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REVIEW

Role of cortical bone in hip fracture

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In this review, I consider the varied mechanisms in cortical bone that help preserve its integrity and how they deteriorate with aging. Aging affects cortical bone in two ways: extrinsically through its effects on the individual that modify its mechanical loading experience and 'milieu interieur'; and intrinsically through the prolonged cycle of remodelling and renewal extending to an estimated 20 years in the proximal femur. Healthy femoral cortex incorporates multiple mechanisms that help prevent fracture. These have been described at multiple length scales from the individual bone mineral crystal to the scale of the femur itself and appear to operate hierarchically. Each cortical bone fracture begins as a sub-microscopic crack that enlarges under mechanical load, for example, that imposed by a fall. In these conditions, a crack will enlarge explosively unless the cortical bone is intrinsically tough (the opposite of brittle). Toughness leads to microscopic crack deflection and bridging and may be increased by adequate regulation of both mineral crystal size and the heterogeneity of mineral and matrix phases. The role of osteocytes in optimising toughness is beginning to be worked out; but many osteocytes die *in situ* without triggering bone renewal over a 20-year cycle, with potential for increasing brittleness. Furthermore, the superolateral cortex of the proximal femur thins progressively during life, so increasing the risk of buckling during a fall. Besides preserving or increasing hip BMD, pharmaceutical treatments have class-specific effects on the toughness of cortical bone, although dietary and exercise-based interventions show early promise.

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Introduction

Recently, we reviewed the data relevant to why the adult risk of hip fracture in economically advanced countries grows 10-fold for every 20-year increase in a person's age.[1] It was argued that as has been appreciated since 1988,[2] measurements of bone density made in two dimensions or three failed to account for the rapidity of this increase; and that many of the hip-weakening mechanisms revealed in the last half century of research were more closely associated with aging, either specifically of bone tissue or more generally of the body as a whole, rather than with net loss of bone tissue, that is, clinical osteoporosis. By this term, I refer to the now standard definition of loss of bone at the femoral neck measured with clinical DXA technology exceeding 2.5 SDs with reference to young normal values.

In view of the many potentially relevant fragility mechanisms, it is now interesting to explore the effects of both age and osteoporosis on the mechanical properties of cortical bone, in light of the known and growing potential of lifestyle choices and licensed pharmacological agents to impede or reverse the deterioration in its material or structural properties. Much current research focuses on the amount and distribution of bone tissue in the proximal femur without considering the effects of the passage of time on the material properties of the bone tissue. Alternatively, it does the reverse. Although this focus on individual elements of inter-connected toughening mechanisms is necessary, it is argued here that an exclusively compartmentalised approach limits our understanding of the general phenomenon of the fragility of the elderly femur, made worse by the absence of good animal models. Here I address both loss of cortical bone tissue as the human body ages and its changing mechanical nature in the context of potential remedies.

The Varied Functions of Cortical Bone

Cortical bone serves three principal mechanical functions: as a foundation for cartilage within joints; as the material basis for mechanical leverage; and as a surface for the attachment of muscles and ligaments that transfers and dissipates the mechanical loads they generate. A fourth function is to encase the bone marrow. The three mechanical functions require different specifications, but if these are compromised the

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likelihood of hip fracture is increased during trauma and the location of a fracture may be influenced.

The Mechanical Requirements of Cortical Bone in the Proximal Femur

Under normal conditions, cortical bone tissue deforms under a mechanical load and regains its previous anatomical form when that load is removed. In simple terms, the elasticity of cortical bone tissue is a measure of resistance to deformation that is reversible and can be quantitated by its modulus (Young's modulus).

In the case of sub-cartilaginous cortical bone, as found inside the hip joint, it is thin and supported by a network of trabecular bone. Locally thickened cortical bone is associated with osteoarthritis,[3] but is of somewhat reduced density since its turnover rate is increased and the role of cortical bone in the pathogenesis of osteoarthritis remains unclear.[4,5] In contrast, the femoral shaft must be relatively stiff, with a high modulus, in deference to the need to run fast and the limited ability of mature bone tissue to deform without developing an irreversible change in shape. This demands a high bending resistance to which a thick cortex contributes.

When a lower elastic modulus is required than is found in the cortical shaft of the femur, the evolutionary solution is to locate a layer of cortical bone external to and strongly connected to a foundation of trabecular bone.[6] Sometimes this type of cortical bone is of comparable thickness to many of its associated trabeculae. Depending on its microscopic arrangement, as well as the thickness of the cortical component, the combined trabecular-cortical bone structure, for example, in the vertebrae where loads associated with locomotion need to be cushioned, can provide a range of elastic moduli at different distances from the inter-vertebral disc or from cartilage. In the proximal femur, to achieve varying mechanical requirements, near the hip joint the cortex is relatively thin and has a well-developed trabecular foundation; while at the mid-shaft where no reduction of modulus is desirable, the cortical bone is thicker and no trabecular bone is found. From the hip joint capsule distally, the ratio of trabecular to cortical bone declines progressively until in the sub-trochanteric region the proportion of trabecular bone becomes very small.

