Relation between age, femoral neck cortical stability, and hip fracture risk


Summary

Background Hip fracture risk rises 100 to 1000-fold over 60 years of ageing. Loss of resistance to bending is not a major feature of normal ageing of the femoral neck. Another cause of fragility is local buckling or elastic instability. Bones adapt to their local experience of mechanical loading. The suggestion that bipedalism allows thinning of the underloaded superolateral femoral neck cortex arises from the failure of walking to transmit much mechanical load to this region. We aimed to measure whether elastic instability increases greatly with age since it might trigger hip fracture in a sideways fall.

Methods We measured with computed tomography the distribution of bone in the mid-femoral neck of 77 proximal femurs from people who died suddenly aged 20–95 years. We then calculated the critical stress, from the geometric properties and density of the cortical zone most highly loaded in a sideways fall, as a threshold for elastic instability.

Findings With normal ageing, this thin cortical zone in the upper femoral neck became substantially thinner. Relative to mean values at age 60 years, female cortical thickness declined by 6·4% (SD 1·1) per decade (p<0·0001), and critical stress by 13·2% (4·3) per decade (p=0·004) in the superoposterior octant compressed most in a sideways fall. Similar, but significantly smaller, effects were evident in men (p=0·004). This thinning compromised the capacity of the femur to absorb energy independently of osteoporosis. Patients with hip fracture had further reduced stability.

Interpretation As women age, hip fragility increases because underloading of the superolateral cortex leads to atrophic thinning. Because walking does not sufficiently load the upper femoral neck, the fragile zones in healthy bones may need strengthening, for example with more well targeted exercise.

Introduction The risk of hip fractures increases ten-fold with every 20 years of age.1 When tubular structures such as long bones are bent, they often fracture through mechanical failure beginning in the cortex under tension. If they have thin walls they can instead break through local buckling of the compression cortex. Galileo pointed out that resistance to a bone’s bending (measured by engineers as section modulus, Z) can be maintained with less material as its diameter is widened.2 However, without increasing the amount of bone tissue, cortical thinning will result, making buckling more likely.

Loss of bending resistance with normal ageing is modest.3 Ageing is unlikely to influence the risk of failure in tension because the thick inferomedial cortex bears this load in most dangerous falls.4 Bone mineral density declines with age, but age has an independent and strong effect on fracture risk after adjustment for bone mineral density. Growing asymmetry of the femur’s internal structure might reduce the ability of the superior cortex either to resist crushing in compression,5 or to increase its tendency to develop local buckling or elastic instability as is generally thought to contribute to other types of fracture (eg, in lytic cancers or Paget’s disease). We aimed to look for a large effect of ageing that, unlike the moderate rise in risk of falling,6 could be primarily responsible for the steeply exponential rise in hip fractures.

The sideways falls that lead to hip fracture7 compress the posterior part of the thin, superolateral cortex of the femoral neck (figure 1). This region is very lightly loaded in walking,8 the main physical activity of middle-aged and elderly people. So, in a sample of normal proximal femurs spanning a wide age range, we have investigated whether the superolateral cortex develops with age a geometry that is structurally unstable. We compared the sample against a large healthy population measured with clinical densitometry to establish that our cadaveric material was representative and also studied material from hip fracture cases.

Methods

Procedures The Victorian Institute of Forensic Medicine obtained the proximal third of the femur under strict ethical regulation from 81 people older than 20 years who died suddenly. Relatives gave permission (initially verbal, later confirmed in writing) for use of the part femurs (66% compliance) and brief medical history data. After dual-energy X-ray absorptiometry scanning to measure the neck shaft angle and distance from head to mid-neck,9 we scanned the 77 (35 female) proximal femurs9 that showed no visible evidence of hip arthritis in a special purpose computed tomography scanner (Denisiscan 1000; Scanco Medical AG, Zurich, Switzerland)10 with a resolution of 0·275 mm to generate 140 serial consecutive 1-mm slices. These slices were imported into Pixotec’s Slicer Dicer software version 4 to create a three-dimensional reconstruction (figure 1), from which the mid-femoral neck cross-
Three-dimensional reconstruction and cross-sectional images of the femoral neck


Figure 1: Three-dimensional reconstruction and cross-sectional images of the femoral neck


Statistical analysis

To determine the age effect on t in each cortical sector, repeated measures MANOVA was used to model statistically the effects of age, height, weight, and sex, including any significant interactions between them (JMP v4.0.2, SAS Institute, Carey, SC, USA). Height and weight made no significant contribution to predicting any variable and the large effect of sex led us to model each sex separately after first contrasting for any significant interactions between them. To examine the uncertainty associated with each of the 16 sectoral regressions on age, individual adjusted r2 values and root mean square errors were calculated. The limited medical history data meant that we could not study confounders like physical activity or medications.

