Osteoporosis II

Pathogenesis of bone fragility in women and men

Ego Seeman

There is no one cause of bone fragility; genetic and environmental factors play a part in development of smaller bones, fewer or thinner trabeculae, and thin cortices, all of which result in low peak bone density. Material and structural strength is maintained in early adulthood by remodelling; the focal replacement of old with new bone. However, as age advances less new bone is formed than resorbed in each site remodelled, producing bone loss and structural damage. In women, menopause-related oestrogen deficiency increases remodelling, and at each remodelled site more bone is resorbed and less is formed, accelerating bone loss and causing trabecular thinning and disconnection, cortical thinning and porosity. There is no equivalent midlife event in men, though reduced bone formation and subsequent trabecular and cortical thinning do result in bone loss. Hypogonadism contributes to bone loss in 20–30% of elderly men, and in both sexes hyperparathyroidism secondary to calcium malabsorption increases remodelling, worsening the cortical thinning and porosity and predisposing to hip fractures. Concurrent bone formation on the outer (periosteal) cortical bone surface during ageing partly compensates for bone loss and is greater in men than in women, so internal bone loss is better offset in men. More women than men sustain fractures because their smaller skeleton incurs greater architectural damage and adapts less effectively by periosteal bone formation. The structural basis of bone fragility is determined before birth, takes root during growth, and gains full expression during ageing in both sexes.

The purpose of bone, like all organs, is to ensure survival of the individual; it is a lever needed for movement and speed. Nature selects materials and structures with properties that meet the contradictory needs of strength and lightness, stiffness and flexibility. Stiffening the rope-like triple helical fibres of type 1 collagen with mineral crystals confers resistance to bending for propulsion, but excessive stiffness produces glass-like brittleness. The collagen weave confers flexibility that allows storage of energy in reversible (elastic) deformation during impact loading or muscle contraction. When the elastic limit is exceeded, bone can store more energy by plastic (irreversible) deformation, but at the price of microdamage. If the imparted energy exceeds the elastic and plastic limits of deformation, fractures arise. Strength and lightness are also achieved by geometrical structure. The long bones are tubular structures that contain a marrow cavity, so that the cortical mass is placed distant from the central long axis, conferring greater resistance to bending. In the axial skeleton, the vertebral bodies have a thin cortical shell and a trabecular spongiosa, or cancellous network, of plates and sheets that absorb energy during compressive loading and that return to their original height when unloaded.

These features, so slowly selected for during evolution, so faithfully reproduced during ontogenesis, and all fully expressed at the completion of linear growth, work well, for a while. Bones do eventually become fragile though, because bone modelling and remodelling, the two cellular mechanisms available to construct and reconstruct the skeleton during ageing, fail to maintain the pristine material and structural properties of bone that confer resistance to structural failure in an individual increasingly predisposed to falls.

Lancet 2002; **359:** 1841–50

Department of Endocrinology, Austin and Repatriation Medical Centre, Heidelberg 3084, Victoria, Australia (E Seeman FRACP)
(e-mail: egos@unimelb.edu.au)

Bone mineral density (BMD) and osteoporosis

The mineralised skeleton is defined externally by its outer (periosteal) surface and by the endocortical, trabecular, and intracortical components of its inner (endosteal) surface (figure 1).[1] Cellular activity on these surfaces produces net bone formation or resorption during growth and ageing, modifying the size, shape, architecture, mass, and strength of the skeleton. Periosteal bone formation defines the cross sectional area of the bone, whereas endocortical bone formation or resorption determine the proximity of the endocortical and periosteal surfaces, and so, cortical thickness—ie, endocortical bone formation thickens the cortex and endocortical resorption brings the endocortical and periosteal surfaces closer together, resulting in cortical thinning (unless concomitant periosteal bone formation compensates). Bone formation on each side of the trabeculae thicken them, whereas resorption thins them, making the trabeculae rodlike or perforated, disconnected, and less able to tolerate loading—ie, fragile.

The bone mineral content of a particular region of the skeleton is quantified by measurement of the degree of attenuation of photons by the mineralised bone mass with bone densitometry (figure 1). Measurement of BMD makes it possible to predict fractures and is an indispensable tool in identification of individuals at high risk of injury. However, bone densitometry provides only

Search strategy

The work is based on review of available international publications, printed in English, collected during the past 20 years, and documented in *Advances of Osteoporosis and Progress in Osteoporosis*; a journal I edit and in which all the published work in osteoporosis is summarised in abstract form. The main published work is based on the major bone journals (*J Bone Miner Res, Bone, Osteoporos Int, Calcif Tissue Intern, J Clin Densitometry*) and journals such as *Lancet*, *N Engl J Med*, *Am J Med*, *JAMA*, *Arch Intern Med*, *Endocrine Rev*, *J Paediatric*, *Paediatrics*, *J Biomechanics*, etc.

