

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

*Paul M Mayhew, *C David Thomas, John G Clement, Nigel Loveridge, Thomas J Beck, William Bonfield, Chris J Burgoyne, Jonathan Reeve

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).⁴ 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,⁵ we scanned the 77 (35 female) proximal femurs⁹ that showed no visible evidence of hip arthritis in a special purpose computed tomography scanner (Densiscan 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-

Lancet 2005; 366: 129–35

See [Comment](#) page 98

Department of Medicine (P M Mayhew PhD, N Loveridge PhD, J Reeve DM), Department of Materials Science (Prof W Bonfield FRS), and Department of Engineering (C J Burgoyne PhD), University of Cambridge, Cambridge, UK; University of Melbourne School of Dental Science, Victoria, Australia (C D Thomas MEng, Prof J G Clement PhD); and Johns Hopkins University Department of Radiology, Baltimore, MD, USA (T J Beck PhD)

*These authors contributed equally to this work

Correspondence to: Dr J Reeve, Box 157, Department of Medicine, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK jr357@cam.ac.uk

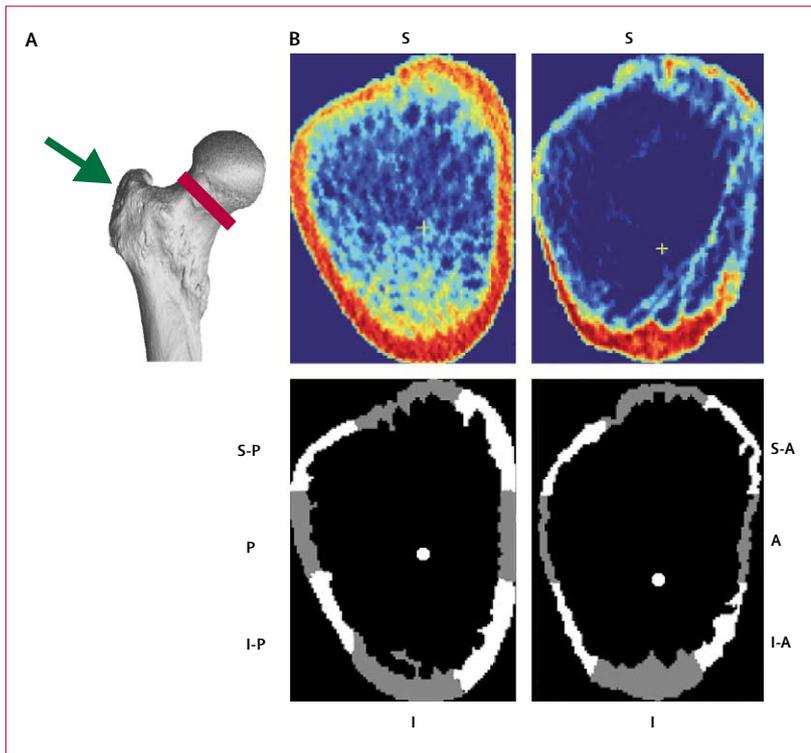


Figure 1: Three-dimensional reconstruction and cross-sectional images of the femoral neck
 A: proximal femur from in front to show position of blow from sideways fall (green arrow). B: cross-sectional quantitative computed tomography images. Upper: images of female femoral neck from 80-year old (right) and 20-year old (left). Pseudo-colours indicate mineral density relative to maximum (red) for image. Bottom: cortices segmented into octants. Red line=location of cross-sectional images. S=superior. S-A=superoanterior. A=anterior. I-A=inferoanterior. I=inferior. I-P=infero-posterior. P=posterior. S-P=superoposterior. White spot=centroid.

sectional image was obtained. We validated this image by comparing reconstructions with the cross-sections measured with quantitative computed tomography from 20 correctly oriented specimens. For cross-section moment of inertia, for Z (section modulus), and for the proportion of marrow space occupied by trabecular bone, r^2 exceeded 0.97 ($p < 0.0001$). We showed previously¹¹ that local measurements of cortical thickness could be used to estimate the same thicknesses measured microscopically on adjacent histological sections (SD < 0.5 mm).