To investigate the effect of a previous hip fracture, we used the British data of Mayhew and colleagues that included any significant interactions between them. To examine the uncertainty associated with each of the 16 sectoral regressions on age, individual adjusted r2 values and root mean square errors were calculated. The limited medical history data meant that we could not study confounders like physical activity or medications.

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included 22 female cases of hip fracture and 24 controls. Finally, to check whether ageing had a similar effect on the distribution of bone in the femoral neck cross section as in a representative population sample, we examined the US NHANES 3 DXA data for 2903 non-Hispanic white women. We examined the effect of age on the distance from the centroid to the superolateral cortical margin using regression analysis while adjusting for height and weight. This distance was used as a surrogate for the combined effects of thinning of the superior cortex and femoral neck cross-sectional expansion with age, as suggested by Yoshikawa and others and Kaptoge and others.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The table shows characteristics of individuals in the study. After adjustment to mean height and weight, areal femoral neck bone mineral density declined in women by a mean of 32% (SD 7) from age 20 to 80 years (adjusted $r^2 0.37, \text{p} < 0.0001$), equivalent to a reduction in T score from 0.0 to $-2.3\ (0.2\ SD\ units\ above\ WHO's\ diagnostic\ threshold\ for\ osteoporosis)$, and similar to the decrease in NHANES 3. For the superior 2 cortical sectors, the distance from the centroid increased by 20% (95% CI 10–30) from age 20 to 80 years. This effect was similar to the 21% increase in the NHANES 3 study previously unreported.

Compressive stress in the superolateral cortex in a so-called standard fall showed no significant increases with age ($\text{p} = 0.9$ and 0.3 for women and men, respectively) with mean values of 198 (SD 42) and 165 (31) MPa, similar to those reported by Yoshikawa and significantly different from each other ($\text{p} < 0.0001$). They were, however, close to the compressive yield strength of cortical bone of about 185 MPa. After the yield strength is reached, provided there is no displacement by buckling, bone can absorb further energy before fracture because of its mechanical toughness.

The elastic stability of the superolateral cortex therefore seemed crucial to avoiding fracture. Cortical thickness is key to maintaining elastic stability. Figure 2 shows scatter plots of cortical thickness versus age in two key sectors. Figure 3 compares the mean female cortical thickness in each of the 16 sectors at two ages: 20 and 80 years. This was dependent on sex across all sixteenths ($\text{p} < 0.001$), but the effects of age ($\text{p} < 0.0001$) and sex ($\text{p} = 0.0004$) differed substantially between individual cortical regions. There was already much asymmetry in cortical thickness at 20 years of age, which greatly increased over the next six decades. Over most of the cortex, thickness decreased in women by 40–75%, although a contrasting increase was evident in the strong inferior cortex loaded most by walking (figure 2).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Female (n=35)</th>
<th>Male (n=42)</th>
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<tbody>
<tr>
<td>Minimum</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Maximum</td>
<td>95</td>
<td>84</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>68.5 (41.0–75.0)</td>
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<table>
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<th>Height (cm)</th>
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<tbody>
<tr>
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<td>153</td>
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<tr>
<td>Maximum</td>
<td>184</td>
<td>190</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>163 (154–167)</td>
<td>170 (166–180)</td>
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<th>Body-mass index (kg/m²)</th>
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<tr>
<td>Minimum</td>
<td>16.9</td>
<td>15.0</td>
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<tr>
<td>Maximum</td>
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<td>35.9</td>
</tr>
<tr>
<td>Median</td>
<td>25.3 (20.0–28.9)</td>
<td>24.9 (22.5–27.8)</td>
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<tr>
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<td>6.60</td>
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<tr>
<td>Maximum</td>
<td>10.74</td>
<td>10.20</td>
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<tr>
<td>Median (IQR)</td>
<td>9.35 (8.18–10.03)</td>
<td>8.57 (7.98–9.21)</td>
</tr>
</tbody>
</table>