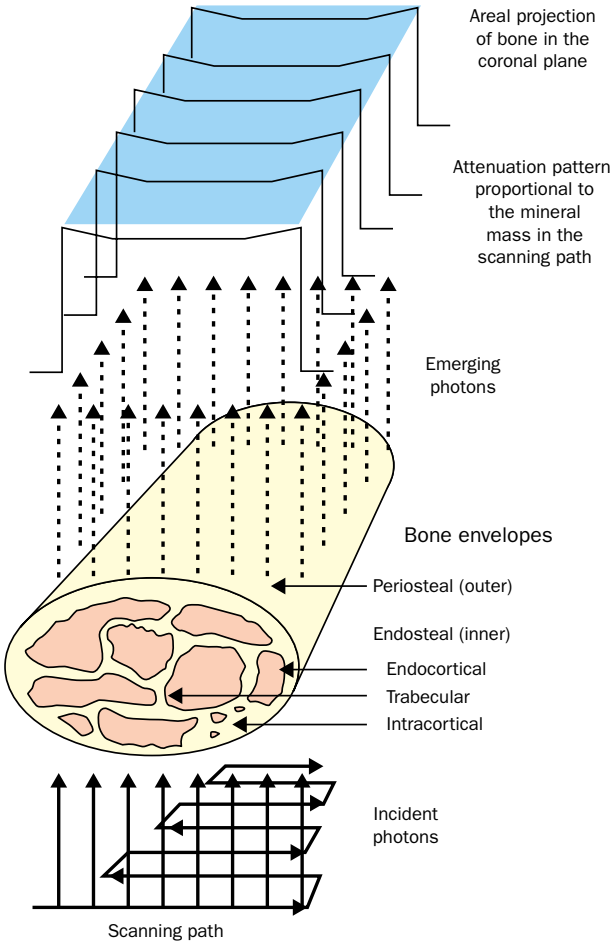

Figure 1: **Structure of bone and process of densitometry**
Reproduced from: Seeman E. Sexual dimorphism in skeletal size, density and strength. *J Clin Endocrinol Metab* 2001; **86:** 4576–84. By permission of The Endocrine Society.

a two dimensional areal view of the three dimensional mineralised mass of bone. The length and width of the scanned bone is known, but not its depth. Since results of densitometry are a widely used endpoint in clinical practice and research, an appreciation of the limitations of this method is needed if the pathogenetic basis of bone fragility is to be understood.[2,3]

During growth, BMD increases, suggesting, incorrectly, that bone density has risen. Enhancement of BMD is mainly caused by the rise in bone size, which results in a proportional rise in the amount of mineralised bone within the periosteal envelope; the volumetric BMD of the whole bone remains constant or increases only modestly (figure 2)[4]—ie, the bone is bigger than it was but not more dense. A bone with greater depth than another absorbs more photons but does not necessarily have more bone mineral (distributed structurally as thicker or more trabeculae or a thicker cortex) within the same external bone volume. To understand the reason for the increase in BMD, regulators of growth in size, not just the mineral accrual within the growing bone, should be studied.

During ageing, bone resorption on the endocortical, intracortical, and trabecular surfaces reduces the amount of bone within the periosteal envelope as trabeculae thin and disappear, and as cortices thin and become porous. Simultaneously, periosteal bone formation partly offsets removal of bone on the inner surface. The net loss of bone (the sum of the amount removed inside plus the amount deposited outside) is less in men than in women because periosteal apposition is greater in men (figure 3).[5,6] A densitometer cannot show surface-specific and sex-specific changes. Bone formation on the outer surface and simultaneous resorption in the inside might not produce a change in BMD, yet changes in bone geometry and strength have taken place. What happens to each surface of the bone should be studied to appreciate the nature of sex differences in bone fragility.

Structural abnormalities

Women and men who sustain fragility fractures do so because they have reduced BMD. The deficits are generalised, but tend to be most severe at the site of fracture—eg, people with fractures of the spine have greater deficits at the spine than at the hip.[7–10]

Individuals with spinal fractures have reduced vertebral BMD for two reasons. Vertebral size is smaller in cross sectional area and height, and there is less bone in the smaller bone—ie, the cortices are thin and porous, especially on the inner third near the bone marrow, trabecular plates and sheets are thinned, and many are rodlike or disappear, particularly horizontal trabeculae, causing loss of connectivity.[11–19] In men, trabecular

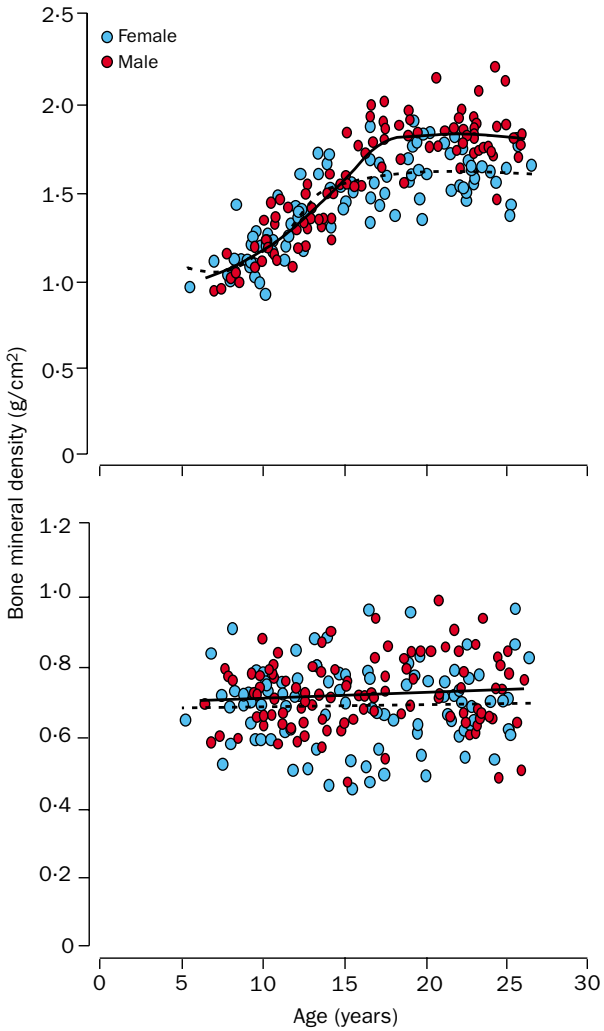

Figure 2: **Femoral shaft areal bone mineral density (upper) volumetric bone mineral density (lower)[4]**
Measured with densitometry. Reproduced from reference 4 by permission of The Endocrine Society.

