of all cases was not possible. However a cross evaluation of bow assessment between readers in a small sample from the two sites showed a good correlation. Neither of these shortcomings precluded appropriate testing of our three hypotheses.

While it has been reasonably established in the literature that atypical femoral fractures can occur from the subtrochanteric region to the supracondylar flare of the femur, this study serves to consolidate the distinct dichotomous distribution since a similar dichotomous distribution but with a different peak propensity has now been demonstrated in another population.\(^{(5)}\)

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References


Table 1. Number of patients in the different subgroups of fracture location, with increased lateral femoral bow and bisphosphonate treatment status.

<table>
<thead>
<tr>
<th>Country</th>
<th>Location</th>
<th>Total number of patients</th>
<th>Patients with bisphosphonate treatment</th>
<th>Patients with increased bow</th>
<th>Total femur length in mm Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore</td>
<td>Subtrochanteric</td>
<td>36</td>
<td>33</td>
<td>10</td>
<td>409(19)</td>
</tr>
<tr>
<td>Singapore</td>
<td>Shaft</td>
<td>39</td>
<td>34</td>
<td>24</td>
<td>417(20)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Subtrochanteric</td>
<td>25</td>
<td>18</td>
<td>3</td>
<td>520(34)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Shaft</td>
<td>118</td>
<td>98</td>
<td>24</td>
<td>526(47)</td>
</tr>
</tbody>
</table>

Table 2. Distance from lesser trochanter to fracture. *The number of patients in the subpopulations for the combined analysis are slightly different from the sum of the separate sites because we made a separate cluster analysis for the combined dataset.

<table>
<thead>
<tr>
<th>Subpop 1 (subtrochanteric)</th>
<th>Subpop 2 (shaft)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Combined</td>
<td>67*</td>
</tr>
<tr>
<td>Singapore</td>
<td>36</td>
</tr>
<tr>
<td>Sweden</td>
<td>25</td>
</tr>
</tbody>
</table>
Figure 1. Identification of atypical femoral fractures in the study populations from Singapore and Sweden. Patients from 2008 in Sweden were women only. *Mechanically altered femurs include patients with knee and hip prostheses, retained plates, screws, intramedullary nails, joint arthrodeses, and other conditions.

Figure 2. Measuring technique: A Proximal segment: A best fit line is drawn parallel to the periosteal surface of the lateral cortex (ignoring the lateral cortical callus reaction). Perpendicular lines are drawn at the level of the most prominent point of the lesser trochanter and at the level of the fracture. The distance between these 2 lines (dotted line) formed the main variable of this study. B Distal segment: Same as above but the distal reference point is at the roof of the intercondylar notch.
Figure 3. Probability density of fracture location in the combined sample (Sweden and Singapore) described as the distance from the lesser trochanter to the fracture.

Figure 4. Probability density curves superimposed. Swedish values reduced by 25%, according to the difference in mean total femoral length.