Structures are susceptible to two modes of failure: material or yield failure (in tension or compression) and buckling (compression only). We modified Yoshikawa and colleagues¹⁵ analysis to assess the more posterior part of the superolateral cortex. The force derived from a fall onto the greater trochanter (figure 1) was resolved into compressive and bending vectors and the load transmitted through the superior cortex calculated with beam theory. Higher values suggest a greater risk of yield. We masked out cancellous bone since it seemed that this anisotropic tissue could contribute little resistance to compression at right angles to its normal loading. Next, we assessed whether the same cortical region might be susceptible to local buckling or instability; if this factor is relevant, the critical stress (σ) should not greatly exceed

the yield stress of cortical bone (about 185 MPa).¹² Because of its asymmetry, the cortex cross section was divided into 16 sectors, each subtending equal angles of arc at the centre of area (figure 1).¹³ We calculated the mean thickness, density, and distance from the centroid (centre of gravity of the bone in the cross-section) for every cortical sector. We also calculated the curvature of the periosteal surface around its perimeter by fitting its digitised edge to a smoothing Fourier function and then for each octant fitting a quadratic polynomial that yields curvature from its second derivative. To avoid the artifactual lowering by the so-called partial volume effect of cortical density in thin cortices, we assumed the true tissue density of cortical bone to have the density of the densest sector, which avoids systematic error.¹⁴ We then adjusted our calculated cortical thickness data so that they matched measurements made histologically by Crabtree and others.¹¹ This adjustment allowed us to calculate the critical stress at which the curved cortical sector of interest becomes critically unstable as:

$$\sigma_{CR} = 0.61 \frac{t}{R} \times E$$

where t is the local thickness of the cortex and E the elastic modulus of bone tissue estimated from the bone density in the densest, usually inferior sector, given by Carter and Hayes¹⁵ as: $\text{density}^3 \times 2875 / \text{sqrt } 2.73$ MPa. The factor 0.61 arises from bone tissue's Poisson's ratio, assumed to be 0.3, and R is radius of curvature in the plane of the cross-section.

Three samples showed no detectable curvature in the region maximumly loaded by a fall. In the absence of curvature, the Euler buckling formula applies:

$$\sigma_{EU} = 0.61 \frac{t^2 \pi^2}{12 L^2} \times E$$

where L is the effective unsupported length of the cortex along the femoral neck's axis and π is 3.142. σ_{EU} provides a lower bound below which σ does not decrease as R is increased.

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 sex. To examine the uncertainty associated with each of the 16 sectoral regressions on age, individual adjusted r^2 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 22 female cases of hip fracture and 24 controls.¹⁰ 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 others⁵ and Kaptoge and others.¹⁶

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, $p < 0.0001$), 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 study³ previously unreported.

Compressive stress in the superolateral cortex in a so-called standard fall showed no significant increases with age ($p=0.9$ and 0.3 for women and men, respectively) with mean values of 198 (SD 42) and 165 (31) MPa, similar to those reported by Yoshikawa⁵ and significantly different from each other ($p < 0.0001$). They were,

	Female (n=35)	Male (n=42)
Age (years)		
Minimum	20	19
Maximum	95	84
Median (IQR)	68.5 (41.0–75.0)	70.0 (44.0–76.5)
Height (cm)		
Minimum	145	153
Maximum	184	190
Median (IQR)	163 (154–167)	170 (166–180)
Body-mass index (kg/m²)		
Minimum	16.9	15.0
Maximum	34.4	35.9
Median	25.3 (20.0–28.9)	24.9 (22.5–27.8)
E (MPa × 10³)		
Minimum	6.19	6.60
Maximum	10.74	10.20
Median (IQR)	9.35 (8.18–10.03)	8.57 (7.98–9.21)