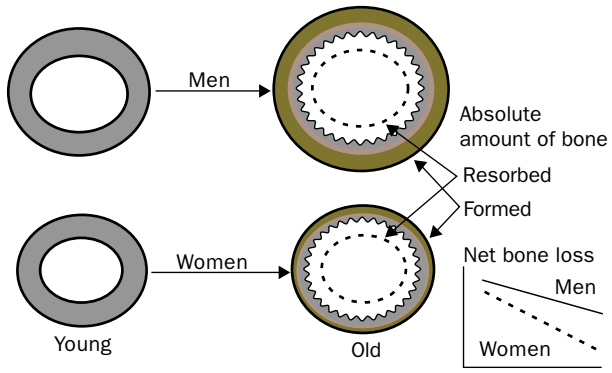

Figure 3: **Position and extent of bone loss in men and women**
Absolute amount of bone resorbed on the inner bone surface, and formed on the outer bone surface is more in men than in women during ageing.

thinning rather than loss of connectivity tends to dominate. However, those with osteoporosis and fractures have greater loss of connectivity than men with osteoporosis but without fractures.[20]

Women and men with hip fractures have normal vertebral size and modest deficits in vertebral BMD.[7,12] In women, femoral neck diameter can be reduced, normal, or increased.[21–24] BMD is reduced because of thinning of cortices, which contain large intracortical cavities.[25] Men have reduced femoral neck diameter with reduced BMD, probably due to cortical thinning.[12] How do these site-specific and sex-specific structural abnormalities develop?

Peak bone size and BMD

Origin of site-specific abnormalities

The site-specific structural abnormalities seen in individuals with fractures have their origins in growth as well as in ageing.[7,26,27] The deficit in BMD in the daughters of women with fractures of the spine, relative to their age-matched peers, is about half that of their mothers, which is consistent with the view that the deficit sustained by their mothers, relative to their age-matched peers, was present when they were premenopausal. Women who begin the menopause with a low peak BMD are disadvantaged, since any further loss of bone, as a result of age and menopause, will make the skeleton fragile and susceptible to fracture with minimum trauma.

Daughters of women with fractures of the hip have only slightly reduced BMD of the femoral neck, suggesting that their mothers' deficit developed during adulthood, perhaps because of coexisting illness, immobility, or secondary hyperparathyroidism. Femoral neck volume is increased in women with hip fractures and increased in their daughters by half that of their mothers, suggesting that the larger bone size in the mother was present when she was premenopausal.[7] Individuals with a large femoral neck, on average, have a narrow cortex, because the wider bone needs less cortical thickness to achieve the same bending strength (Seeman E, unpublished data). Reduced peak cortical thickness confers a disadvantage when the inner cortical surface is eroded as a person gets older, thinning the already thin cortex and predisposing to buckling.[28]

Cause of late-onset site-specific deficits

The effects of illness, risk factors, or hormonal deficiency and excess during growth depend on the severity and duration of the illness, but also on the maturational state of the region of bone affected by illness. Time of illness is important since the axial and appendicular skeleton behave differently during growth. For example, growth velocity of total body length is high immediately after birth, slows rapidly, then accelerates at 12 months of age. This acceleration is site-specific and is caused by quickened appendicular, not axial, longitudinal growth.[29–31] Appendicular growth remains more rapid than axial growth until puberty. At puberty, with secretion of the sex steroids, long bone growth slows and epiphyses begin to fuse. At this stage, axial growth accelerates. Exposure to illness or risk factors before and during puberty therefore results in greater deficits at a site than exposure after puberty, when the site is more maturationally advanced in size and mass.[31] If a disease

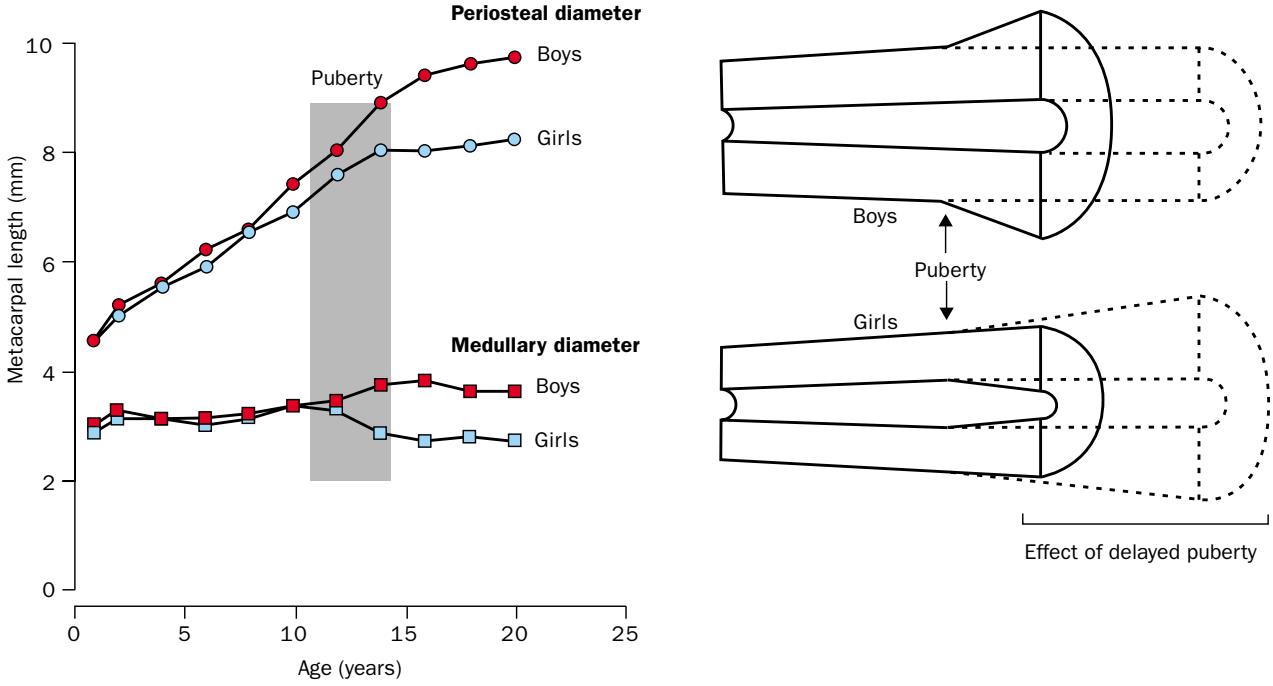

Figure 4: **Effects of puberty and delayed puberty on bone development in boys and girls**

affects oestrogen production or its action during a person's growth phase, epiphyseal growth continues, producing greater leg length, but the axial growth spurt is inhibited, resulting in a shorter trunk. Such a pattern is seen in men with Klinefelter's disease, oestrogen receptor abnormalities, and aromatase deficiency.[32–34] Individuals who develop anorexia nervosa before puberty have deficits in vertebral body and femoral neck width, since both regions are far from their peak, whereas individuals with later onset disease have deficits confined to the vertebral body, because the appendicular skeleton is nearer completion of its growth.[35]

