Physiology of Aging
Invited Review: Pathogenesis of osteoporosis

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Seeman, Ego. Invited Review: Pathogenesis of osteoporosis. J Appl Physiol 95: 2142–2151, 2003; 10.1152/japplphysiol.00564.2003.—Patients with fragility fractures may have abnormalities in bone structural and material properties such as larger or smaller bone size, fewer and thinner trabeculae, thinned and porous cortices, and tissue mineral content that is either too high or too low. Bone models and remodels throughout life; however, with advancing age, less bone is replaced than was resorbed within each remodeling site. Estrogen deficiency at menopause increases remodeling intensity: a greater proportion of bone is remodeled on its endosteal (inner) surface, and within each of the many sites even more bone is lost as more bone is resorbed while less is replaced, accelerating architectural decay. In men, there is no midlife increase in remodeling. Bone loss within each remodeling site proceeds by reduced bone formation, producing trabecular and cortical thinning. Hypogonadism in 20–30% of elderly men contributes to bone loss. In both sexes, calcium malabsorption and secondary hyperparathyroidism increase remodeling: more bone is removed from an ever-diminishing bone mass. As bone is removed from the endosteal envelope, concurrent bone formation on the periosteal (outer) bone surface during aging partly offsets bone loss and increases bone’s cross-sectional area. Periosteal apposition is less in women than in men; therefore, women have more net bone loss because they gain less on the periosteal surface, not because they resorb more on the endosteal surface. More women than men experience fractures because their smaller skeleton incurs greater architectural damage and adapts less by periosteal apposition.

bone loss; pathogenesis; peak bone mass

BONE FRAGILITY IS A PROBLEM IN BIOMECHANICS

To serve the differing functions of the skeleton, bone must have contradictory properties: it must be stiff and able to resist bending for load bearing and propulsion against gravity but yet be flexible, that is, able to absorb energy by deforming during impact loading without fracturing. Bone must also be light for speed of movement yet strong for load bearing. Bone achieves these contrasting features through its material composition and its structural properties (14).

Nature varies the stiffness of bone material by modulating the concentration of the crystals of hydroxyapatite-like mineral in the triple helix of type 1 collagen matrix. Higher mineral content increases stiffness but sacrifices flexibility. If the mineral content is excessive for the function required, brittleness results; cracks occur with slight deformation. For example, vibrating ossicles are 90% mineral. Although the degree of stiffness produced is well suited to their function as sound transducers, their low flexibility causes them to crack if even slightly loaded. By contrast, antlers, which must be springlike, have a tissue mineral content of only ~40%, conferring flexibility for head butting in mating season. If mineral content of this appendage is increased, the deer would soon be extinct as fractured antlers in a suitor are a disincentive to a doe. Human bone is ~65% mineralized. If undermineralized (due to high remodeling states), it becomes too flexible and will bend “too much” in loading and crack; if overmineralized (if remodeling is greatly suppressed), it will bend too little and crack.

Bone material is fashioned into three-dimensional architectural masterpieces of biomechanical engineering, with size and shape optimized according to whether the main function is as a lever or as a spring. For load bearing and leverage, the need for stiffness and lightness is favored over flexibility by fashioning the mineralized tissue into long bones with a marrow cavity, displacing the mineralized cortex distant from the neutral bone axis (51). For vertebral bodies, springlike shock absorbers, stiffness, and peak load bearing are sacrificed for flexibility by use of an open-celled
porous cancellous structure able to deform and return to its original size and shape without cracking (19). Thus nature selects the material and structure most suited to their usual function by varying the mineral content of the material and the degree of porosity, which is minimal in cortical bone and maximal in trabecular bone.

Bone material and structural properties degrade with age because the mechanisms constructing (modeling) and reconstructing (remodeling) the skeleton eventually fail (54). Remodeling repairs microdamage; however, during aging, less bone is deposited than removed in each remodeling or basic multicellular unit (BMU). After menopause, increased remodeling with a more negative bone balance in the many BMUs removes more bone more rapidly from an ever-diminishing and architecturally disrupted bone.