Table: Characteristics of people studied

Figure 2: Age-related change in cortical thickness in women aged 20–95 years in (A) the superoposterior sector (304º) and (B) the inferior sector (169º) Solid line=linear regression between cortical thickness and age. Dotted line=95% CI.
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and figure 3). In the region most compressed by a fall, these reductions in women amounted to 4·2% (SD 1·5) in the superior octant (p=0·002), 6·4% (1·1) in the superoposterior octant (p<0.0001), and 10·2% (1·8) in the posterior octant (p<0·0001) per decade compared with their mean values at the mean age of 60 years. Local curvature (1/R), when added as an independent determinant of the thickness of the posterior part of the superolateral cortex, increased it (0·072 mm increase in thickness per 1 SD increase in 1/R, p=0·0026), whereas the age effect was little changed, and r² for model increased from 0·40 to 0·54, F=8·0, p=0·008. Estimated critical stress (σ) for the superoposterior octant fell with age by 13·2% (4·3) per decade of the mean value at 60 years (p=0·004), such that by age 80 years, a quarter of women were estimated to have values equal to or lower than the compressive yield stress of cortical bone. σ₀ was 2·2 times higher on average than σ₀ at an unsupported length of 5 mm along the femoral neck axis, and they were correlated (adjusted r²=0·67, p<0.0001). Men showed smaller effects of age, such that superior cortical thickness declined more slowly than in women (figure 4). Of the three octants mentioned, only the posterior declined significantly by 4·2% (1·6) of the mean thickness at 60 years (p=0·013) per decade in men.

Our cases of hip fracture showed additional adverse changes. There were significant (p=0·001) reductions in inferior and anterior cortical thickness,20 but thickness was similar to that of age-matched controls in the superoposterior cortex. However, because E was reduced by 17% in the study cases, elastic stability was lower and σ₀ values were typical of those of controls a decade older.

Discussion

We have shown that there is substantial loss of elastic stability with age, such that tissue toughness—the capacity to absorb energy through microscopic damage—might become unable to contribute to fracture prevention. This loss is mainly due to thinning of the superolateral cortex. These findings could profitably redirect the search for the real cause of the steep increase in hip fragility with age. In young people, a sideways fall will only fracture the femoral neck if the applied load is substantially higher than received from a fall to the ground. This is because a load equal to the yield stress can cause microscopic damage; but the energy absorbed by this damage will allow the femur to remain intact with a microscopic degree of impaction at worst. However, toughness is only of use in preserving the femur’s integrity if its elastic stability is sufficient. If the structure becomes elastically unstable at or around the yield stress, displacement of tissue will be too great to allow bone’s toughening mechanisms to operate and the energy of the fall will likely deliver a complete fracture. The importance of our study lies in clearly showing how substantial the effect of superolateral cortical thinning and associated loss of elastic stability is and in showing the need, apparently unmet, either for increased local curvature or for the preservation of stout trabecular connections in this region of femoral cortex. Hip fracture cases showed some additional reduction of the elasticity of bone, due in part to increased porosity18 and in part to a true reduction in mineralisation density.19

After four decades of controversy it is now certain that the femoral neck diameter slowly enlarges with age.20,21 This effect explains how bone mineral density

Figure 3: Age differences in cortical thickness in women as estimated by MANOVA
Data are for each of 16 cortical sectors labelled by their angular rotation from superior (anterior 90º, posterior 270º).

Figure 4: Age differences in cortical thickness in men as estimated by MANOVA
Data are each of 16 cortical sectors labelled by their angular rotation from superior.
can decrease while bending resistance does not: the former is inversely related to femoral neck diameter and the latter is directly related. The subperiosteal bone formation responsible for expansion is positively associated with reported physical activity\(^2\) and with growing internal porosity of the femoral cortex.\(^2\) These associations suggest that in adult life, as during growth,\(^2\,2,3\) maintenance of structural stability as well as of bending resistance can result from the periosteal response to mechanical loading. Experimentally, the same result applies to animals and the balance of subperiosteal expansion with internal bone destruction is very sensitive to the quantity of mechanical loading applied locally.\(^2,2,3\) Our findings suggest that elastic stability can also decline in quite a localised way; even to dangerous levels in old people, some of whom might not have generalised osteoporosis.