In this review, I examine the biological mechanisms associated with the maintenance and subsequent loss of a satisfactory mechanical specification for cortical bone in the femur.

Age-related Osteoporosis and Cortical Bone

The term cortical osteoporosis has evolved to include mechanically inappropriate cortical thinning as well as excessive porosity. In the femur, sub-periosteal bone formation continues throughout life as does endosteal resorption, leading in adulthood to a gradually expanding bony envelope.[7] This age-related expansion can maintain bending resistance even as the clinical measure of osteoporosis, a bone mineral density T-score reading of < -2.5, is approached.[8]

Cortical Bone as a Tough Material

Toughness, the obverse of brittleness, is a property indicating high resistance to complete rupture even when a material is subjected to a mechanical load that results in permanent deformity. Almost a century ago, Griffiths pondered the brittleness of some materials like plate glass that can shatter when loads are applied that are many orders of magnitude lower than the weakest of the atomic bonds within them.[9] It is now accepted that solid materials do not experience a uniform distribution of load at the molecular level: instead applied loads are highly concentrated in microscopic locations, which can then experience a microcrack through the locally applied forces being sufficient to overcome the local atomic bonds. Once a sub-microscopic crack has initiated, within brittle materials it accelerates under ongoing load to grow into a macrocrack. Conversely, tough materials like normal bone are resistant to crack growth.

Microscopic mechanisms at the nanoscale that underpin toughness depend on bone's composite nature. Bone as a material is formed of platelet-shaped crystals arranged in overlapping patterns within a proteinaceous substrate. Recently, it has been shown that citrate in bone has a critical role in anchoring mineral platelets to their collagenous matrix.[10] Also, trapped between the platelets are many water molecules.[10] The ratio of length to thickness in mineral platelets (their 'aspect ratio') is critical in delivering the stiffness needed in properly functioning cortical bone. Young adult bone tissue achieves toughness both through limiting the growth of crystal size and through the behavioural properties of the proteinaceous substrate when subjected to shear forces.[11] The aqueous and proteinaceous nature of the substrate protects the elongated or high-aspect-ratio mineral crystals from buckling under load. Bone also contains large amounts of lactate with no certain mechanical role. The very recent discovery of the bridging role of citrate has opened up greatly increased opportunities for understanding molecular-level toughening mechanisms and their disorders.

The femur has additional mechanisms at more macroscopic levels to inhibit the development of complete fracture should it be subjected to loads that overcome these molecular-level protective mechanisms. This has led to the evolutionary concept that fracture resistance has developed a hierarchical structure in which there are multiple fail-safe mechanisms operating at different scales of magnitude should a dangerous crack initiate at nanoscale (**Figure 1**).

Multiple Toughening Mechanisms Delivered at Differing Length Scales

It is evident that to be clinically significant an effect observable at a microscopic level must result in reduced mechanical performance at a more macroscopic scale—immediately or after some delay.[12] The most macroscopic and obviously imperfect level of defence against fracture, here called Level 1 (Length scales are ordered from largest to smallest because of the potential need to add further scales at the more microscopic levels), is personal and societal and depends on modifying or adapting to the environment. It is outside the scope of this article. The second level of fracture resistance relates to the architectural structure of the femur as visible by the naked eye. The third level is provided by the femur's microstructure as visualised in conventional bone histomorphometry. Microscopic sculpting at both these length scales in adult life is accomplished by teams of osteoblasts and osteoclasts

