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CLINICAL REVIEW 137

Sexual Dimorphism in Skeletal Size, Density, and Strength

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Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?
From *The Rock* by T. S. Eliot

Techniques are not ends in themselves, they are only as good as the answers they provide. The answers are only as good as the questions, and the questions are only as good as the insights generated from observations made using the technique. Problems arise when the technique takes over, like HAL in Stanley Kubrick's *2001: A Space Odyssey*, driving inquiry because of the accessibility of its "ON" button, but misdirecting inquiry by producing flawed inferences due to the technique's unrecognized limitations (1, 2).

Although the bone densitometer has a central role in the diagnosis, prevention, and treatment of osteoporosis in clinical practice, it has taken over in clinical research ("I'm sorry Dave, ... I can't do that. . . . "), and its printout, the bone "density" measurement, has become an end in itself, producing conceptual errors because of its technical limitations.

The use of densitometry has led to several misconceptions: 1) volumetric bone mineral density (BMD) increases during growth. It does not. Growth builds a bigger, not more dense, skeleton; 2) peak volumetric BMD is higher in men than women. It is not. Bone size is greater; 3) women lose more trabecular bone from the spine than men. No so, there are qualitative, not quantitative, differences; 4) cortical bone loss is less in men than women during aging. This is not so; the amount of bone resorbed from the endocortical (inner) surface of the cortical shell is similar in men and women. The amount of bone formed on the periosteal (outer) surface during aging is greater in men so that "net" cortical bone loss is less in men; and 5) bone mass is reduced in patients with fractures. It certainly is, but the deficit is exaggerated in patients with smaller bones than controls and underestimated in patients with larger bones than controls. These erroneous notions are produced by uncritical use of densitometry.

Density and confusion

Bone consists of the mineralized matrix fashioned into a cortical shell and a trabecular network of plates within a marrow cavity. Only the mineralized mass of bone is seen by the photons so that the degree of attenuation of the photons during their transmission through the bone is a measure of the bone mineral content (BMC) of the whole bone, not all of which is mineralized tissue. The image produced during scanning is like a silhouette, just a two-dimension image of the three-dimensional structure, an "areal" projection of the bone in the coronal plane (Fig. 1A). The length and width of the scanned bone is known, but not its depth. Because the depth of the bone is not seen, a bone with greater depth will attenuate more photons and will be reported as being more dense. The bone is not more dense, it does not have a greater amount of bone mineral distributed (as thicker trabeculae, more trabeculae, a thicker cortex) within the periosteal envelope, the bone is just larger; there is more mineral, but this mineral is distributed in the larger volume of the whole bone.

The measurement obtained is the BMC per unit projected bone area of the bone in the coronal plane, or an areal BMC (g/cm^2). "Areal" is deleted, and "content" is replaced by density, so BMC per unit projected area is called "bone mineral density" or "BMD." The problems that follow from this poor choice of language affect the interpretation of every aspect of the pathophysiology of skeletal growth, aging, and drug therapy in which densitometry is used.

The areal BMD measurement is a function of the size of the bone and the amount of bone within its periosteal envelope; its volumetric BMD. The problems arise because bone size and the amount of bone within it change independently during growth and aging, and often in opposite directions. For example, during growth, external bone size increases with a proportional increase in the amount of bone within its periosteal envelope so that the volumetric BMD remains constant, but areal BMD increases because the bone is bigger. During aging, the amount of bone within the periosteal envelope decreases as bone resorption results in thinning and loss of trabeculae, thinning, and increased porosity of the cortex (Fig. 1B).

However, aging is also associated with simultaneously occurring periosteal apposition, which enlarges the bone and offsets resorptive removal of the mineralized matrix (3–5). Consequently, the net loss of bone (the sum of bone deposit on the outside and removed on the inside) underestimates the absolute bone lost by resorptive removal inside the bone. Patients with spine fractures have smaller bones than con-

Abbreviations: BMC, Bone mineral content; BMD, bone mineral density; BMU, basic multicellular unit.