The increased remodeling and negative bone balance produce bone loss, trabecular thinning and loss of connectivity, cortical thinning, and porosity. Older, more mineralized interstitial bone, distant from surface remodeling, accumulates microdamage, whereas more superficial bone is replaced with younger less mineralized bone, reducing stiffness (16). Bone modeling by periosteal apposition reduces compressive stress by distributing loads on a larger area and partly maintains bending strength (15, 16). It may be impaired due to abnormalities in periosteal osteoblast function, osteocyte signaling, or deficiency.

A rational approach to intervention requires the precise and unambiguous definition of 1) each of the material and structural determinants of strength embraced by the word “quality,” 2) the mechanisms responsible for the decay of these material and structural properties, and 3) knowledge of the main structural determinants responsible for fragility in individuals, that is, defects in one or more of the following: bone size; cortical thickness; porosity; trabecular number, thickness, and connectivity; bone tissue mineral content; microdamage burden; remodeling rate; the extent of resorption and formation in each BMU; osteocyte viability; and periosteal apposition. There is progress in this direction.

LOW BONE MINERAL DENSITY AND OSTEOPOROSIS

The mineralized skeleton is defined by its periosteal (outer) surface and by the endocortical, trabecular, and intracortical components of its inner (endosteal) surface. Cellular activity on these surfaces produces net bone formation or resorption, which modifies the size, shape, architecture, mass, and strength of the skeleton throughout life. Periosteal bone formation defines the bone’s cross-sectional area (CSA), whereas endocortical bone formation or resorption determines the proximity of the endocortical and periosteal surfaces and thus cortical thickness. Endocortical bone formation thickens the cortex. Endocortical resorption approximates the endocortical and periosteal surfaces, producing cortical thinning. Bone formation on trabeculae thickens them, whereas resorption thins the trabeculae.

Women and men with fragility fractures have reduced bone mineral density (BMD). The deficits tend to be most severe at the site of fracture (17, 49). Women and men with spine fractures have reduced vertebral BMD because the vertebral size is smaller in CSA and height, and there is less bone in the smaller bone (24, 55, 73). In men, trabecular thinning rather than loss of connectivity tends to dominate, but men with osteoporosis and fractures have greater loss of connectivity than do men with osteoporosis without fractures (38, 45). Women and men with hip fractures have normal vertebral size and modest deficits in vertebral BMD (68). For women with hip fractures, the femoral neck diameter may be reduced, normal, or increased (3, 5, 10, 34). BMD is reduced due to thinning of cortices, which contain large intracortical cavities (32). For men with hip fractures, the femoral neck diameter is reduced; the BMD is also reduced, probably due to cortical thinning. How do these structural abnormalities develop?

GROWTH-RELATED ORIGINS OF STRUCTURAL ABNORMALITIES

The deficit in BMD in daughters of women with spine fractures relative to their age-matched peers is about one-half that of their mothers, consistent with the view that the deficit in their mother’s BMD relative to their age-matched peers was present when they were premenopausal (12, 56). The daughters of women with hip fractures have only slightly reduced femoral neck BMD, suggesting that the deficit in BMD in the mothers developed during adulthood. Femoral neck volume is increased in the women with hip fractures and their daughters (by one-half that of their mothers), suggesting that the larger bone size in the mother was present when she was premenopausal (68).

The effects of exposure to illness or risk factors during growth depend on the maturational state of the region at the time of exposure. Growth velocity of total body length is high after birth; it slows rapidly to accelerate at 12 mo of age due to acceleration in appendicular, not axial, growth velocity (70) (Fig. 1). Appendicular growth remains more rapid than axial growth velocity in the prepubertal years. At puberty, long bone growth slows, whereas axial growth accelerates. Thus illness or risk factors may produce greater deficits at a site growing more rapidly or at a site more distant from its peak than a site more maturationally advanced. If a disease affects estrogen production or its action, epiphyseal growth continues producing greater leg length, whereas the failure of the axial growth spurt results in a shorter trunk (4, 9, 62). Patients developing anorexia nervosa before puberty have deficits in vertebral body and femoral neck width, as both regions are far from their peak of growth; those with later-onset disease have deficits confined to the vertebral body because the appendicular skeleton is nearer completion of its growth (58).