The more rapid appendicular than axial growth before puberty and the later onset of puberty in men results in them having longer legs than women, with less sex difference in trunk length. Sex differences in bone width are established during puberty. Cortical width increases by periosteal bone formation in men, and by less periosteal bone formation but by more endocortical apposition in women.[31,36–38] Androgens, growth hormones, and growth hormone insulin like growth factor 1 (IGF-1) independently and additively stimulate periosteal apposition in men, whereas oestrogens inhibit periosteal apposition, resulting in narrower bone in women than in men (figure 4). Oestrogen stimulates endosteal apposition in women.[36] Thus, men have longer and wider long bones with only a slightly thicker cortex than do women—we look at each other with less obliquity when we are seated.[31,38] The cortical mass is placed further from the neutral axis of the long bone in men, conferring greater resistance to bending by the correspondingly larger muscle mass.[32] The greater centrally placed endocortical contribution to cortical thickness in women could be the reserve for fetal skeletogenesis; a feat achieved without compromising the bending strength of bone.

Patients with delayed puberty have reduced BMD.[39–42] The bone is smaller with a thinner cortex in men because of the loss of periosteal apposition. In women, bone width is sometimes increased because of the removal of the inhibitory effects of oestrogen on periosteal apposition.[43] The cortex is thin because endocortical apposition does not happen (figure 4). The reduction in bone strength caused by delayed puberty is likely to be more severe in men than in women in view of the importance of periosteal apposition in determination of the bending strength of bone. The smaller femoral neck diameter in men with hip fractures,[12] and the larger femoral neck diameter in women with hip fractures,[7] could be the result of sex steroid deficiency during growth.

Volumetric density

As a long bone grows, the mass of bone inside the periosteal envelope is fashioned into a cortex with a thickness determined by the growth of the endocortical surface relative to the periosteal surface. The accrual of mass happens in proportion to the enlarging whole bone, so the volumetric BMD is constant or increases slightly during growth and is no different in either sex (figure 2).[4,44] The greater strength of long bones in men than in women is the result of differences in size and geometry, not density. Growth builds a bigger bone, not one that is more dense; why would it? A denser bone is difficult to move and is costly to maintain.

Vertebral body volumetric BMD is also independent of age until puberty (figure 5).[45,46] Trabecular numbers are determined at the growth plate and do not increase with age.[47] At puberty, trabecular BMD grows because of thickening of trabecular thickness. This increase is similar in men and women of the same ethnic origin, but is

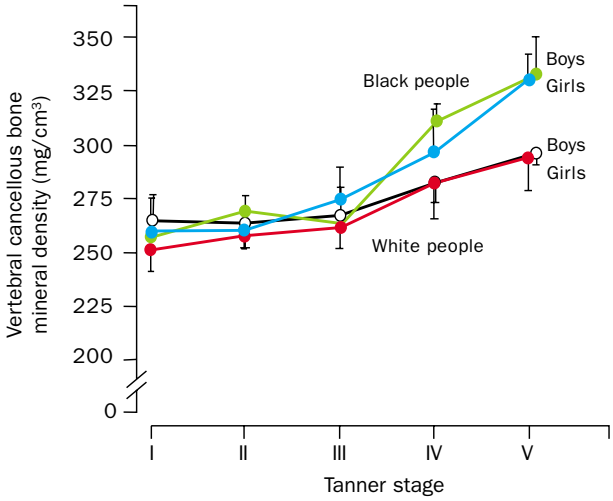

Figure 5: **Vertebral trabecular volumetric bone mineral density in African American and white boys and girls[46]**
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greater in African American than in white populations.[45] The physiological basis for the race-specific but sex-independent thickening of trabeculae at puberty is unknown.[3] Men have wider and only slightly taller vertebral bodies. Peak volumetric BMD is no different between the sexes but is higher in African Americans. Thus, growth does not build a denser skeleton in men than in women, it builds a bigger skeleton in men. Black people have a higher trabecular volumetric BMD because they have thicker trabeculae; the tissue density—ie, the mineral content per unit volume of bone tissue—is no different irrespective of ethnic origin or sex.[3]

The constancy of volumetric BMD before puberty suggests that it is determined before birth.[4,40] Vertebral body volumetric BMD maintains the same position in the normal population distribution—ie, individuals with volumetric BMD at the lowest, middle, or highest part of the distribution early in life probably remain in this position during growth and ageing.[48] In view of the wide range of values in volumetric BMD, some individuals must accrue more bone per unit volume of whole bone than others—ie, some individuals must have less peak cortical thickness, fewer or thinner trabeculae per unit external bone volume than others, placing them at greater risk of fragility fractures when age-related bone loss begins to erode these already thin structures. The genetic factors that account for the differing structural features that underlie high or low peak volumetric BMD are unknown because they have not been studied.

The larger skeleton in men produces a stronger bone—ie, a bone that can tolerate a larger load than can that of the bone of a women. The absolute load imposed on the vertebral body is greater in young men than women because men are taller and heavier. But the load per unit area (stress) on the vertebral body is no different between the sexes.[6] Fragility fractures are uncommon in young men and women because loads are well below the ability of the bone to withstand them. Bone fragility emerges as a person gets older though, since the two mechanisms responsible for maintaining the material and structural properties of bone begin to fail.