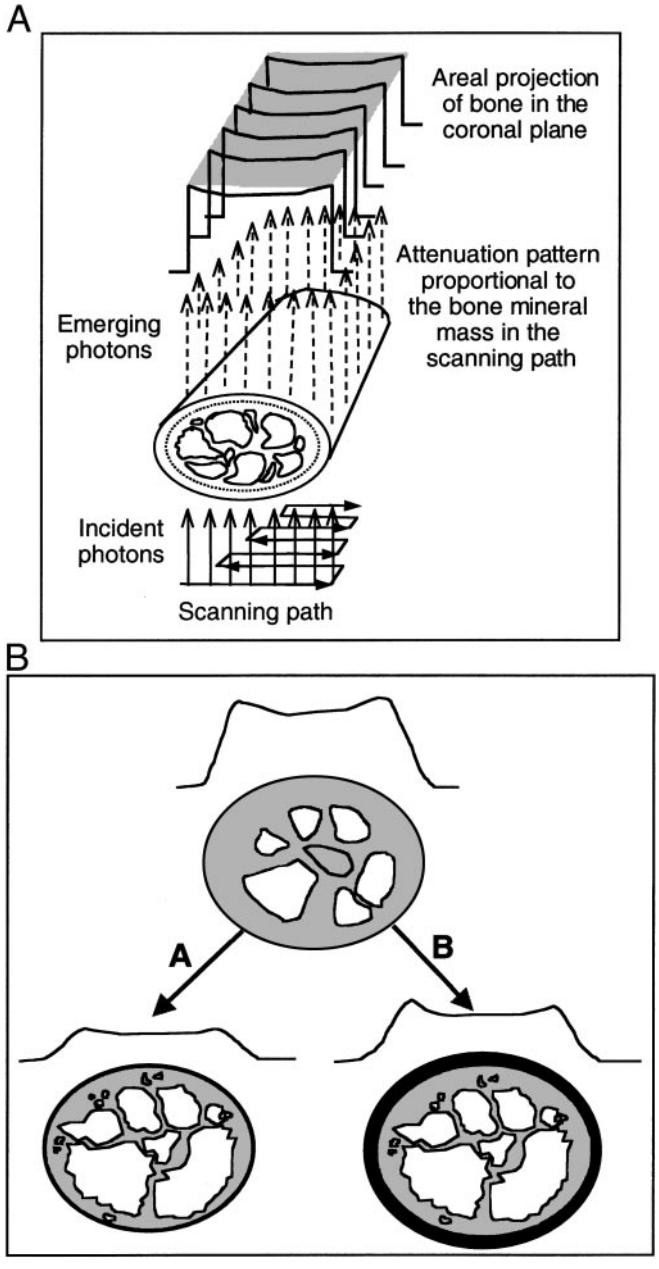

FIG. 1. a, Photons are attenuated during transmission, producing an attenuation wave profile proportional to the mass of mineralized bone in the scanning path. The attenuation produced by each passage is summated to derive the BMC subtended by the projected area of the bone in the coronal plane. [Reproduced with permission from E. Seeman.]. b: A, Age-related bone loss reduces the amount of bone within the periosteal envelope so that the photon attenuation profile is reduced (more are transmitted through the porous bone); B, Age-related periosteal apposition offsets bone loss, the photons are more greatly attenuated even though the same bone loss has occurred inside the bone. [Reproduced with permission from E. Seeman.]

trols (6). Because the areal BMD measurement only sees less bone mineral mass without distinguishing whether its due to a smaller bone, less bone in the bone or both, the lower areal BMD in patients with fractures overestimates the deficit in bone mass inside the smaller bone (produced by excessive bone loss or reduced accrual). The densitometric measurement does not see these opposing surface-specific changes but rather integrates their net effects.

The purpose of this commentary is to describe the structural and biomechanical basis of: 1) the greater gain bone strength during growth in men than in women; 2) the lesser decline in bone strength in men than in women during aging; and 3) bone fragility in patients with fractures drawing attention to the conceptual errors produced by densitometry in the clinical context of skeletal growth and aging.

Growth-designing structure for function

Bone mass increases during growth because bone length and diameter increase. The mass of bone contained within the periosteal envelope of the bone also increases. The growing bone is fashioned into a structure adapted to carry out specific functions. The vertebral bodies consist of an interconnecting trabecular network of plates and sheets forming a marrow filled spongiosa, a mass of cancellous bone contained within a thin cortical shell.

The design secrets of weight-bearing structures were known by the Ancients and are still standing despite thousands of years of gravity. Long bones like the radius and femur grow in length and diameter. The mineralized bone mass within their periosteal envelope is not formed a solid column that will easily tolerate loads but will remain immovable no matter how hungry the owner, or how delicious the meal scurrying by. The mineralized mass of bone within the periosteal envelope of the long bones is modeled into hollow cylinders with splayed ends containing trabecular bone. These structures are architectural masterpieces of minimalism, created using the least amount of material needed for optimum function—lightness for speed, strength for loading—ensuring the organism can find dinner, rather than be dinner.

Growth fashions a bigger, not denser, skeleton. BMD increases during the pre- and peripubertal years because long bones increase in size (Fig. 2, *top*) (7). The densitometer sees a bigger bone and prints out that the bigger bone has a higher areal BMD, a higher density, giving the impression that as children grow their bones have somehow become more dense. Similarly, in late puberty, when boys have long bones of greater diameter than girls, the densitometer sees a bigger bone and prints out a higher areal BMD in boys, giving the impression that somehow boys have grown denser bones than girls. This is not so.

As the bone grows in length and diameter, the mass of bone inside the periosteum increases in proportion to the enlarging volume of the whole bone including the marrow space. This mass of bone is fashioned into a cortex of a given thickness. Volumetric BMD of long bones, like the radius or femur, is independent of age and no different in boys and girls (Fig. 2, *bottom*) (7–9). In young adulthood, men and women have the same volumetric BMD, but men have a bigger bone than women. Thus, if the strength of the radius or femur is greater in older than younger children, or greater in males than females, it is due to differences in size, not density, not the amount of bone within the periosteal envelope of that bone.