Table: Characteristics of people studied

however, close to the compressive yield strength of cortical bone of about 185 MPa.¹⁷ 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 ($p=0.001$), but the effects of age ($p < 0.0001$) and sex ($p=0.0004$) 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

See <http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>

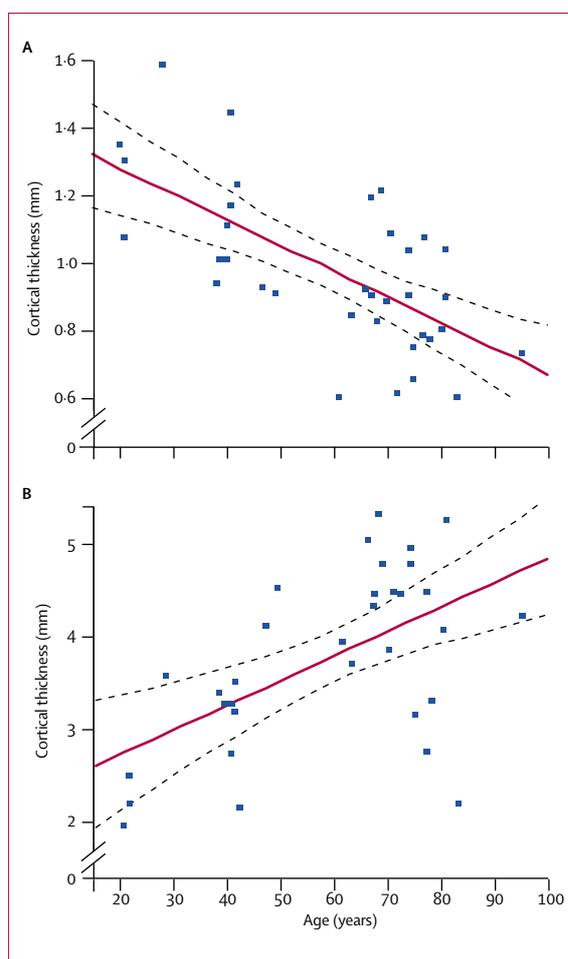


Figure 2: Age-related change in cortical thickness in women aged 20–95 years in (A) the superoposterior sector (304°) and (B) the inferior sector (169°)

Solid line=linear regression between cortical thickness and age.

Dotted lines=95% CIs.

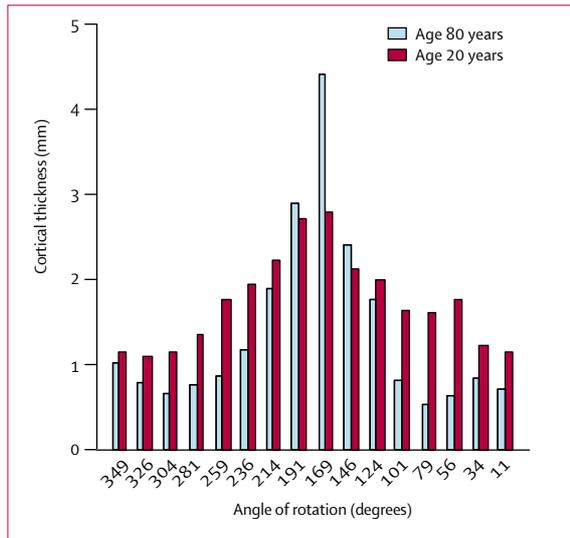


Figure 3: Age differences in cortical thickness in women as estimated by MANOVA
 Data are for each of 16 cortical sectors labelled by their angular rotation from superior (anterior 90°, posterior 270°).