The nature of bone loss during ageing

Structural basis of irreversible bone loss

After longitudinal growth has stopped and peak bone size and peak BMD have been reached, bone remodelling

continues on the endosteal surfaces. Osteoclasts resorb a volume of bone, leaving a focal resorptive cavity on the trabecular and endocortical surfaces or a cutting cone within the cortex (figure 6).[49] After a delay, osteoblasts fill the cavity with a volume of new bone that undergoes rapid primary then slower secondary mineralisation. Provided that the volumes of bone removed and replaced within each focal remodelling or basic multicellular unit are the same, no net bone loss or structural damage arises. The necessary and sufficient structural requirement for bone to be irreversibly lost is that the volume of bone resorbed is greater than the volume of bone formed.

Although there is thought to be a period of stability after completion of growth, during which time there is neither gain nor loss of skeletal mass from any surface of bone, ageing probably begins when growth ceases. BMD decreases at the spine and proximal femur in women before menopause.[50–53] Bone is lost during the early adult years in men and in women because negative basic multicellular unit balance may begin at this time, in the third decade, well before menopause in women. The negative balance is probably the result of an early reduction in bone formation within each individual unit, and not due to an increase in the focal resorptive removal of bone.[54] The hormonal and cellular factors responsible for the fall in bone formation early in life are unknown. Whether loss of bone is an appropriate response to reduced loading in a less active person, or an abnormality produced by reduced osteoblast lifespan, increased osteoclast lifespan, or abnormal osteocyte mechanical signalling is uncertain, but the effect is the same—bone loss and structural damage.

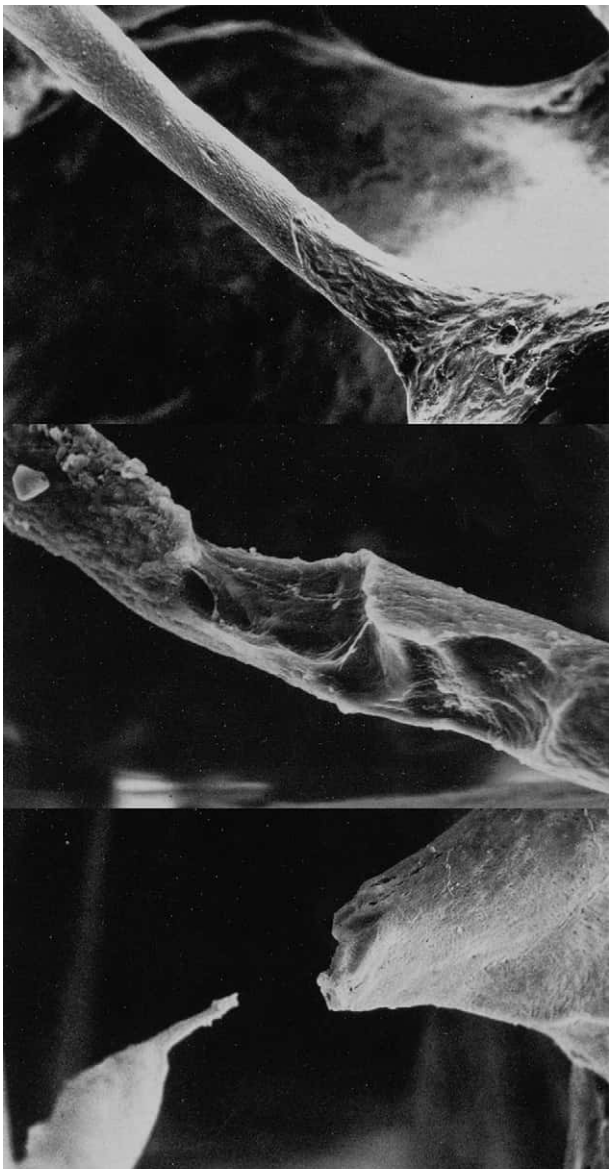

Figure 6: **Bone remodelling imbalance with less bone formation than resorption results in thinning and eventual loss of trabecular connectivity[49]**
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Oestrogen deficiency

Oestrogen deficiency during growth and ageing is likely to be a most important factor in the pathogenesis of bone fragility.[55–58] Bone loss accelerates in women once they reach the menopause for several reasons. First, oestrogen withdrawal is associated with an increase in the intensity of bone remodelling (activation frequency). There are many more discrete foci on the endosteal surfaces remodelling bone, each of which results in bone loss because of the negative basic multicellular unit balance present.

The initial accelerated phase of bone loss is a so-called remodelling transient, indicating the rapid fall in bone mineral mass produced by the increase in numbers of multicellular units, which raises the porosity of bone as remodelling moves from a lower to a higher rate.[59,60] The fall or step down in BMD is the result of the normal delay in initiation of bone formation and its slower completion within the now higher numbers of resorption cavities. The rate of decline in BMD slows as bone formation (which is coupled to resorption) goes to completion in these high numbers of remodelling sites.

Steady state is restored at the higher postmenopausal remodelling rate and irreversible bone loss continues more rapidly from the lower BMD than before menopause because basic multicellular unit balance is more negative and the remodelling rate is higher at this time. Post menopause, the unit balance is more negative because oestrogen deficiency increases the lifespan of osteoclasts, so more bone is resorbed in the basic multicellular unit, and decreases the life span of osteoblasts, so less bone is formed.[61,62] The increased numbers of remodelling sites and the deeper resorption lacunae produce loss of connectivity in women.