Volumetric BMD also remains independent of age for the

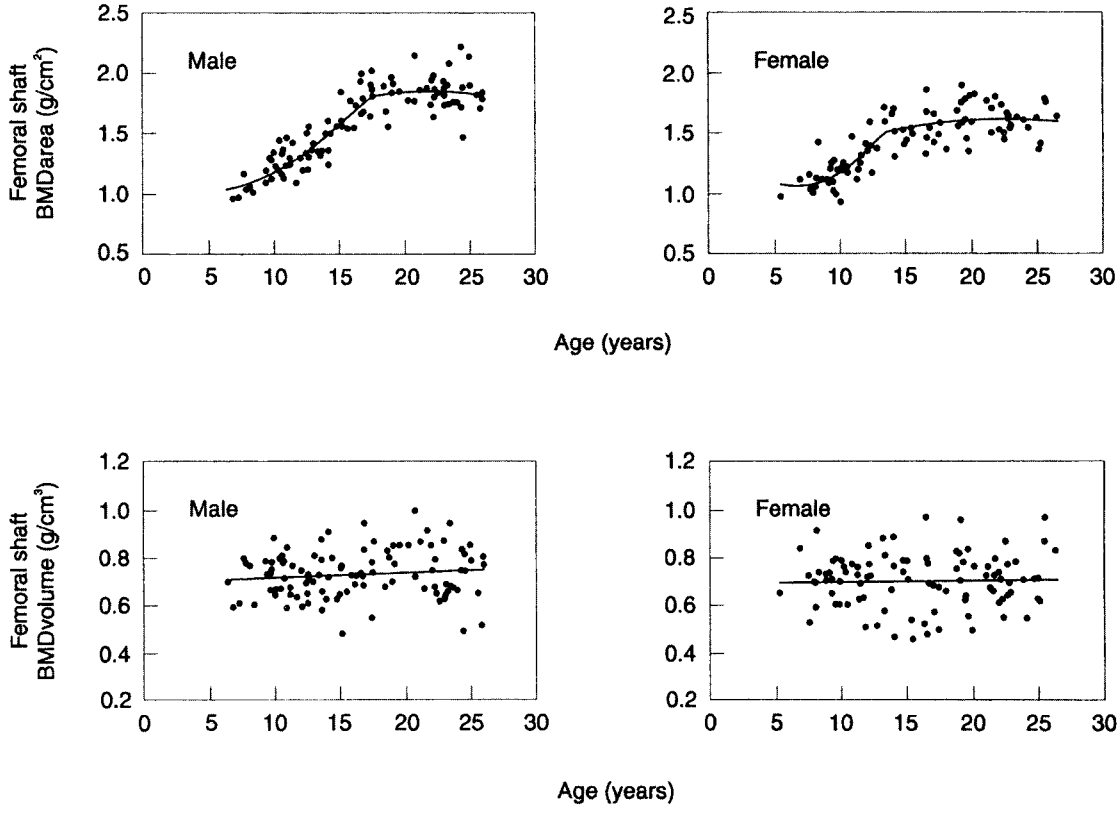

FIG. 2. Femoral shaft areal BMD increases with age, but volumetric BMD is independent of age in males and females. [Reproduced with permission from P. W. Lu *et al.*: *J Clin Endocrinol Metab* 81:1586–1590, 1996 (7), ©The Endocrine Society.]

vertebral body, at least until puberty (10). In this case, the mass of bone is fashioned as a trabecular network. The length and thickness of the intersecting trabecular sheets increases in proportion to the enlarging medullary space containing them. The number of trabeculae, established at the growth plates, do not increase with age (11). At puberty, trabecular BMD increases and does so to a similar degree in boys and girls (Fig. 3) (10), perhaps because trabeculae continue to thicken while growth in external size of the vertebral body ceases. Growth in external size ceases sooner than the accrual of bone within its periosteal envelope (12–14). However, longitudinal studies documenting the precise temporal relationship of cessation of growth in external size and accrual of mass within the vertebral body are lacking.

Thus, throughout prepubertal and pubertal growth, and in the fully grown young adult, males and females have the same trabecular BMD (number and thickness of trabeculae) within the vertebral body; what differs is vertebral body size. Men have a wider and only slightly taller vertebral bodies. Thus, growth does not build a denser skeleton in males than females, it builds a bigger skeleton. If the strength of the vertebral body is greater in young males than females, it is due to gender differences in size, not density, not the amount of bone within the periosteal envelope of that bone.

The position of volumetric BMD in normal distribution is determined before birth. The constancy of volumetric BMD before puberty has very important implications. First, if volumetric BMD is independent of age, then the position of an individual's volumetric BMD must be determined before birth. Second, volumetric BMD of the spine probably tracks (remains in the same position in the population distribution as age advances) (15). Volumetric BMD is a function of the relative growth in size of the whole bone and the mass accrued within it, not the absolute growth in size or mass. Thus, there must be regulators and coregulators of bone size and mineral accrual that ensure that growth of size is matched precisely with a given proportional growth in mass within it.

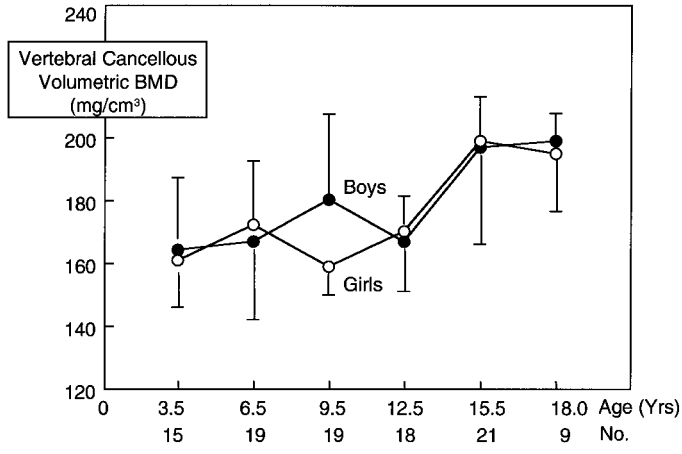

FIG. 3. Vertebral trabecular volumetric BMD is similar in boys and girls and is independent of age until puberty then increases comparably by gender. Adapted from Gilsanz *et al.* (10).