These observations are understandable in the light of recent experiments.\(^7,2,3\) A persuasive explanation for loss of elastic stability with age follows partly from Lovejoy's description of the structural differences in the femoral neck between the young people and arboreal apes,\(^8\) which have almost symmetrically thick cortices. He attributed this divergence to reduced mechanical loading of the human superolateral cortex (and its comparatively heavier inferomedial loading) during bipedal locomotion compared with tree climbing. As people age, they reduce their physical activity and its variety, so that the femur becomes loaded more exclusively by walking.

How could loss of integrity of a small part of the femoral neck cortex lead to complete fracture? A compression crack would be started and such cracks would accelerate while energy from a fall\(^9\) remains to drive them. If this energy propelled a crack across half the width of the femoral neck, then (from beam theory) the bending resistance (\(Z\)) of the so far unfractured cortical cross-section would be greatly reduced because its width would be halved, and \(Z\) depends on the square of width. Tensile or torsional stresses should rise in the unfractured remainder of the neck to several times the theoretical possibility that trabecular stiffening might increase \(\sigma_{\text{sc}}\) in particular; and since this acts as a minimum value for \(\sigma\) it should be investigated. But some effects of the cancellous network are impossible to model without microfinite element methods,\(^9\) which require many months of supercomputer level resources. The quantitative estimation of instability is quite imprecise and engineering design relies on experiment or provision of generous safety margins for its avoidance, especially where the value of \(\sigma\) is close to the yield stress where failures in engineering structures have unexpectedly occurred due to local imperfections.

These data raise the exciting possibility that three-dimensional imaging, such as computed tomography, could be used to measure local thickness and curvature of the superolateral cortex, and hence to improve the prediction of fragility. More important still, there are practical implications for understanding and controlling the hip fracture epidemic. A stereotyped gait-related stimulus might maintain bending resistance while still...
allowing elastic instability to develop. Walking protects against hip fracture in old people, but it may not be through directly strengthening the hip. To preserve the stability of the cortex, regular loading targeted to the superolateral cortical might need to be lifelong, as occurs naturally when the femur is straightened (extended) at the hip from a flexed position.

In many societies in which sitting near ground-level is usual, hip fracture is rare, even when most women older than 65 years have osteoporosis, as in The Gambia. This paradox might be due to the beneficial loading effect on the upper femur of regular standing up from squatting or of subsistence farming. Several popular forms of exercise also involve extension of the flexed femur under load (cycling, sculling, gymnastics, weights). Some should be investigated for their potential to protect, as part of our society’s drive to increase physical activity for health. Targeting technologies might direct the new generation of anabolic treatments to the upper femoral neck in vulnerable and frail people. Previously unrealised opportunities now exist for devising testable interventions to strengthen the ageing hip.

Contributors
P M Mayhew applied the concept of critical buckling stress to the femoral neck, scanned the femurs, and with C D Thomas, wrote the MATLAB programs. He also did statistical analyses under J Reeve’s guidance. C D Thomas and J G Clement founded the Melbourne Femur collection, organised, funded, and maintained it, and so made possible the collaboration J Reeve had sought since reading Lovejoy. C D Thomas also provided perspective on stress distributions in cortical bone. N Loveridge developed on the concept of two-stage fracture and provided access to the NHANES3 raw data. All authors contributed to developing the concepts expressed, also to the writing of the final version of the report, which was drafted by J Reeve with help from N Loveridge. J Reeve is guarantor of the data.

Conflict of interest statement
JR has been a paid consultant for Eli Lilly and Procter and Gamble, consulted on one occasion each for three other pharmaceutical companies and received a small research grant from Lilly (1997). JGC had some shares in NMS Pharmaceuticals in evaluating drug treatments for osteoporosis. WB is Director of the Pfizer Institute for Pharmaceutical Materials Science, a member of the Smith and Nephew Orthopaedic Materials Science, a member of the Smith and Nephew Orthopaedic Review Board, a non-executive Director of ApaTech Limited, and Chairman of the Scientific and Medical Advisory Board of Biocompatibles International. The other authors declare that they have no conflict of interest.

Acknowledgments
We thank Stephen Kaptoge for analysing the effect of age on the distances from centroid to superior femoral neck cortical margin from the NHANES3 data. The authors gratefully acknowledge the continuing assistance with the collection of bones given by Stephen Cordner and by the staff of the Donor Tissue Bank. We also thank the consenting relatives for their continued support and interest in our work. JR and NL were UK Medical Research Council external scientific staff (PMM was funded through G93215356). Support for the bone collection has come, in part, from the Australian Research Council through SPIRT Grant Number C00001921.

References