Oestrogen deficiency increases bone remodelling and is accompanied by osteoclastogenesis. Although the mechanisms responsible for this action are incompletely understood, the marrow microenvironment plays an essential part, providing cytokines such as tumour necrosis factors and interleukins. Systemic factors—eg, parathyroid hormone, oestrogen, 1,25 dihydroxyvitamin D3, and local factors regulate osteoclastogenesis function via receptors expressed in cells of the osteoblast lineage. Therefore, the systemic and local factors that cause bone resorption rely on signals generated by osteoblasts to mediate their effects.[63,64] Because of this reliance, the osteoblast cells were thought to have a cell surface molecule, known as osteoclast differentiation factor, which acted on haemopoietic precursors to promote osteoclast formation.[65] Ironically, the discovery of an effective inhibitor of osteoclast formation, osteoprotegerin, a soluble member of the tumour necrosis factor receptor superfamily, provided the means to identify and clone the elusive osteoclast differentiation factor, now known as receptor activator of nuclear factor-kappa B ligand or RANK ligand (RANKL), the common

factor mediating osteoclast formation in response to all known stimuli.[66,67] Osteoblasts and stromal cells are also the source of macrophage colony stimulating factor (M-CSF), which plays a crucial part in osteoclast formation through promotion of the proliferation of precursors. When haemopoietic cells are treated with M-CSF and RANKL, osteoclasts are formed without participation of osteoblasts or stromal cells.[68] The communication with the haemopoietic lineage results from RANKL binding to its receptor RANK on the osteoclast lineage cells. These discoveries have been validated in animals. Overexpression of osteoprotegerin results in mice with osteopetrosis because of failure to form osteoclasts.[66] Genetic ablation of osteoprotegerin leads to osteoporosis.[69] Genetic ablation of RANKL results in osteopetrosis because RANKL is necessary for normal osteoclast formation.[70] Genetic ablation of RANK also leads to osteopetrosis because it is the receptor for RANKL.[71] An understanding of these local mechanisms will make it possible to interpret how oestrogen deficiency results in bone loss in women.

Oestrogen deficiency is also important in men. Men do not undergo a comparable midlife acceleration in bone remodelling.[72] Nevertheless, the increase in BMD in young men and the decline in older men is related to circulating free oestrogen, not testosterone.[55–58] The findings of a prospective study[58] suggest that age-related decreases in bioavailable oestradiol concentrations to below 40 pmol/L is an important cause of bone loss in elderly men. Falahati-Nini and colleagues[56] suggest that oestrogen regulates bone resorption and that both oestrogen and testosterone regulate bone formation.

Biochemical measurements of bone remodelling rise modestly and usually at a late stage of life in men.[72] The loss of trabecular bone in men proceeds in a linear fashion with thinning of trabeculae rather than complete loss, as is seen in women.[73] Bone loss is the result of a reduction in the volume of bone formed rather than the result of an increase in the volume of bone removed in the basic multicellular units, so trabecular connectivity is better maintained in men than in women (figure 7). As trabeculae are lost, the trabecular surface available for remodelling diminishes. However, the surface available for trabecular remodelling in old age is better preserved in men than in women.[73] Therefore, men continue to lose bone from the trabecular compartment longer than do women in old age. Despite the accelerated loss of bone in women, the overall loss of trabecular bone in men and women is similar in quantitative terms (suggesting trabecular bone loss continues in men for longer than in women; figure 8).

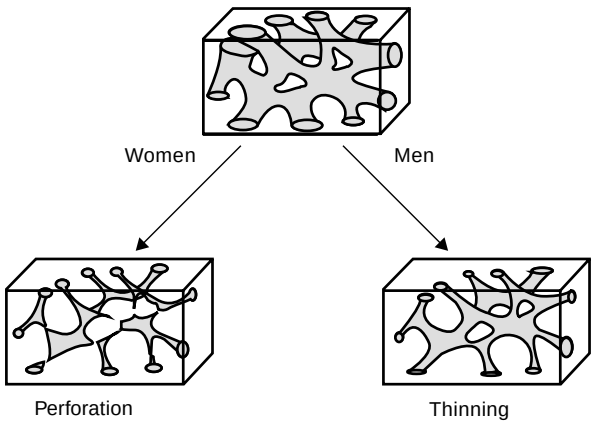

Figure 7: **Mechanisms of loss of trabecular bone in women and trabecular thinning in men**
Bone thinning predominates in men because of reduced bone formation. Loss of connectivity and complete trabeculae predominates in women.

Late in life, endocortical and intracortical remodelling increase and bone loss comes mainly from cortical bone, since remodelling is surface based and the surfaces within cortical bone increase because of raised intracortical porosity. Cortical porosity increases with age or can decline as pores coalesce, predisposing to fractures at cortical sites such as the proximal femur.[74] Cortical bone effectively becomes trabecularised, especially on its inner third. The total surface available for bone remodelling does not diminish with age, but moves from the trabecular to the cortical compartment.

Secondary hyperparathyroidism might increase remodelling further in elderly men and women, because intestinal calcium malabsorption reduces serum calcium, producing compensatory increases in parathyroid hormone to ensure maintenance of serum calcium, but at the price of increased cortical bone remodelling. Bone loss accelerates in old age because the reduced mineralised mass of bone (thinner porous cortices, thinner and fewer trabeculae) is subjected to the same or higher intensity of remodelling—ie, the same or a larger volume of bone is being removed from an ever decreasing mass of bone. Consequently, structural damage and bone fragility increase out of proportion to the reduction in bone mass.

Loss of bone mass and of bone mineral mass differ

Loss of bone mineral occurs out of proportion to the loss of bone mass (produced by the negative basic multicellular unit balance) because the high remodelling rate results in a fall in bone mineral content of the existing bone tissue; old bone that has undergone more complete secondary mineralisation is removed and replaced by younger bone that has undergone primary, but less complete secondary, mineralisation. The bone densitometer measures bone mineral mass and cannot distinguish whether the fall in density is due to proportionate loss of bone mass with its mineral (due to the negative balance) or whether it is the result of higher remodelling replacing more mineralised old bone with less mineralised young bone. The biomechanical importance of the different mineral content is uncertain, but bone that is too highly mineralised could become more brittle, and bone that is incompletely mineralised could lose its stiffness.[75,76]