Consequently, a person's volumetric BMD at axial or appendicular regions tracks through growth maintaining the

same position in the normal distribution at 18 yr of age as was present at 2 yr of age. This tracking is well documented in the pediatric literature for height, weight, skull size, and many other traits. Third, for there to be variation in volumetric BMD, some individuals must accrue more bone per unit external volume of bone than others to be placed at the 95th percentile, whereas others must accrue less bone per unit external volume of bone to be placed at the 5th percentile (*i.e.* some individuals must have less cortical thickness, fewer or thinner trabeculae per unit external bone volume than others, placing them at greater risk for fragility fractures during aging).

What genetic, hormonal, biomechanical and other factors account for the *variance* in volumetric BMD? What determines the relationship between the growth of the skeleton in size and the mass within it? What regulates the *variance* in shaft width, cortical thickness, trabecular number for a given bone length? We will not know until we define the age- and gender-specific *variance* of these structural components of areal BMD (not areal BMD) and then study the candidate genes or environmental factors that account for components of the *variance* in each of these structural components (not areal BMD).

The absolute and relative movement of the periosteal and endosteal surfaces determine bone size and its mass. The gender difference in leg length is the result of a longer prepubertal period of growth in the male (16). During this time, growth is more rapid in the legs than spine (14). The pubertal growth spurt occurs 1 yr later in boys, and pubertal growth velocity is greater and more protracted than in girls. At puberty, growth velocity of the appendicular skeleton slows and then ceases whereas growth velocity of the spine accelerates to exceed that of the legs and continues longer. The difference in height at peak between women and men is primarily in leg length, not trunk length. (Spouses should negotiate sitting, not standing.) The long bones and vertebrae are also wider, but the vertebrae are only slightly taller in men than women.

The absolute and relative movements of the periosteal and endosteal surfaces determine the diameter of the long bone, the mass of cortical bone, cortical thickness, and the distance this cortical mass is placed from neutral axis of the bone. If both periosteal and endocortical surfaces expand in parallel, cortical thickness of the enlarging bone will remain unchanged. If endocortical expansion is excessive relative to the extent of periosteal expansion, the enlarging bone will have a progressively thinner cortex, which is not good. If periosteal expansion occurs with no endocortical expansion, or less periosteal expansion occurs with endocortical contraction, the same cortical thickness is produced. However, the latter bone will be smaller, and its cortical mass will be nearer the neutral long axis of the bone so that bending strength will be less.

Periosteal apposition increases bone width in boys and girls during prepubertal growth. Puberty is associated with accelerated periosteal apposition with less endocortical expansion in boys, resulting in enlargement of the bone diameter, cortical thickening, and an increase in the medullary diameter. Most of the increase in cortical thickness is achieved by accelerated periosteal apposition, a process that is likely to be regulated by T directly (via the androgen receptor), GH, and IGF-I (17, 18). In addition, aromatization of T may influence GH and IGF-I. When females enter puberty, periosteal apposition is inhibited, probably due to the inhibitory effect of estrogen on periosteal bone formation, whereas endocortical bone formation is stimulated, increasing cortical thickness and narrowing the medullary cavity (17–20). This gender-specific and surface-specific behavior was documented 33 yr ago in beautiful studies of the surfaces of the metacarpal bones (Fig. 4) (19). Endocortical contraction may also be region specific, occurring less at weight-bearing regions such as the femur (14, 21), than metacarpals or radius (8, 19).

The gender difference in bone size and strength is established in puberty. The greater periosteal and endocortical expansion before puberty and minimal endocortical contraction during puberty in men places the cortical bone mass further from the neutral axis of the long bone in men than women. (Although cortical thickness is similar in males and females, the mass of cortical bone is greater because of the greater perimeter of the bigger bone.) Bone placed further from the neutral axis by periosteal apposition confers more strength in bending than bone deposited by endocortical apposition nearer the neutral axis of the long bone (22).

In a recent issue of the *JCEM*, Schoenau *et al.* (23) reported the results of a study of the growth in mass and strength of the proximal radius in 273 females and 187 males aged 6–40 yr. Bone mass, measured by peripheral quantitative computed tomography, was expressed as BMC of a 2-mm thick slice of cortical bone measured at the distal radius. Gender differences emerged at the age of 16–17 yr. BMC increased in men and women because the bone slice widened by periosteal expansion in males and females and endocortical contraction in females. Males had ~20% higher BMC due to placement of bone further from the neutral axis of the long