Sex differences in bone width are established during the peripubertal period. Cortical width increases by
periosteal bone formation in boys and by less periosteal bone formation but by more endocortical apposition in girls (2, 6, 20, 53) (Fig. 2). Androgens, growth hormone, and the growth hormone insulin-like growth factor I axis independently and additively stimulate periosteal apposition in men, whereas estrogens inhibit periosteal apposition, resulting in a narrower bone in girls than in boys. Estrogen stimulates endosteal apposition in females. Thus boys build a longer and wider long bone with a cortex only slightly thicker than that in girls. The cortical mass is placed further from the neutral axis of the long bone in males, conferring greater resistance to bending by the correspondingly larger muscle mass. Delayed puberty in boys removes the androgen-dependent periosteal apposition, whereas in girls estrogen deficiency removes the inhibitor of periosteal apposition and stimulator of endocortical apposition. Sexual dimorphism is reduced, as the bone of the male individual is more like that of the female individual and the bone of the female more like that of the male (Fig. 2).

As a long bone grows, the mass of bone “inside” the periosteal envelope is fashioned into a cortex by endocortical remodeling, which creates the marrow cavity; the cortex has a thickness determined by the growth of the endocortical surface relative to the periosteal surface. The accrual of mass occurs in proportion to the enlarging whole bone, so the volumetric BMD is constant or increases slightly during growth and is no different in men and women (77). The greater strength of long bones in men vs. women is the result of differences in size and geometry, not density. Growth builds a bone that is bigger, not a more dense bone.

Vertebral body volumetric BMD is also independent of age until puberty (24) (Fig. 3). Trabecular numbers are determined at the growth plate and do not increase with age (46) (Fig. 4). At puberty, trabecular BMD increases because of a comparable increase in trabecular thickness in men and women of the same race but is greater in blacks than in whites (26). Men have a wider and only slightly taller vertebral bodies. Peak volumetric BMD is no different by sex but is higher in blacks than in whites. Thus growth does not build a “denser” skeleton in men than in women, but it builds a bigger skeleton in men. Blacks have a higher trabecular volumetric BMD because blacks have thicker trabeculae.

The larger skeleton in men produces a bone that can tolerate a larger load than the bone of women. The absolute load imposed on the vertebral body is greater in young men than young women because men are taller and heavier. However, the load per unit area (stress) on the vertebral body is no different in young men vs. young women. Fragility fractures are uncommon in young men and young women because loads are well below the ability of the bone to withstand them. Bone fragility emerges during aging because the two mechanisms responsible for maintaining bone’s material and structural properties fail.

AGE-RELATED BONE LOSS

After the cessation of longitudinal growth, bone remodeling continues on the endosteal surfaces. Osteo-
clasts resorb a volume of bone, leaving a focal resorptive cavity on the trabecular and endocortical surfaces or a cutting cone within the cortex. After a delay, osteoblasts fill the cavity with a volume of new bone that undergoes rapid primary and then slower secondary mineralization. Provided that the volumes of bone removed and replaced within each focal remodeling or BMU are the same, no net bone loss or structural damage occurs. For bone to be lost, the volume of bone resorbed must be greater than the volume of bone formed.

BMD decreases at the spine and proximal femur in women before menopause (23, 33, 50). Bone is lost during the early adult years in men and in women because the negative BMU balance probably begins in the third decade, before menopause in women. The purported negative BMU balance may be the result of an early reduction in bone formation within each individual BMU and not due to an increase in the focal resorptive removal of bone.

Estrogen deficiency during growth and aging is important in the pathogenesis of bone fragility (14, 44, 57, 61). Bone loss accelerates in women at menopause because estrogen withdrawal increases the rate of bone remodeling; like a sudden rain storm on a lake, there are many foci of bone resorption on the endosteal surfaces. At each remodeling site, more bone is resorbed than replaced, producing a net negative BMU balance, which is the basis of bone loss. The initial very rapid fall in BMD is the result of the many BMUs increasing the porosity of bone, as remodeling moves from a low rate before menopause to a high rate after menopause (18, 35, 48, 67).