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 r^2 for model

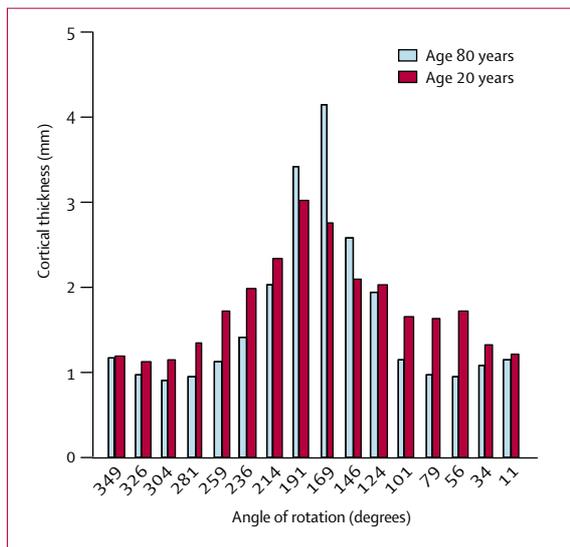


Figure 4: Age differences in cortical thickness in men as estimated by MANOVA
 Data are each of 16 cortical sectors labelled by their angular rotation from superior.

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. σ_{CR} was 2.2 times higher on average than σ_{EU} at an unsupported length of 5 mm along the femoral neck axis, and they were correlated (adjusted $r^2=0.67$, $p<0.0001$). 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,¹⁰ 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 σ_{CR} 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

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 activity²⁰ and with growing internal porosity of the femoral cortex.²¹ These associations suggest that in adult life, as during growth,^{22,23} 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.^{22,23} 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.^{22,23} 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 fall²⁴ 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 strength of bone, and the bone's toughness would probably not be sufficient to allow redistribution of stress to prevent complete fracture.

Our data are therefore compatible with a model of the ageing femur in which femoral neck Z is well regulated so as to remain in equilibrium with changing loading patterns. Expansion of diameter allows less bone tissue to maintain a constant Z ; moreover, net bone loss should be exacerbated by reduced skeletal loading in less active elderly people. The changing character of the load on the femoral neck seems to play an unfortunate part in increasing fragility. The thickening of the inferior part of the femoral neck, associated with walking,²⁰ means that Z should increase unless balanced by loss of bone tissue in the upper neck.⁵ This would reduce structural stability. If patients with

osteoporosis who suffer hip fracture have reduced responsiveness to mechanical loading, this loss may be evident as relatively lower values of both σ and Z , as our previous studies suggest.^{10,25} Therefore the effects of osteoporosis and of ageing on the femoral neck are different: osteoporosis affects bending resistance and stability rather similarly, whereas ageing has a larger effect on cortical geometry and thickness, but affects bending resistance little. Instead of the expected finding that cortical stability was upheld by compensatory thickening in less curved posterior superolateral cortices we found the opposite, suggesting the absence of a specific response to maintain elastic stability.

This study incorporates simplifications. We could not investigate the effects of medications or specific categories of physical activity that might have changed the tendency for underloaded bone to weaken with age. For example, use of hormone replacement therapy might have preserved endosteal bone, and exercise involving hip flexion might have targeted mechanical loading to help preserve the most vulnerable regions of the femoral neck. No allowance was made for the differences in material properties between young and old bone in its propensity to crack,^{26,27} nor in the effects of these properties or of microarchitectural changes²⁸ on crack propagation in the femoral neck cortex. Superior spongy bone makes little contribution to strength: more than half of 300 people aged 65 years and older had no radiologically detectable superior trabecular arcades.²⁹ Gracile radial trabeculae of thickness 0.05–0.15 mm attach to the inner cortex at intervals of about 1.4 mm and might have a damping function, and would provide some contribution to cortical stability. In osteoporosis, many trabeculae are disconnected or missing and whole regions without bone can arise in the femoral marrow space,³⁰ substantially elongating the femoral neck's effectively unsupported length. Nevertheless, there is the theoretical possibility that trabecular stiffening might increase σ_{EU} in particular; and since this acts as a minimum value for σ it should be investigated. But some effects of the cancellous network are impossible to model without microfinite element methods,³⁰ 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 σ 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,³¹ but it may not be through directly strengthening the hip. To preserve the stability of the cortex, regular loading targeted to the superolateral cortex 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,^{32,33} even when most women older than 65 years have osteoporosis, as in The Gambia.³⁴ 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 with T J Beck used their published data to adjust the MATLAB cortical widths for femoral neck location and partial volume effects. C J Burgoyne, W Bonfield, and T J Beck guided the interpretation of structural strength concepts from materials and mechanics perspectives and T J Beck provided access to 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 a research grant from MSD (about 1995). CJB holds some shares in Glaxo. TJB had done bone geometry analyses under contract to Eli Lilly, Aventis, Merck, and NPS 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 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 Corder 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 G9321536). Support for the bone collection has come, in part, from the Australian Research Council through SPIRT Grant Number C00001921.