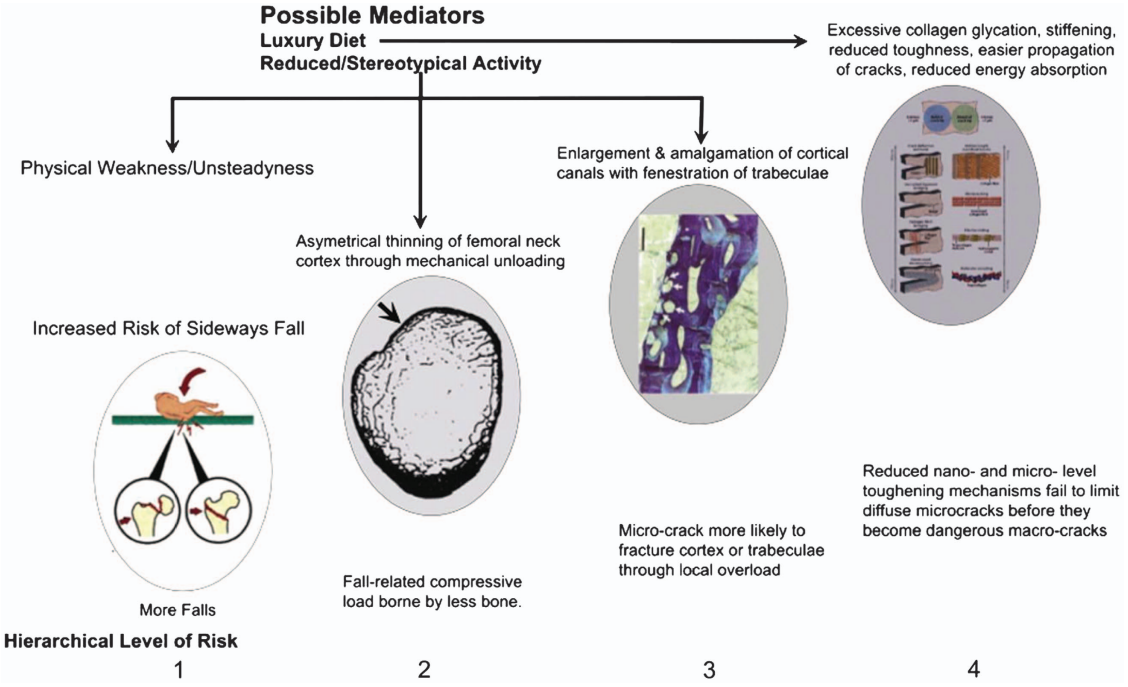

Figure 1 Risk mechanisms arising from aging-related failures in biological protection against hip fracture. These are classified by length scale aligned with the protective mechanisms seen in younger bone. (Scale) Level 1: Failure to avoid sideways falls, involving personal physical decline and societal acceptance of fall risk to preserve personal freedom. Repeated falls might in principle weaken the femoral cortex through the sort of 'delamination' mechanisms that can occur in man-made composites and making a fracture more likely at the next fall (see text). Level 2: Thinning of the superolateral half of femoral neck cortex leads to risk of its local buckling or crushing under compression in a sideways fall, progressing inevitably to complete intracapsular hip fracture. Level 3: Increased remodelling with simultaneous resorption of several adjacent canals (or trabecular surfaces) can destroy the integrity of bone's microstructure if thin bone structures are fenestrated. Here 4 osteons are arrowed: two are undergoing resorption and are about to amalgamate with two others in the resting phase near the periosteal surface of the femoral neck. The walls between osteons are hard to re-create subsequently and the resulting composite osteons have been postulated to constitute the first phase in the gradual 'trabecularisation' of the femoral neck cortex with aging.[57] Level 4: The multiple toughening mechanisms operating at nano- through microscale are shown in this cartoon from Launey *et al.*[15] to which the reader is referred for a detailed explanation. The known or postulated effects of age-related disease and disabilities to limit the effectiveness of these mechanisms include: exposure to products that glycate collagen, so stiffening it (especially in diabetes mellitus) and, for example, fracturing crack bridges; loss of heterogeneity of mineralisation that might otherwise deflect growing cracks with energy absorption; increased crystallinity that might make some abnormally large apatite crystals vulnerable to fracture; loss with cell death or dysfunction of defined low density structures such as osteocyte canaliculi that deflect cracks; (see text). Figure previously published in *Bone*.[1]

organised into the multicellular Basic Metabolic Units (BMUs), which create structural units (BSUs), known as osteons in cortical bone, that are 'glued' together by a collagen-poor osteopontin-containing cement[13] that appears as so-called 'cement-lines' under the microscope. There is circumstantial evidence that at the second level, different BMUs act co-operatively.

Fourth and higher levels of organisation (up to seven have been proposed) are common to the whole skeleton and extend from the micro- through the nanoscales. The reasons normal bone tissue is resistant to crack growth at the more microscopic levels have been recently reviewed by Ritchie and colleagues in this journal[14] and elsewhere.[15] As a consequence of these mechanisms, human cortical bone accumulates microcracks, each of which is thought to record a damaging loading event that was aborted. Seref-Ferlengez *et al.*[16] discussed the role of microcracks in preserving bones like the femur from fracture and showed that it was over-simplistic to assume that a high density of microcracks reflects a high propensity to fracture. Arguing that the relationship of microcracks to fracture risk is complex, they pointed out that the apparent density of microcracks depends on the rate at which a region of femoral cortex is subjected to loads high enough to initiate microscopic cracking; and inversely on the rate at which cortical bone is remodelled.

The integrity and health of cortical bone is considered critical to preventing fractures, because in a fall onto the femur the cortex generally experiences the highest mechanical loads. But, whether the microcrack whose initiation leads to a complete fracture seems to be most plausibly located within cortical bone[17] or subcortical trabecular bone[18] remains controversial.

This article now considers level 2 and level 3 toughening mechanisms and their age-related decline leading to increased cortical fragility. New approaches to fracture prevention are then discussed in light of their impact at different length scales.