Periosteal bone formation and bone fragility

As endosteal bone loss proceeds as a person ages, periosteal apposition takes place, increasing the cross sectional area of bone and resulting in the dispersion of the load on a larger area—ie, reducing the load/unit area (stress) on the bone. Furthermore, periosteal apposition reduces the net loss of bone from the whole bone. Consequently, the fall in volumetric BMD of the whole bone is less than would have occurred had there been no periosteal apposition.[7] Cortical bone loss is less in men than in women because periosteal bone formation is greater, not because endosteal resorption is greater in women than men (figure 3).[7] On the contrary, the absolute amount of bone lost from the endosteal surface is greater in men than in women because they have a larger skeleton; it is less when expressed as a proportion of their (larger) peak bone mineral mass (40% in men and 46% in women). Thus, bone loss reflects the net result of all the periosteal bone formed during ageing minus all the bone irreversibly removed from the endosteal surface, which is itself a function of the size of the negative bone balance in each basic multicellular unit and the number of

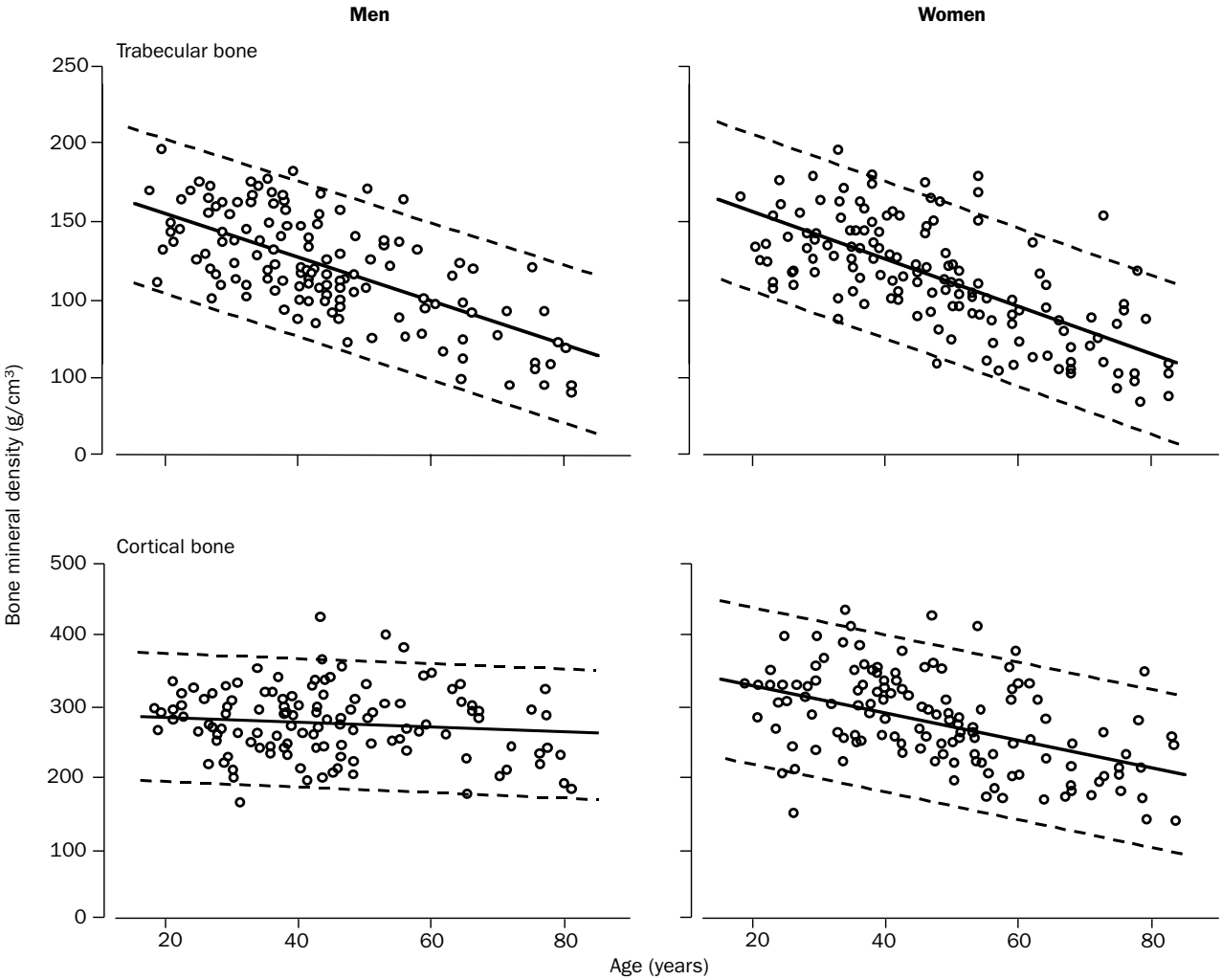

Figure 8: **Vertebral body trabecular bone density and cortical bone mineral density in men and women**[50]
Measured with dual energy quantitative computed tomography. Reproduced from reference 50 by permission of Elsevier Science.

units (the remodelling rate). How can genetic and environmental factors responsible for bone loss be identified if a decline in BMD with age in cross sectional or longitudinal studies is used as the phenotype? The hormonal factors that determine periosteal apposition in men and women have not been studied.

Genetics of bone fragility—a lamentation

Findings of studies in twins and family members have established that differences in traits such as bone size, shape, and BMD between individuals of the same age are largely attributable to differences in their genes, not differences in environmental exposures.[77–79] Although associations between these traits and polymorphisms in candidate genes encoding type 1 collagen, oestrogen, androgen, vitamin D receptors, and many local factors have been reported, the associations are inconsistent and, when identified, only a small proportion of trait variance, 1–3%, is explained by the association.[80–85]