The rapid fall in BMD is the result of the normal delay in initiation of bone formation and its slower completion within the many resorption cavities. These many cavities partially fill with bone formation as it finally “catches up,” resulting in slowing of bone loss; however, the bone loss continues at a new steady state characterized by a high remodeling rate (Fig. 5). In addition, bone loss continues more rapidly because BMU balance is more negative due to estrogen deficiency increasing the life span of osteoclasts so more bone is resorbed in the BMU. The life span of osteoclasts, however, decreases, also resulting in less bone formed (31, 40). The increased numbers of remodeling sites and the deeper resorption lacunae produce loss of connectivity in women.

Estrogen deficiency produces osteoclastogenesis because cytokines (tumor necrosis factors, interleukins) and systemic factors (parathyroid hormone, estrogen, and 1,25-dihydroxy vitamin D3) act via receptors in cells of the osteoblast lineage (42, 64, 65). Discovery of the inhibitor of osteoclast formation, osteoprotegerin (OPG), provided the means of identifying and cloning receptor activators of NF-κB ligand or RANK ligand (RANKL), the factor mediating osteoclast formation (59, 76). Osteoblasts and stromal cells provide macrophage cerebrospinal fluid, which plays a crucial role in osteoclast formation. When hemopoietic cells are treated with macrophage cerebrospinal fluid and RANKL, osteoclasts are formed without need of osteo-
blasts or stromal cells (66). The communication with
the hemopoietic lineage results from RANKL binding
with its receptor RANK on the osteoclast lineage cells.
Overexpression of OPG results in mice with osteopero-
tosis because of failure to form osteoclasts. Genetic
ablation of OPG leads to osteoporosis (7). Genetic ab-
lation of RANKL results in osteopetrosis because
RANKL is necessary for normal osteoclast formation
(36). Genetic ablation of RANK also leads to osteope-
trosis because it is the receptor for RANK (39).

Estrogen deficiency is also important in the patho-
genesis of osteoporosis in men. Men do not undergo a
comparable midlife acceleration in bone remodeling
(63). Nevertheless, increases in BMD in young men
and declines in older men are related to circulating free
estrogen, not testosterone (18, 48, 67). Age-related
decreases in bioavailable estradiol below 40 pmol/l may
be an important cause of bone loss in elderly men (18).
Estrogen may regulate bone resorption, whereas both
estrogen and testosterone may regulate bone formation.

Biochemical measurements of bone remodeling rise
modestly late in life in men. The loss of trabecular bone
in men proceeds in a linear fashion with thinning of
trabeculae (1) (Figs. 6 and 7). Bone loss is the result of

Fig. 5. Diagram showing slow loss of
bone before menopause due to the neg-
ative bone balance in the basic multi-
cellular unit (BMU) but slow remodel-
ing rate. At menopause, increased re-
modeling sites and depth of remodeling
produces a fall in BMD, but the rate of
loss slows as bone formation goes to
completion, filling the remodeling
space to the level that is now deter-
mimed by the activity and life span of
the osteoclast and osteoblast cells in
the BMU.

Fig. 6. Loss of bone occurs by in-
creased resorption cavities in women
more than in men, whereas mean wall
thickness declines in men more than
women. Trabecular width is better
maintained in women than in men,
whereas trabecular numbers are better
maintained in men than in women.
Trabecular surfaces available for re-
sorption are higher in men than in
women late in life. [Adapted from
Aaron et al. (1).]
a reduction in the volume of bone formed rather than the result of an increase in the volume of bone removed in the BMU; therefore, connectivity is better maintained in men. As trabeculae are lost, the trabecular surface available for remodeling decreases. However, the surface available for trabecular remodeling in old age is better preserved in men. 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 longer than in women (Fig. 8).

Late in life, endocortical and intracortical remodeling increase and bone loss comes primarily from cortical bone because remodeling is surface based and the surfaces within cortical bone increase due to increased intracortical porosity (28). Cortical bone becomes “trabecularized.” The total surface available for bone remodeling moves from the trabecular to the cortical compartment.

Fig. 7. Loss of trabecular bone in women occurs by increased resorption with loss of trabecular numbers and connectivity. Trabecular thinning due to reduced bone formation occurs in men.