Organisation Level 2: the Architecture of the Proximal Femur

Since Galileo's time, investigators have pondered the mechanical requirements of the mammalian femur.[19] Darwin observed that the heavier wing and weaker leg bones of the wild compared with the domestic duck reflected different patterns of mechanical usage.[20] Next, Wolff proposed that bones adapt their internal structure efficiently so as to minimise the effects of the mechanical loads placed upon them.[21] This hypothesis requires that in regions exposed to higher than average strains, there is a net imbalance favouring bone formation over resorption.

Compression, for example, in a sideways fall, might cause fracture in other ways than through bending. Bone can disintegrate by crumbling under high compression, although thin or unsupported bony structures may sometimes buckle at rather lower strains. Buckling may explain the collapse of osteoporotic cancellous bone in the spine.[22] In a fall onto the greater trochanter, the superolateral cortex, normally loaded weakly in tension, becomes heavily loaded in compression. Because of its thinness in the elderly,[23–27] this cortex is interesting for its potential to buckle in a sideways fall.

Forces leading to fracture in bending in the absence of buckling were first estimated from DXA by Yoshikawa *et al.*[28] It was found that the resistance to bending of the hip remains nearly constant during normal aging.[29] This contrasts with the fact that, from age 40 years, there is a 10-fold increase in hip fracture risk every 20 years.[30] Rapid loss of hip-bending resistance occurs only with the onset of frailty.[8] Prior to that, DXA BMD (in g cm^{-2}) typically declines somewhat faster than bending resistance. This is explained by the gradual widening of the femoral neck diameter with age,[7] which for algebraic reasons reduces BMD simultaneously with increasing section modulus (a common DXA-derivable measure of bending resistance). Widening of the femoral neck is driven by periosteal bone formation associated with compensatory endosteal resorption[31] and is associated with markers of sex hormone deficiency.[32] In the absence of an increase in available cortical bone tissue, widening leads to cortical thinning and consequent increases in the risk of a buckle.

The contrast between the thickness of the inferomedial and the thinness of the superolateral femoral neck cortex increases with aging because the inferomedial remains largely unchanged as the superolateral grows thinner.[24–26] This change has a small effect on bending resistance while increasing the risk of buckling or crushing superolaterally. In a sideways fall, an elderly and thinned superolateral cortex taking the full impact load might fracture through either mechanism.

Architectural changes associated with hip fracture

After matching for age, female cases of hip fracture had substantially reduced DXA-assessed bending resistance compared to controls, equivalent to 2 decades of age-related changes;[8,33] but there was substantial between-group overlap. Cases also had thinner[34,35] bone cortices. But re-calculated 2D DXA estimates of bending resistance (reflected in Section Modulus) were somewhat[36] or little better than BMD in predicting hip fracture.[37,38] Computed 3D tomography studies combined with finite element analysis (FEA) are generally superior to 2D DXA for predicting strength.[39] In the Age, Gene, Environment Study, Rejkyavik (AGES Study) population-based cohort study, aging of the individual was associated with loss of FEA-assessed strength[40] of the hip in both stance and falling configurations and thinning of the superior femoral neck cortex.[26] This was more rapid in women than men, while in contrast hip fracture prediction was improved more in men than women. These findings were supported by two case-control studies,[35,41] one suggesting that patchy as well as uniform thinning of the superolateral cortex could promote hip fragility.[41]

The femoral neck cortex and the lesser trochanter contains regions of highly mineralised calcified cartilage, that are anatomically associated with tendon and capsular insertions and appear to grow in relative surface area with age.[42] Observationally, periosteum and the bone-cartilage tidemark have been shown to form a continuum anatomically[43] and any growth in the proportion of calcified cartilage in the femoral neck with age is likely to degrade its mechanical properties through the inferior strength of calcified cartilage or even through stress-shielding of subcortical trabeculae which are only weakly compressed during slow walking. The extent of calcified cartilage in the cortex has so far not been compared between hip fracture cases and controls.

Localised cortical thinning and fracture mechanics

Cortical thinning is almost certainly relevant to hip fracture in the elderly proximal femur, as far distally as the level of the lesser trochanter. In the sub-trochanteric region, the cortex generally remains too thick for cortical thinning alone to be a primary cause of fracture. Fast cinematographic investigation of experimental (ex vivo) hip fracture has shown that the initiating crack in a basi-cervical hip fracture frequently begins in the superolateral cortex.[17] It can be shown mathematically that section modulus of the femoral neck collapses suddenly once the crack becomes macroscopic; the inferomedial cortex, no longer braced by the superolateral cortex, then fractures in bending as a secondary event.[24] If the initial mode of cortical failure is by buckling not crushing, supporting trabeculae which become reduced locally with age[44–46] may be critical to cortical integrity because they have a surprisingly large effect to prevent buckling while having little capacity to prevent crushing.[44,47,48] It should be noted that the so-called 'buckling ratio' derived from DXA studies may not be linearly related to the load required to cause buckling in life, since for the two quantities to be so related requires that the femur at the point of measurement is made of homogeneous material of uniform thickness distributed in a circular cross-section.