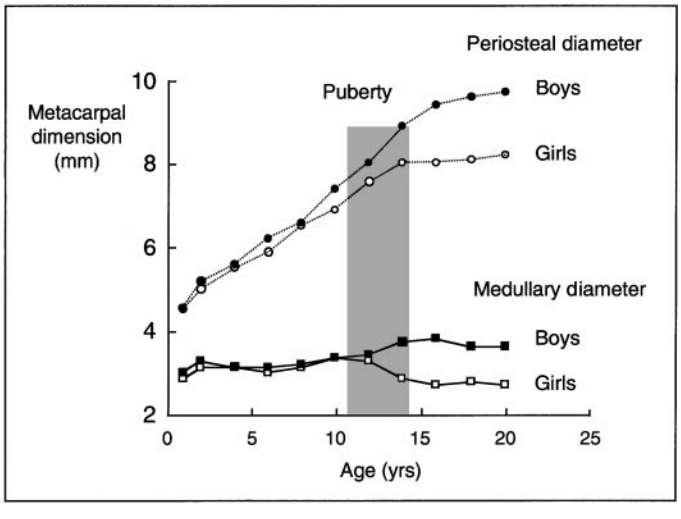

FIG. 4. Periosteal diameter of the metacarpal bones does not differ before puberty in boys and girls. During puberty the periosteal diameter expands in boys and ceases to expand in girls whereas medullary diameter remains fairly constant in boys throughout growth but contracts in girls. [Reproduced with permission from S. Garn: *Nutritional Perspectives*, Charles C. Thomas, Springfield, IL, 1970 (19).]

bone. Bone strength increased in both genders, but the gender difference in strength was the result of the gender difference in bone geometry, not bone mass. The same authors report constant volumetric BMD of the radius in an earlier study (9), so that the literature is consistent in this notion of the constancy of the amount of bone in the growing bone (volumetric BMD).

Thus, the absolute and relative growth of these surfaces varies by gender, pubertal stage, the type of bone, and probably varies in degree at every position along the length of bone from proximal to distal, medial, lateral, anterior, and posterior, so that these long bones differ in size, shape, cortical thickness, and medullary diameter throughout their whole length. At each level, these traits will be determined by the interaction between bone formation on the periosteum, and the interaction of endocortical bone resorption and formation adjacent to marrow. For the endocortical expansion to occur, resorption must exceed bone formation; for endocortical contraction to occur, bone formation must exceed resorption. If resorption and formation are equal there will be no net movement of the endocortical surface.

The complex and irregular periosteal and endocortical perimeters of long bone shafts are created by the differing modeling and remodeling occurring in adjacent regions that share the same marrow. An enigmatic example of this surface-specific modeling and remodeling is described in one of the few histomorphometric studies of skeletal growth (11). Outward growth of the ilial wings of the pelvis is achieved by periosteal apposition and endocortical resorption on the outer cortex and endocortical apposition and net periosteal resorption on the inner cortex. What regulates endocortical resorption of the outer cortex and periosteal apposition on the inner cortex when these surfaces share the same marrow?!

Clinical relevance of the differing behavior of bone surfaces during growth. The gender differences in the behavior of these surfaces at puberty suggest that delayed puberty produces gender-specific structural abnormalities. To speculate, boys will lose the pubertal component of periosteal apposition, leaving a smaller bone with a thinner cortex but normal medullary diameter (Fig. 5, *top*). Areal BMD will be reduced because bone size is reduced, and volumetric BMD may be normal if the reduction in size and accrual are proportional. Girls will lose the pubertal endocortical apposition, leaving a normal or larger bone (periosteal apposition continues in absence of the inhibitory effect of estrogen) with a thinner cortex and larger medullary diameter (Fig. 5, *bottom*). Thus, areal BMD may be normal or reduced depending on bone size, but volumetric BMD will be reduced because the normal or larger bone will have less bone mass accrual within it. Because of reduced bone size in boys and normal (or larger) bone size in girls, the biomechanical consequences of delayed puberty may be worse in boys than girls, even though areal BMD may be similarly reduced.

Reduced areal BMD is reported in boys with delayed puberty (24–27). Two of the studies reported normal volumetric BMD (26, 27), suggesting the deficit in areal BMD was only due to smaller bone size. This observation was challenged and rebutted (28, 29), but the inconsistency is more apparent

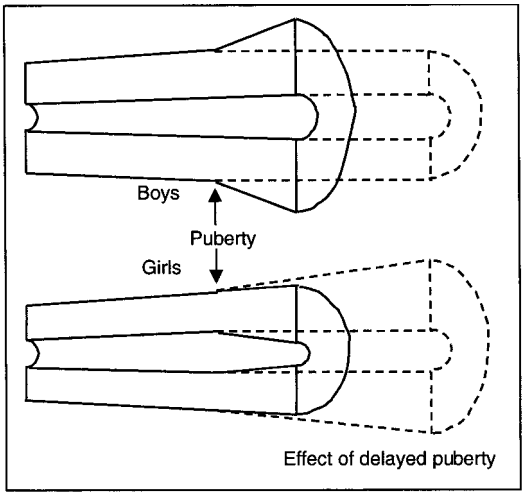

FIG. 5. In boys, delayed puberty may reduce periosteal apposition, leaving a smaller bone with a thinner cortex but normal medullary diameter (*top*). In girls, delayed puberty may result in reduced endocortical apposition, leaving a normal or larger bone (if periosteal apposition continues in absence of the inhibitory effect of estrogen) with a thinner cortex and larger medullary diameter (*bottom*). [Reproduced with permission from E. Seeman.]

than real. Reduced bone size accounts for the low areal BMD, but the amount of bone in the smaller bone is normal. Similar observations are found in Turner's syndrome; areal BMD is reduced because bone size is reduced, but volumetric BMD is normal (30). Confusion will cease when the limitations of densitometry are acknowledged. The three-dimensional world cannot be seen using two-dimensional images of vertebrae or long bones (1, 2).