References

- Melton III LJ. A "Gompertzian" view of osteoporosis. *Calcif Tissue Int* 1990; **46**: 285–86.
- Galileo Galilei Linceo. *Discorsi e dimostrazioni matematiche intorno a due nuove scienze attenti alla macanica e i movimenti locali*. Leiden: Elsevier, 1638.
- Beck TJ, Looker AC, Ruff CB, Sievanen H, Wahner HW. Structural trends in the ageing femoral neck and proximal shaft: analysis of the third national health and nutrition examination survey dual-energy X-ray absorptiometry data. *J Bone Miner Res* 2000; **15**: 2297–308.
- Lotz JC, Cheal EJ, Hayes WC. Stress distributions within the proximal femur during gait and falls: implications for osteoporotic fracture. *Osteoporos Int* 1995; **5**: 252–61.
- Yoshikawa T, Turner CH, Peacock M, et al. Geometric structure of the femoral neck measured using dual-energy X-ray absorptiometry. *J Bone Miner Res* 1994; **9**: 1053–64.
- O'Neill TW, Varlow J, Reeve J, et al. Fall frequency and incidence of distal forearm fracture in the UK. *J Epidemiol Community Health* 1995; **49**: 597–98.
- Nevitt MC, Cummings SR. Type of fall and risk of hip and wrist fractures: the study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc* 1993; **41**: 1226–34.
- Lovejoy CO. Evolution of human walking. *Sci Am* 1988; **259**: 118–25.
- Thomas CD, Stein MS, Feik SA, Wark JD, Clement JG. Determination of age at death using combined morphology and histology of the femur. *J Anatomy* 2000; **196**: 463–71.
- Mayhew P, Kaptoge S, Loveridge N, et al. Discrimination between cases of hip fracture and controls is improved by hip structural analysis compared to areal bone mineral density. An ex vivo study of the femoral neck. *Bone* 2004; **34**: 352–61.
- Crabtree N, Loveridge N, Parker M, et al. Intracapsular hip fracture and the region-specific loss of cortical bone: analysis by Quantitative Computed Tomography (pQCT). *J Bone Miner Res* 2001; **16**: 1318–28.
- Burstein AH, Reilly DT, Martins M. Ageing of bone tissue: mechanical properties. *J Bone Joint Surg Am* 1976; **58**: 82–86.
- Timoshenko SP, Gere JM. Sections 11.1 and 11.3. *Theory of Elastic Stability*. New York: McGraw-Hill, 1979.
- Hangartner TN, Gilsanz V. Evaluation of cortical bone by computed tomography. *J Bone Miner Res* 1996; **11**: 1518–25.
- Carter DR, Hayes WC. The compressive behavior of bone as a two-phase porous structure. *J Bone Joint Surg (Am)* 1977; **59**: 954–62.
- Kaptoge S, Dalzell N, Loveridge N, Beck TJ, Khaw KT, Reeve J. Effects of gender, anthropometric variables and aging on the evolution of hip strength in men and women aged over 65. *Bone* 2003; **32**: 561–70.
- Van Buskirk WC. Elementary stress analysis of the femur and tibia. In Cowin SC, ed. *Bone Mechanics*. Boca Raton: CRC Press, 1989: 43–52.
- Bell KL, Loveridge N, Power J, Stanton M, Meggitt BF, Reeve J. Regional differences in cortical porosity in the fractured femoral neck. *Bone* 1999; **24**: 57–64.
- Loveridge N, Power J, Reeve J, Boyde A. Bone mineralization and femoral neck fragility. *Bone* 2004; **35**: 929–41.
- Kaptoge S, Dalzell N, Jakes R, et al. Hip section modulus, a measure of bending resistance, is more strongly related to physical activity than BMD. *Osteoporos Int* 2003; **14**: 941–49.
- Power J, Loveridge N, Lyon A, Rushton N, Parker M, Reeve J. Osteoclastic cortical erosion as a determinant of sub-periosteal osteoblastic bone formation in the femoral neck's response to BMU imbalance. Effects of stance-related loading and hip fracture. *Osteoporos Int* (published online Nov 26, 2004); DOI:10.1007/S00198-004-1803-2.
- Mosley JR, March BM, Lynch J, Lanyon LE. Strain magnitude related changes in whole bone architecture in growing rats. *Bone* 1997; **20**: 191–98.
- Noble B, Peet N, Stevens H, et al. Mechanical loading: biphasic osteocyte survival and targeting of osteoclasts for bone destruction in rat cortical bone. *Am J Physiol Cell Physiol* 2003; **284**: C934–43.