It is now understood[49] that local critical stress, in which both the stresses experienced by a section of femoral neck cortex and its curvature normal to that stress are important determinants, is a measure of resistance to buckling.[24,44,50] While *in vivo* CT-based 3D studies modelled with finite element analysis (FEA) can assess the potential for crushing[51] of the thinned superolateral cortex, realistic predictions of cortical buckling, which has an absolute requirement for non-linear modelling and other refinements to avoid unrealistic stress calculations at the individual voxel level, needs to be incorporated into future FEA modelling studies of hip fracture.

Organisation Level 3: the Cortical Osteon and Regulation by its Osteocyte Network

Parfitt estimated that there are 21×10^6 cortical osteons in the human skeleton.[52] As life progresses, the older osteons are progressively resorbed in whole or in part through remodelling by newly developing osteons. Collectively, partially resorbed osteons are referred to as interstitial bone. Macromechanical measures of femur strength are partly predictable from cortical porosity and much less predictable from other tests of micromechanical properties of cortical bone.[53] Hence it is important to understand how the remodelling osteon achieves or fails to achieve complete refilling.

New osteons within the cortex are created by advancing teams of osteoclasts. In-filling of the spaces created within the cortex typically takes in excess of three months simply because the work rate of osteoblasts is such that removal of bone by osteoclasts is much more rapid than its osteoblastic replacement. This creates a temporary remodelling space that may become permanent if in-filling is incomplete.[52] On periosteal and endosteal surfaces, erosion by osteoclasts results in rough or scalloped surfaces that are likely to generate so-called 'stress risers' that might attract crack formation until they are subsequently smoothed over by osteoblastic bone formation. So much is now well understood; and it is commonly believed that the anti-fracture efficacy of anti-osteoporotic agents that reduce bone formation depends in part on retaining smooth bone surfaces that do not attract crack initiation.

A good deal is now known about the endocrine regulation of the balance between bone formation and resorption and how it interacts with bone cells' intrinsic regulation mechanisms; but less is known about the local detailing of bone modelling and remodelling. Recently, the contrasting effects of local geometry on bone formation in biological models of trabecular or 'hemi-osteonal' bone formation (in Parfitt's terminology[54]) and in cortical osteonal bone formation were demonstrated by Bidan *et al.*[55] They derived a plausible explanation for how the 'trabecularisation' of the bone cortex (that is, excavation and partial resorption of cortical bone to give it a trabecular structure) as seen in growth and old age could become irreversible. The periodic tethering of formative cells to the forming surface was associated in this model with smoothing and in-filling of hemi-osteonal resorption pits of semi-circular cross-section through the generation of tension via 'actin chords'. This reduces surface curvature. In contrast, osteonal canal surfaces develop increased curvature as their canals narrowed. Extrapolating to *in vivo* cortical remodelling, where large composite canals are formed in the elderly femoral neck cortex from the merging of neighbouring canals undergoing simultaneous resorption,[56,57] surface curvature might be reduced rather than increased, resulting in permanently enlarged spaces much larger than a normal cortical Haversian canal. With repetition, this could create trabecular bone by sculpting it out of previously solid cortex. On the basis of computational modelling of microradiographic scan data, Fernandez *et al.*[58] have postulated that an additional effect of osteocyte loss, which is prevalent in femoral cortical bone in the elderly, is to enlarge Haversian spaces.

The role of osteocytes in orchestrating the remodelling process is gradually becoming clearer but from our current perspective more complex. The young person's osteon or Bone Structural Unit (BSU), contains osteocytes at varying densities estimated with 3D synchrotron radiation techniques as between 20×10^3 and $90 \times 10^3\,mm^{-3}$;[59,60] lining cells interposed between the matrix and the osteocytes' source of nutrition; and, only if it is actively undergoing renewal, osteoblasts and osteoclasts respectively increasing or reducing its mineralised mass. The remodelling BSU is called a BMU and is supervised by endocrine, paracrine and possibly sympathetic[61] pathways.

Osteocytes are now understood also to have crucial roles in both sensing and initiating responses to mechanical loading by regulating the composition of the mineralised matrix[62,63] and deploying a range of local and systemic signals, including nitric oxide,[64] prostaglandins, RANK ligand[65] and the osteoblast inhibitor sclerostin.[66] They also regulate plasma phosphate levels, which if depressed leads to osteomalacia. However, it is principally through vitamin D deficiency that osteomalacia is implicated in a minority of hip fracture cases.[67,68] Hence, osteocytes might be key regulators of cortical bone's toughness from the length scale of the osteon down to that of the mineral matrix interface.