Aging and the behavior of the periosteal and endosteal surfaces

During aging, periosteal apposition continues as it did during growth but much more slowly. Bone remodeling occurs at discrete sites or basic multicellular units (BMUs) on the trabecular, endocortical, and intracortical components of the endosteal (inner) surface of the skeleton. However, the remodeling within each BMU is imperfect because the volume of bone removed by bone resorption is not matched by the same volume of bone formed within the BMU. The resulting negative bone balance within each BMU is the structural basis of irreversible bone loss. The loss of bone within each BMU produces cortical thinning and intracortical porosity, especially near the bone marrow, trabecular thinning, complete loss of trabecular plates, and loss of connectivity.

The prevailing view derived using bone densitometry is that men lose less bone than women at the spine (Fig. 6, *top*) (31). This notion is produced by the fact that densitometry summates the bone deposition on the periosteal surface plus the loss occurring inside bone. Examination of the age-related changes that occur within the trabecular compartment inside bone and on its periosteal surface reveals that the amount of trabecular bone lost during aging in women and men is similar, or only slightly less in men than women (Fig. 6, *middle*) (32). This has been confirmed using histomorphometry at the iliac crest, quantitative computed tomography at the spine, and ashing of vertebrae (32–36).

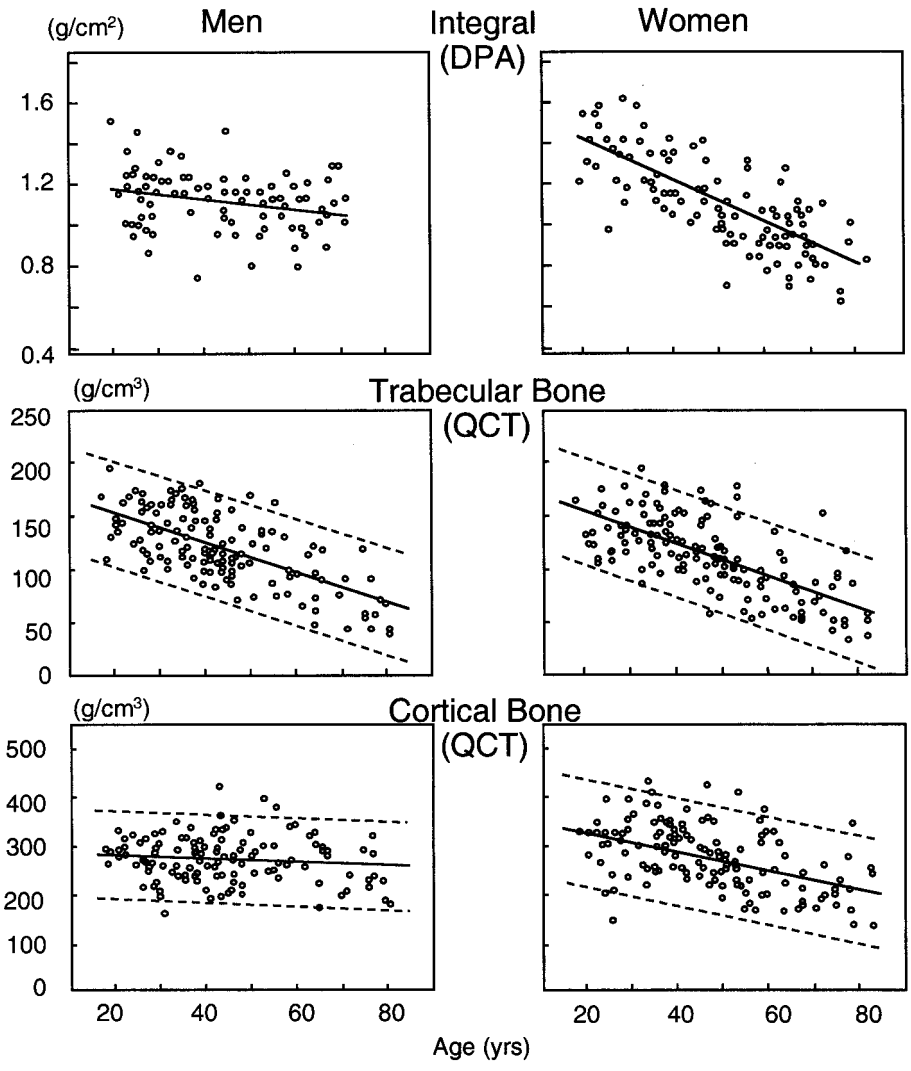

FIG. 6. *Top*, The age-related diminution in areal BMD (vertebral body plus posterior process) using dual photon absorptiometry. [Reproduced with permission from B. L. Riggs *et al.*: *J Clin Invest* 67:328–335 (31).]. *Middle* and *bottom*, The age-related diminution in vertebral body trabecular and cortical BMD of the vertebral body measured using dual energy quantitative computed tomography. Adapted from Kalender *et al.* (32).

The pattern of trabecular bone loss differs by gender, occurring mainly by thinning in men and mainly by loss of connectivity in women (36). Trabecular bone loss accelerates in midlife in women due to the increased surface remodeling that accompanies estrogen deficiency at menopause. The contribution of trabecular bone loss to overall bone loss decreases as trabecular plates perforate and disappear because there is less trabecular surface available for remodeling. In men, there is no midlife acceleration of bone remodeling because men do not go through menopause, but bone loss occurs due to reduced bone formation and thinning of trabeculae. Relatively greater maintenance of connectivity results in persistence of the trabecular surfaces available for remodeling so that trabecular bone loss probably continues longer in men than in women. That is why final trabecular bone volume is similar in men and women. The amount of trabecular surface available for bone remodeling in old age seems to be greater in elderly men than women (36).