No gene has been consistently and convincingly shown to account for biologically and clinically important differences in formation of trabecular numbers at the growth plate, their thickening before and during pubertal growth. No gene loci or gene products have been reported to regulate or coregulate periosteal apposition and endosteal remodelling, which together form peak cortical thickness during growth. There is no evidence that candidate genes regulate the rate of endosteal remodelling (activation frequency), the volumes of bone formed and resorbed in each basic multicellular unit, and so the size of the bone imbalance in each unit during ageing or menopausal, or periosteal apposition during ageing, which together determine the net amount of bone lost during ageing. No gene has been convincingly shown to identify individuals at risk for fractures with sufficient sensitivity and specificity to justify use in clinical practice. Furthermore, there is no methodologically sound evidence, based on stratification by genotype and randomisation to placebo and intervention groups, to indicate that individuals with a particular genotype are more sensitive to calcium supplementation, exercise, drug therapy, or corticosteroids than others.[86–90]

Progress in the study of the genetics of bone fragility is slow because the phenotype is poorly defined; fractures are too rare to allow detection of an association with genes that regulate a structural determinant of bone strength. BMD, the two dimensional estimate of mineral mass, is too ambiguous a phenotype to allow detection of the cell-specific and surface-specific genetic determinants of the above complex traits. Advances have happened at a more reductionist level in studies in animals;[91–97] identification of gene regulation of osteoclastogenesis and osteoblast differentiation, and identification of quantitative trait loci for strength with inbred strains of mice has met with

success. However, the gene loci, their products, the structures formed, and the genetic regulation involved with adaptation of bone to changing loads remain undefined. The null hypothesis states that no biologically meaningful effect exists between genotypes, skeletal growth, ageing, and effects of treatment. This hypothesis cannot be rejected.

Heterogeneous basis of bone fragility

More women sustain fractures than men because they start with a smaller skeleton at peak and trabecular bone loss proceeds by more architectural disruption; women have a skeleton that adapts less well to ageing by periosteal apposition—ie, periosteal bone formation increases the cross sectional area of the bone less, so that the load per unit area on the bone decreases—and bone loss is offset less in women. Consequently, a higher proportion of elderly women than elderly men have bone size and volumetric BMD reduced to below a critical level at which the loads on the bone are near to, or greater than, the bone's structural ability to tolerate them.

The structural differences responsible for higher fracture rates in women than in men could be used as a model to explain the structural basis of differences in fracture rates within a sex. The reduced vertebral size in women and men with spinal fractures, compared with age-matched and sex-matched controls, is growth related and could be partly the result of reduced age-related periosteal apposition. The reduced volumetric BMD in women and men relative to controls is probably the result of attainment of a lower peak cortical thickness, and fewer and thinner trabeculae. Bone loss during ageing and after the menopause in women, or hypogonadism in men, reduces the already reduced peak volumetric BMD, and produces architectural damage that predisposes to vertebral fracture with minimum trauma. Women and men with normal or larger peak bone size might have a skeleton that better tolerates bone loss until old age, when continued cortical bone loss thins the cortex and increases intracortical porosity, further reducing bone strength at a time when increased prevalence of muscle weakness, reduced coordination, and propensity to fall predisposes to hip fractures.

Whether women and men who sustain fractures have excessive or more rapid bone loss than the rest of the population is not clear. The notion of excess bone loss needs evidence of greater net resorption in individuals with than without fractures. This idea requires evidence of a more negative bone balance in the basic multicellular units of patients (due to a greater volume of bone resorbed in each unit, a lower volume of bone formed in each unit, or both). Alternatively, if basic multicellular unit imbalance is negative, but no more negative in patients than in controls, greater bone loss requires evidence of a higher remodelling rate in patients with fractures than in controls. Histomorphometric and biochemical evidence for higher resorption in the basic multicellular unit, lower bone formation in the unit, or higher remodelling rate in fracture cases than in controls is conflicting.[14–19,98,99] Although a higher group mean for indices of resorption, or a lower group mean for indices of bone formation, is reported in people with fractures, the range of the data is more impressive than the difference in the means, suggesting reduced volumetric BMD in patients is likely to have a heterogenous cause.

Conclusion

Osteoporosis or low BMD has no single cause. In thinking about the pathogenesis of structural failure, bone fragility is probably a better term to use than osteoporosis. The epidemiology, pathogenesis, prevention, and treatment of bone fragility better conveys the breadth, depth, and heterogeneous nature of the biomechanical problem of structural failure. To group individuals into one seemingly homogeneous group because they have a BMD below –2·5 SD, one or more spinal fractures, or a hip fracture sustained during a fall from no greater than the standing position obscures the heterogeneity in the structural, cellular, and biomechanical basis of bone fragility, and the varying contributions of growth-related and age-related mechanisms responsible for the condition. The development of methods for the precise measurement of fracture risk and for the prevention and reversal of bone fragility will be impeded if this heterogeneity is ignored by use of phenotypes such as BMD.

Conflict of interest statement

None declared.

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Uses of error

Iatrogenic adrenergic crisis

Rosa Corcoy

In the late 1980s, I was called in the middle of the night to see a female patient with urticaria. She was about 50 years old, had hyperthyroidism, and had developed an upsetting urticarial reaction while taking an antithyroid drug (probably methimazole). Oral antihistamines did not help. She was distressed, and did not have any risk factors for coronary artery disease, so I gave her 0·5 mg adrenaline, subcutaneously. My experience had been that patients were relieved of their symptoms after a few minutes, despite a bit of tachycardia. However, 5 minutes later, this patient was striding along the corridor, yelling that her head was going to explode. Her blood pressure was about 250/150 mm Hg. I tried to calm her down, gave her sublingual nifedipine (which would not be a correct decision today), and finally had to use intravenous nitroprusside to get her blood pressure back within the normal range. By this time, morning had arrived, and I was having a shower and thinking about this unanticipated hypertensive crisis, so reminiscent of a phaeochromocytoma. Everything suddenly became clear; she was also on propranolol, and the adrenaline I had injected could only bind to alpha receptors, resulting in a pure alpha-crisis. Some minutes later I was explaining my reasoning to the residents in charge of her case, who did not seem very convinced. As the urticaria had not resolved, they asked a dermatologist to see her. He advised oral ephedrine, and a second hypertensive crisis ensued.

Hospital de Sant Pau, Barcelona 08025, Spain (R Corcoy MD)