The role of osteocytes in age-related bone loss has recently been reviewed by ourselves[1] and others.[69] Osteocytes are characterised by their dendrites, which interconnect with other osteocytes, surface lining cells and the cement line that defines where the formative phase began. These dendrites track through microscopic canaliculi that extend mostly radially across the thickness of the osteon. Canaliculi may also have an important permissive role in absorbing the energy associated with the microcracks that can develop under load.[70]

Compared with controls, in cases of hip fracture, full osteonal closure appeared delayed, explaining in part the observed increases in cortical porosity.[71] As the resorption cavity is filled in, osteocytes are embedded at progressively declining densities, the rate of decline being steeper in hip fracture cases.[59,72] In fracture cases, the proportion of osteocytes expressing sclerostin also increased more rapidly with maturation of the osteon[73] than in controls, while also expressing nitric oxide synthases (NOS) less frequently;[74,75] NOS are involved in osteocytic endocrine signalling.[76] Whenever ongoing mineralisation and canal closure were observed in controls, they were associated with a higher density of recently embedded osteocytes adjacent to the osteonal canal; such densities were rarely achieved in the osteons of hip fracture cases.[72]

Osteocyte Aging and Death

Osteocyte death is widespread in the elderly proximal femur[77,78] where, due to the femur's low rate of remodelling,[79] the average newly entombed osteocyte must wait two or more decades before liberation from its surrounding bone matrix. Although osteocytes are frequently located 0.1 mm or further from their source of nutrients, osteocyte death is much less prevalent in more actively remodelling bone such as the iliac crest, suggesting that aging of the embedding tissue or of the osteocyte itself might contribute to its death. In the femoral shaft, individual osteocyte lacunae shrink in volume as the subject ages, but the numbers of lacunae in the matrix per unit volume of bone tissue does not change.[60] Experimentally, Noble *et al.*[80] showed that bone experiencing reduced loading contained higher proportions of osteocytes undergoing apoptosis. When loading exceeded normal limits, rapidly developing microdamage developed that was associated[81] with greatly increased osteocyte apoptosis. This preceded the appearance of florid osteoclastic resorption and remodelling followed by in-filling.[80] Parathyroid hormone (PTH), which experimentally promotes a younger osteocytic phenotype,[82] and oestrogen can also promote osteocyte survival[83,84] and encourage a positive remodelling balance through increasing bone formation. There has been speculation that osteocyte apoptosis is an important mechanism in the initiation of normal remodelling in femoral cortical bone. This remains unproven. Indeed, empty osteocyte lacunae accumulate with age suggesting that sometimes osteocyte death fails to trigger the

remodelling of the cell's surrounding matrix. Sclerostin, a powerful inhibitor of bone formation, is normally secreted by osteocytes and chondrocytes but not by osteoblasts or lining cells[66,85,86] and is likely to modify the local architecture of remodelling bone—an effect lost necessarily in bone lacking osteocytes.

Osteocytes: Additional Regulatory Roles?

Proximity to an osteocyte is associated with greater regularity in the size, orientation and satisfactory mechanical characteristics of bone crystals.[87] In crystals up to 30 nm in length crystal imperfections (for example, those arising from inclusions of proteinaceous material) had little effect on tensile strength.[88] To achieve adequate mechanical properties, larger crystals had an increased requirement for perfection. Crystal size grows with tissue aging[89] sometimes spectacularly in hip fracture cases.[90] Osteocytes may also function collectively as a syncytium:[91] they are sensitive to mechanical loading, promote[65] bone breakdown and regulate its growth,[66] may locally regulate matrix mineralisation[92] and also mobilise calcium[63,93] in response to PTH signalling.[94] Their functions in vertebrates may have evolved with terrestrial living.[95] The concept that osteocytes function collectively has given rise to the idea that they might form part of a so-called 'small world network',[96] which is a way of efficiently delivering a complex service at low economic or biological cost in systems as diverse as parts of the brain[97] and large airline networks. Osteocytes so organised might deliver diverse and complex interactions with other cells and systems such as osteoblasts, osteoclasts, phosphate and calcium homeostasis in both plasma and local bone matrix. Any small world network carries with it a potential risk of systemic breakdown in the event that a few key elements (for example, certain osteocytes or groups of osteocytes) became disabled. Conversely, the majority of less important elements may be lost with only local consequences. In summary, quiescent cortical osteons are assigned multiple endocrine and paracrine tasks in addition to their structural role. These functions depend on osteocyte survival, but it is not clear what proportion of osteocytes must survive, nor how to identify which osteocytes are especially critical to the optimum biological functioning of cortical bone in the femur.