- 24 Robinovitch SN, Hayes WC, McMahon TA. Prediction of femoral impact forces in a fall on the hip. *J Biomech Eng* 1991; **113**: 366–74.
- 25 Crabtree NJ, Kroger H, Martin A, et al. Improving risk assessment: hip geometry, bone mineral distribution and bone strength in hip fracture cases and controls. The EPOS Study. *Osteoporos Int* 2002; **13**: 48–54.
- 26 Zioupos P, Currey JD. Changes in the stiffness, strength and toughness of human cortical bone with age. *Bone* 1998; **22**: 57–66.
- 27 Vashishth D, Tanner KE, Bonfield W. Experimental validation of a microcracking-based toughening mechanism for cortical bone. *J Biomech* 2003; **36**: 121–24.
- 28 Bell KL, Loveridge N, Jordan GR, Power J, Constant CR, Reeve J. A novel mechanism for the induction of the increased cortical porosity in cases of intra-capsular hip fracture. *Bone* 2000; **27**: 297–304.
- 29 Wand JS, Hill ID, Reeve J. Coxarthrosis and femoral neck fracture. *Clin Orthop Relat Res* 1990; **278**: 88–94.
- 30 Van Rietbergen B, Huiskes R, Eckstein F, Ruegsegger P. Trabecular bone tissue strains in the healthy and osteoporotic human femur. *J Bone Miner Res* 2003; **18**: 1781–88.
- 31 Coupland C, Wood D, Cooper C. Physical inactivity is an independent risk factor for hip fracture in the elderly. *J Epidemiol Community Health* 1993; **47**: 441–43.
- 32 Yan L, Prentice A, Wang X, Golden MH. Epidemiological study of hip fracture in Shenyang, People's Republic of China. *Bone* 1999; **24**: 151–55.
- 33 Adebajo AO, Cooper C, Evans JG. Fractures of the hip and distal forearm in West Africa and the United Kingdom. *Age Ageing* 1991; **20**: 435–38.
- 34 Aspray TJ, Prentice A, Cole T, Sawo Y, Reeve J, Francis RM. Low bone mineral content is common but osteoporotic fractures are rare in elderly rural Gambian women. *J Bone Miner Res* 1996; **11**: 1019–25.