The periosteal bone formation occurring during aging offsets bone loss from the endosteal surfaces in both men and women, but for reasons that are not understood, periosteal apposition is greater in men than women so that the (similar) loss of bone inside bone is more greatly offset in men than in women (4–6). For example, Ruff and Hayes (4) report greater gender differences in periosteal bone formation than endosteal bone resorption at tibia. Per decade, tibial cross-sectional area (reflecting absolute periosteal bone formation) increased by 2.5% in men and 1.1% in women. Endosteal area (reflecting absolute bone resorbed) increased similarly in men and women (7% *vs.* 8%, respectively).

Thus, the lesser decrease in areal BMD at the spine in men than women is due to the lesser decrease in cortical bone in men than in women (Fig. 5, *bottom*) (32). However, the lesser decrease in cortical mass is the result of greater periosteal bone formation in men, not less resorptive removal of bone from the endosteal surface.

The densitometer is blind to all this surface-specific bone formation and resorption. The lesser diminution in areal BMD in men than women across life in cross-sectional studies is responsible for the belief that men lose less bone than women. The missing word is "net"—net bone loss is less in men than women because men form more bone during aging on the outside surface of the bone, not because the lose less bone on the inside of the bone.

The gender difference in peak bone size is not why fewer men than women have fragility fractures. The larger skeleton achieved during growth in men produces a stronger bone than in women (*i.e.* a bone that tolerates larger absolute loads). But, this is not the explanation for the lower incidence of fragility fractures in elderly men than in elderly women. An elephant has a bigger and stronger bone than a mouse but has to cope with the forces generated by an elephant's bigger muscle. A fall on the outstretched hand loads the distal radius of a man with the kinetic energy generated by the man's height and weight, not a woman's height and weight. The absolute load imposed on the vertebral body is greater in young men than women because men are taller and heavier (3, 5). However, the relative load—the load per unit area (stress) imposed on the vertebral body—is no different in young men and women, because the larger bone is subjected to correspondingly larger loads (5). The ratio of periosteal perimeter of the radius to muscle area is the same in boys and girls (37). There is scaling in nature—a bigger bone has a bigger muscle—a relationship that is likely to be largely determined by genes regulating size, not necessarily the amount of exercise undertaken (38).

Fragility fractures are uncommon in young men and women because loads (determined by weight, height, and bending moments) are well below the ability of the bone to withstand them (determined by cross-sectional area and volumetric BMD). Structural failure emerges during aging in men and women because of the changing relationship between the imposed load and the bone's ability to tolerate that load.

Periosteal apposition has two effects, it increases the cross-sectional area of the bone more in men, so that load imposed per unit area decreases more than in women. Second, greater periosteal apposition adds more bone to the outer perimeter of the bone in men than women offsetting the age-related endosteal bone loss more in men than women so that the fall in volumetric density of the whole bone is less in men than in women.

Thus, among men and women surviving to endure old age, both the load imposed per unit area of bone decreases more, and strength of the bone decreases less, in men than in women so that a lower proportion of elderly men than elderly women have bone size and volumetric BMD reduced below a critical level (or fracture threshold), where the loads on the bone are greater than the bones structural ability to tolerate them (5). Structural failure occurs less in men than and women because the relationship between load and bone strength is better maintained in men than in women (3, 5).

Patients with fragility fractures have reduced volumetric BMD, but they may also have reduced bone size relative to controls (39–42). As the bone size difference is not taken into account in the BMC measurement, and only partly taken into account in the areal BMD measurement, the deficit in bone mass is exaggerated if the bone size is reduced relative to controls. This exagerated deficit will be attributed to reduced accrual, or (as usually the case) to excessive bone loss. Thus, the investigator is misled by the areal BMD deficit if the effect of the smaller bone size is not appreciated. If bone size in fracture cases is increased relative to controls, as reported in women with hip fractures (Duan, Y., and E. Seeman, submitted for publication), then the deficit in BMC or areal BMD will be underestimated and may obscure any deficit in volumetric BMD due to reduced accrual or excessive bone loss. Failure to account for differences in bone size in fracture cases and controls will then lead the investigator to falsely conclude that there is no deficit in volumetric BMD and, therefore, no disease process producing a deficit in volumetric BMD.

A fascinating possibility is that both deficits in bone size and volumetric BMD in women and men with spine fractures are the result of reduced periosteal apposition during aging (3). Reduced periosteal apposition during aging will 1) result in a smaller bone that tolerates bending loads less well, and will 2) fail to offset endosteal bone loss so that volumetric BMD (of the whole bone) will be lower than it otherwise would be had periosteal apposition occurred.

Summary: study the surfaces of the skeleton

Growth produces a bigger not denser skeleton in males and females (Fig. 7). Greater periosteal growth during puberty produces a skeleton that is just the right size to accommodate the larger skeleton of the male. The smaller skeleton of the female is just the right size to accommodate the smaller skeletal mass fastened to its surface. Periosteal apposition assembles most of the cortical mass in males. Endocortical apposition at puberty assembles about 25% of cortical thickness at nonweight-bearing bones in females nearer the neutral axis where it confers less biomechanical advantage during bending than a comparable amount produced by periosteal apposition. Less strength is needed at nonweight-bearing sites, and it makes sense that endocortical apposition contributes proportionally less cortex at weight-bearing sites. Whether this estrogen-dependent endocortical accrual is the reserve for skeletogenesis of a fetus without compromising the mother's bone strength is a plausible hypothesis in need of testing.