Mineralised Bone Tissue Heterogeneity

The lamellar structure of mature osteonal bone with its alternating densities may assist in the deflection of cracks.[98] In hip fracture cases naive to anti-osteoporosis treatment, there were decreases in matrix mineralisation in the cases[99,100] together with reduced heterogeneity of both the mineral:matrix and carbonate:phosphate ratios and increased crystallinity.[101] In contrast, cases and controls had similar indentation modulus and hardness. This suggests compensation for reduced mineralisation by a stiffer organic phase in hip fracture cases, making the bone tissue potentially less tough,[99,100] consistent with the finding of Norman *et al.*[102] that reduced mineralisation is positively associated with diffuse damage and microcrack density.

Cortical osteons in young people have a steeper gradient of mineralisation from the canal to the cement line than in older subjects, with the highest mineralisation levels being adjacent to the canal,[103] where the volumetric density of osteocytic nuclei is lowest.[59,72] This mineralisation gradient may have been the first demonstration of an important source of heterogeneity. It also raises the question whether reduced heterogeneity and increased stiffness of the organic phase in hip fracture cases might be related to the ages of the osteons studied.

Remodelling and Fracture Risk

Increased osteonal age as a potential contributor to hip fracture risk appears at first sight paradoxical in view of the well-known increase in remodelling post-menopause contributing to osteoporosis. The paradox might be resolved if this type of remodelling caused net bone loss or created new bone with sub-optimal mechanical properties such as reduced heterogeneity. Remodelling osteons are clustered anatomically.[56,57] A mechanism whereby remodelling osteons, which amalgamate to form giant composite osteons, might promote the trabecularisation of the cortex received some support from Bidan *et al.*'s investiogations already referred to.[55] Subcortical femoral trabeculae, in contrast to most iliac trabeculae, when viewed under polarised light show that their internal lamellae are usually not parallel to either trabecular surface, suggesting they might have been sculpted out of pre-existing compact cortical bone by osteoclasts.[104]

New imaging techniques now make it possible to investigate the detailed 3D structure of individual osteons in the femoral cortex and the anatomical relationships between them.[105,106] These offer new avenues for understanding how conversion of the cortex to trabecular bone, leading to cortical thinning,[104,107] develops and to how osteonal structures might help preserve the toughness of bone once a crack threatens to expand beyond the osteon's own territory.[108]

Another cause of increased remodelling is the secondary hyperparathyroidism associated with reduced vitamin D levels, commonly seen in the elderly. Before it develops into frank osteomalacia with demineralisation of bone tissue, this can result in accelerated net bone loss, cortical thinning and trabecular fenestration as reviewed by Chavassieux *et al.*[109]

Finally, in view of its location at the potentially highly stressed cortical surface of the femur, sub-periosteal bone remodelling deserves attention. Power *et al.* found that the extent of sub-periostal alkaline phosphatase in the femoral neck (reflecting new bone formation) was associated with the proportion of crenellated intracortical canals apparently undergoing osteoclastic resorption.[110]

Organisation Level 4: Sub-microscopic Toughening Mechanisms

These have been extensively reviewed recently and the reader is referred to excellent summaries in this journal and elsewhere.[14,15,111,112] The prevalence of mechanical stress-concentrators such as notches and flaws must inevitably be increased in the cortex by increased remodelling, typically seen after menopause. Normal mature human femoral bone subjected to cyclic loading develops microcracks that grow then rapidly decelerate,[113] reflecting multiple toughening mechanisms absorbing the energy associated with cracking without excessive sacrifice of strength.[108,114] Their length scales range from the molecular (for example, re-formable

bonding of collagen[115] and cross-links[116] through that of the potentially crack-deflecting osteocyte canaliculus (~250 nm diameter).[70]

The Behaviour of Cracks

Crack energy is directional: deflection absorbs a crack's energy. When the matrix of bone is not homogeneous, a developing crack will experience deflections.[117] So heterogeneity of its material properties is desirable and intrinsic to normal lamellar bone.[112,118]

On a larger length scale, osteons also absorb or deflect cracks.[119] Repair of bone sufficiently damaged by the development of an enlarging crack may necessitate remodelling. Because femoral cortical bone is more liable to crack longitudinally, cracks that start transversely are usually diverted longitudinally so that an undetectable tendency to cortical splitting, akin to the delamination of plywood, might be the first adverse consequence of a heavy fall onto the greater trochanter. However, the superolateral cortex of the femoral neck can become as thin as 0.5–1.0 mm in old age,[44,120] so because of their size few osteons capable of crack capture can remain within it. This makes thin cortices (like trabeculae) dependent on the more microscopic crack-capturing mechanisms.