Fig. 8. Dual-energy quantitative computed tomography measurements suggest that the age-related diminution in vertebral body trabecular bone density is similar in men and women (A), whereas cortical BMD decreases less in men (B). [Adapted from Kalender et al. (33).]
Secondary hyperparathyroidism may increase remodeling further in elderly men and women because intestinal calcium malabsorption reduces serum calcium, producing compensatory increases in parathyroid hormone to maintain serum calcium at the price of increased cortical remodeling. Secondary hyperparathyroidism may also be the result of vitamin D deficiency. Bone loss accelerates in old age because the reduced mineralized mass of bone is subjected to the same or higher intensity of remodeling so that the same or a larger volume of bone is removed from a decreasing mass of bone; structural damage and bone fragility increase out of proportion to the reduction in bone mass. Loss of mineral occurs out of proportion to the loss of tissue mass because the high remodeling rate produces a fall in bone mineral content of the tissue. Old, more completely mineralized bone is removed and replaced by younger, less completely mineralized bone, which may be less stiff (14).

As endosteal bone loss proceeds, concurrent periosteal apposition increases bone’s CSA, reducing the stress on the bone and partly offsetting bone loss so net bone loss is reduced. Cortical bone loss is less in men than in women because periosteal bone formation is greater (Fig. 8B and Fig. 9). Bending strength of bone is maintained in men because of periosteal apposition; the extent of endocortical resorption is similar in men and women (Fig. 10).

**THE GENETICS OF BONE FRAGILITY**

Studies in twins and family members establish that differences in skeletal traits between individuals of the same age are largely attributable to differences in their genes and not differences in environmental exposures (44, 57, 61, 72). Associations between skeletal traits and polymorphisms in candidate genes have been reported, but these associations are inconsistent (21, 29, 30, 37, 52, 75). In human subjects, no gene has been shown to account for differences in formation of trabecular numbers, their thickening, endosteal remodeling, activation frequency, the volumes of bone formed and resorbed in each BMU, or periosteal apposition. No gene has been shown to identify individuals at risk for fractures with sensitivity and specificity to justify its use in practice. Nor is there evidence reporting that individuals with a given genotype are more sensitive to calcium supplementation, exercise, drug therapy, or corticosteroids (22, 41, 69, 74). No studies have been done with groups divided by genotype and then randomized to placebo vs. an intervention within each genotype. This design would control for covariates that cannot be controlled for in post hoc analyses.

Progress in the genetics of bone fragility is slow because the phenotype is poorly defined; fractures are too uncommon to allow detection of an association with
genes that regulate a structural determinant of bone strength. BMD is too ambiguous to allow detection of the cell- and surface-specific genetic determinants of the complex traits. Advances have occurred at a reductionist level (8, 11, 27, 28, 43, 60, 71). Studies identifying the gene regulators of osteoclastogenesis and osteoblast differentiation and identifying quantitative trait loci for strength with the use of inbred mouse strains have been successful. However, the gene loci, their products, the structures formed, and the genetic regulation involved with adaptation of bone to changing loads remain undefined.

SUMMARY AND CONCLUSIONS

The reduced vertebral size in women and men with spine fractures is probably growth related and may also be the result of reduced age-related periosteal apposition. The reduced volumetric BMD is likely to be partly due to attainment of a lower peak cortical thickness and fewer and thinner trabeculae. Bone losses during aging and after menopause in women or as a result of hypogonadism in men further reduce volumetric BMD, producing architectural damage predisposing individuals to vertebral fractures with minimal trauma. Women and men with normal or larger peak bone size may have a skeleton that better tolerates bone loss until later in life, when continued cortical bone loss thins the cortex and increases intracortical porosity, further reducing bone strength at a time when falls predispose these individuals to hip fractures.

Osteoporosis has no single cause. Individuals with osteoporosis (BMD less than –2.5 SD), one or more spine fractures, or a hip fracture sustained during a fall from no greater than the standing position are not a single group. They represent a sample in whom structural failure has a widely heterogeneous structural, cellular, and biomechanical bases with a varying contribution of growth- and age-related mechanisms responsible for the bone fragility. Ignoring this heterogeneity will impede progress in the field.

REFERENCES


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