Men have a skeleton that adapts better to aging by greater periosteal apposition that increases bone size and offsets bone loss more than in women so fewer males than females are at risk for fracture in old age. Patients with SPINE fractures have both smaller VERTEBRAL BODY SIZE and less bone in the smaller bone. The pathogenesis of each of these deficits requires the study of the surfaces of the skeleton during growth and aging.

Bone densitometry is an important tool for the clinical practice of fracture prevention. It has made valuable contributions in terms of quantitating the age- and gender-specific normal distribution of bone mass, providing a quantitative definition of "osteoporosis" and so defining the size of the problem of osteoporosis. Areal BMD is a predictor of fracture risk and so is indispensable in identifying individuals at risk of fracture who should be considered for treatment. These are valid and useful clinical applications of the method.

For clinical research, the excessive dependency on bone densitometer creates problems in understanding the structural basis of underlying the attainment of bone strength during growth, bone fragility during aging, as well as the structural basis of the slowed progression of bone fragility associated with antiresorptive drug therapy because densi-

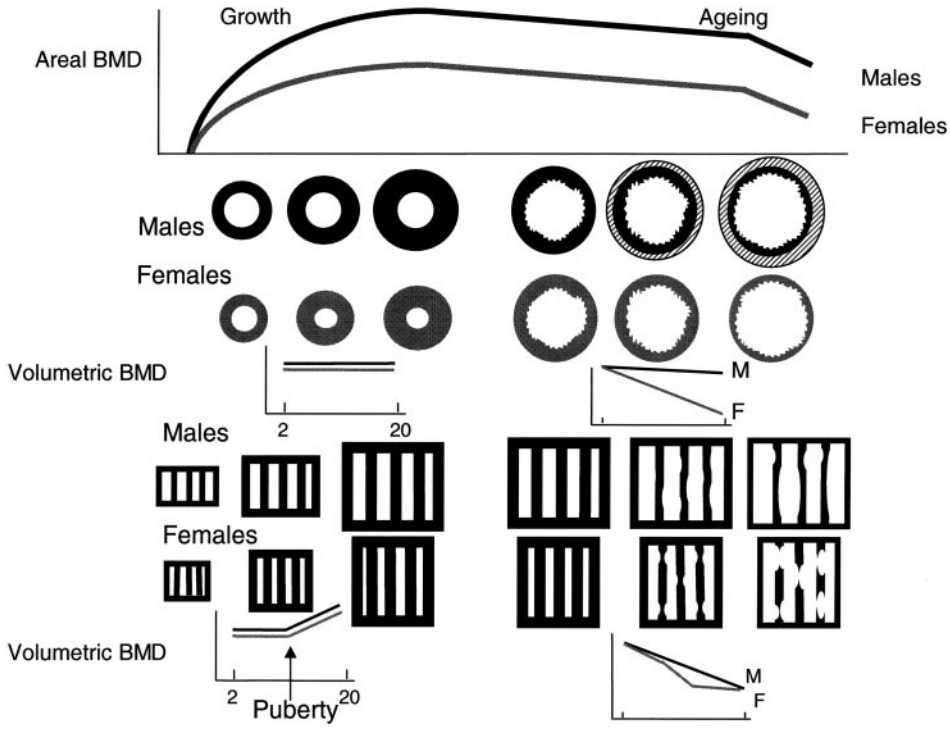

FIG. 7. During growth, areal BMD increases because bone size increases. Areal BMD is higher in men because bone size is greater than in women; there is no sex difference in peak volumetric BMD. In long bones, volumetric BMD is independent of age. At the spine, volumetric BMD increases at puberty. During aging, men and women lose similar amounts of bone by endosteal resorption. Men have greater periosteal apposition than women, so that net bone loss is less in men than women. Trabecular bone loss occurs by loss of complete trabecular elements in midlife in women and by continued trabecular thinning in men. [Reproduced with permission from E. Seeman.]

tometry is blind to bone size and shape, critical determinants of bone strength.

Osteoporosis begins by picking the wrong mother and father, it gains expression in the follies of a misspent youth and the excesses of adulthood, and strikes those forced to endure the futility of old age, inheriting its gifts, like senility and fractures. The word "osteoporosis" carries dangers for those interested and challenged by the need to understand the pathophysiology of bone fragility. Replace the word "osteoporosis" with "bone fragility"(. . . the epidemiology of . . . bone fragility, the pathogenesis of . . . bone fragility, the prevention and treatment of . . . bone fragility); this terminology conveys the true sense, intimidating breadth, depth, and complexity of the pathophysiology of growth and aging of the skeleton.

Unless the complexity of the structural basis of attainment of bone strength during growth, and its decay during aging, is recognized and studied, young investigators entering the field will search for a single cause of a single disease where there is no one of either. The absolute and relative movement of the periosteal and endosteal surfaces produced by bone formation and bone resorption during growth and aging determine the size, mass, geometry and architecture of the skeleton, and, so, its strength. The nobility of the task will remain unfathomable while the face of bone fragility remains invisible, hidden in the vagaries of "osteoporosis" and structural ambiguities of "low areal BMD." When these terms are abandoned, the wider tapestry of bone fragility will appear resplendent in its variety.

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