Un-remodelled cracks accumulate with aging in the femur.[121] Zioupos and Currey[122] and Diab *et al.*[123] showed *ex vivo* that older bone formed linear microcracks in preference to diffuse damage with an exponential decrease in fatigue life with age.[123] By analogy with man-made composites, longitudinal splitting short of generating a clinical fracture, in which cracking occurs parallel to the periosteal surface,[17] must increase the tendency of the superolateral cortex to buckle under load in a future fall.[124]

At the nanoscale level, collagen molecules undergo increased glycation with ageing, which is likely to make bone harder and reduce toughness.[14,125] Femoral cortical bone tissue turnover has only rarely been studied, Wand *et al.*[79] estimating its half life as approaching two decades, which gives plenty of time for exposure to circulating glycating sugars to increase collagen cross links.[126]

Hazards Associated with the Type 2 Diabetes Epidemic

The recent increase in consumption of thermally processed foods resulting in high levels of pro-oxidant advanced glycation end-products (AGEs) likely increases glycation rates. These molecules also promote inflammation (which when local can lead to bone loss) and appetite, so are of mutual interest in both the study of hip fracture and type 2 diabetes.[127] Diabetics provide about 10% of hip fracture cases and have a 1.6 to 1.7-fold increased risk after adjusting for BMD.[128,129]

Reducing Hip Fracture Risk: Current Approaches and Future Prospects

Because healthy bone strength is organised so that it can prevent cracks propagating both while they are still at the nanoscale or at any larger scale up to that of the whole femur, effective anti-fracture interventions might reduce fracture risk by enhancing protection at any length scale. Moreover, the comparative lack of correlation of measurements related to bone strength at the nano- and microscales with those at the level of the whole femur[53] should be viewed positively, as it offers the additive potential for simultaneously intervening at multiple length scales.

Lifestyle and Dietary Interventions

In men, in their seventh decade, substantial local increases in superolateral cortical thickness were achieved in a clinical trial with targeted mechanical loading, through regular hopping on one leg 50 times daily.[130] This level of physical activity, quite easily achieved in healthy 60-year-old men, is likely unachievable in people beginning exercise from their eighth decade after lifelong sedentary behaviour; but, it reinforces observational studies suggesting that commitment to a physically active lifestyle in older persons postpones the age-related increase in hip fracture risk.

The need to trial the effects of reducing consumption of AGEs on risk of type 2 diabetes is self-evident. There is a similarly strong case for including older subjects at risk of hip fracture to measure the intervention's effect on femoral strength and integrity.

Pharmaceutical Interventions

Broadly speaking, currently prescribed bisphosphonates and other anti-resorptive agents such as denosumab reduce the risk of all types of hip fracture[131] other than the so-called atypical sub-trochanteric fracture. Bisphosphonates have an effect that is several-fold larger in reducing trochanteric and intra-capsular fractures than can be explained by their effect to increase bone density. Two ideas have been put forward to explain this dissociation:[132] because they reduce remodelling, anti-resorptive agents must also reduce the number of mechanical stress-concentrating resorption pits where a dangerous crack might initiate; and because they might have a beneficial effect on osteocyte function. These ideas are extensively discussed by Geissler *et al.*[133] in light of the adverse effects of bisphosphonates and probably other anti-resorptive agents[134] on sub-trochanteric fracture in long-term therapy.

There might be several factors contributing to this increased risk: the reduced birth rate of osteocytes in bisphosphonate-treated cortical bone, coupled with their longer potential dwell-time in the matrix (and hence risk of death *in situ*), that results from reduced remodelling; enhanced accumulation of AGEs due to the effect of bisphosphonates to prolong the life of bone tissue; and possibly a specific bisphosphonate-effect to enhance the long-term accumulation of deleterious cross-links.[135,136]

In vitro mechanical testing suggested that bone anabolic agents do one of two contrasting things besides increasing bone formation. They either increase the heterogeneity of cortical bone in the case of PTH receptor type 1 agonists; or in the case of anti-sclerostin antibodies they appeared to leave heterogeneity unchanged.[137,138] The potentially toughening effect of teriparatide and abaloparatide is predicted from their effects to reduce the overall bone tissue age in treated patients and increase tissue heterogeneity. Anti-sclerostin antibodies might only reduce bone tissue age.[138,139] Close attention will now be paid to contrasting the effects of the PTH1 receptor binders and the anti-sclerostin antibodies in their long-term

effects on those fractures associated with the brittleness of ageing cortical bone.

Conclusions

The 1992 NIA Bone quality workshop[140] stimulated many research studies reviewed here aimed at understanding what, apart from BMD, makes the femur fracture-resistant. Hopefully we shall soon understand why physically active and generally osteoporotic elderly osteoporotic women in rural equatorial Africa have tough if osteoporotic bones and rarely suffer hip fractures,[141] whereas in the affluent world more sedentary elderly women, even those without osteoporosis, are at much greater fracture risk. What seems certain is that our improving understanding of the role of cortical bone in the femur will continue to promote improvements in the clinical management of hip fracture in the years ahead.

Conflict of Interest

The author declares that in the last two years he has received compensation for providing written advice to Eli Lilly on the history of publicly funded research on the use of hPTH(1-34), that is, teriparatide, for treating osteoporosis. Prior to 2012 the author received compensation for providing scientific advice to Procter and Gamble, Novartis, Lilly and Merck.

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