



Establishment of peak bone mass

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Osteoporosis is a disease characterized by low bone mass and micro-architectural alterations of bone tissue leading to enhanced bone fragility and increased fracture risk [1]. Although research in osteoporosis has focused mainly on the role of bone loss in the elderly population, it is becoming increasingly clear that the amount of bone that is gained during growth is also an important determinant of future resistance to fractures. Thus, considerable interest is being placed on defining preventive strategies that optimize the gain of bone mass during childhood and adolescence. Knowledge of the determinants accounting for the physiologic variations in bone accumulation in children will provide the best means toward the early diagnosis and treatment of osteoporosis. This article reviews the techniques available for bone mass measurements in children and the major determinants influencing bone accretion during childhood and adolescence.

Bone measurement techniques

The development of precise noninvasive methods for measuring bone mineral content (BMC) has significantly improved our ability to study the influence of genetic and environmental factors on the attainment of bone mass. These techniques have helped to quantify the loss of bone associated with the various disorders that cause osteopenia in children [2] and have

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improved our understanding of the childhood antecedents of a condition that happens to manifest in adults—osteoporosis.

Dual energy X-ray absorptiometry (DXA) has become the most commonly used technique worldwide for the assessment of BMC [3]. Bone mineral measurements by DXA rely on the attenuation (absorption) of energy that occurs as the x-ray beam scans across the region of interest [4]. Two energy settings are used to optimize the separation of mineralized and soft tissue components in the area analyzed. Because DXA bone determinations are based on a two-dimensional projection of a three-dimensional structure, the values are a function of three skeletal parameters: the size of the bone being examined, the volume of the bone, and the mineral density of the bone [5]. These values are referred to as measures of BMC (expressed as g/cm), which can also be expressed as bone mineral content per surface area (ie, bone mineral density [BMD]) (expressed as g/cm²) when the projected area of the bone is taken into account. However, because scan radiographs provide only an approximation of bone size, bones with equal mineral density but different cross-sectional dimensions may result in different BMC and BMD values [5]. Attempts to overcome this disadvantage with the use of correction factors (eg, the squared root of the projected area; the height of the subject; the width of the bone; assuming the cross-sectional area of the vertebrae is a cube [5–7], a cylinder with a circular base [8,9], or a cylinder with an elliptic base area [10], etc.) are subject to error because there is no closed formula that defines the size of the vertebrae. Similarly, correction formulas that have been proposed for the femur and the mid-radius [8,11–13] are also prone to error because they cannot account for the marked changes in the size and shape of the bone during growth.

DXA values are also influenced by the unknown composition of soft tissues in the beam path of the region of interest. Because corrections for the soft tissues are based on a homogeneous distribution of fat around the bone, inaccuracies in DXA measurements are observed if fat is distributed inhomogeneously around the bone being measured [14]. Although this is not a limitation when studying subjects whose weight and body size remains constant, DXA bone measurements in growing individuals reflect a large number of biologic parameters.

Quantitative computed tomography (QCT) using conventional CT scanners or with peripheral QCT scanners allows for the independent study of the marked alterations that occur in the size and the shape of the skeleton during growth. The concomitant changes in the bone volume and bone density can also be accurately measured without the influence of surrounding soft tissues [15,16]. The densities of cortical and trabecular bone can be separately assessed using QCT.

Although MRI is an ideal modality for measuring the volume of any tissue, including bone, the value of this technique in measuring the density of bone is in its developmental stage [17]. Ultrasound has also been used as a bone measurement technique [17,18]. Because, in adults, ultrasound

can predict fracture risk in patients with osteoporosis, these measurements must be related to some aspects of bone strength [17,18]. Unfortunately, the values are dependent on so many structural parameters, yet to be fully defined, that it is difficult to use this information in a meaningful way in children [17].

Bone mass accrual

Importance of peak bone mass

The amount of bone in the skeleton at any age is the result of the amount of bone gained during growth, from uterine life to skeletal maturity, and the loss of bone that occurs with aging. Many factors contribute to the achievement of peak bone mass (PBM), which is regarded to be the bone bank for the remainder of life. Acquiring a solid “account” contributes to counteracting the inevitable bone loss caused by aging, illness, and other insults. Understanding the mechanisms that regulate PBM allows the institution of early preventive strategies aimed at maximizing the amount of bone that can be gained during growth.

The exact age at which values for bone mass reach their peak has received considerable attention that has produced varying results. It is likely that the timing of peak values differs between the axial and appendicular skeletons and between men and women. Moreover, differences among studies are in part a reflection of the different modalities used for measuring bone mass.

In the axial skeleton, bone mass achieves peak values by the end of the second decade of life. Studies in women using CT have demonstrated that the density and the size of vertebral bone reach their peak soon after the time of sexual and skeletal maturity [19,20], corroborating anatomic data indicating trabecular bone loss as early as the third decade of life and no change in the cross-sectional area of the vertebral body from 15 to 90 years of age [21–23]. The data regarding whether vertebral cross-sectional area in men continues to grow after cessation of longitudinal growth is controversial; whereas some authors find no change in the cross-sectional dimensions after skeletal maturity, others have suggested that vertebral size increases with age throughout adulthood [23].

In the appendicular skeleton, the range of ages published in cross-sectional studies for the timing of PBM has varied significantly, from 17 to 18 years of age to as late as 35 years of age [24–27]. Longitudinal DXA studies indicate that the rate of increase in skeletal mass slows markedly in late adolescence and that peak values in the femoral neck, like those in the spine, are achieved near the end of puberty in normal girls [10,12,28]. In men and women, the cross-sectional dimensions of the long bones in the appendicular skeleton continue to grow throughout adulthood and into old age by subperiosteal bone apposition. This increase in bone width occurs in all sample populations studied [29].

Critical years of bone mass increments

Skeletal mass increases from approximately 70 to 95 g at birth to 2400 to 3300 g in young women and men, respectively [30]. These gains are achieved through longitudinal growth and bone modeling and remodeling, which proceed at different rates at various skeletal sites [31]. Longitudinal studies of total body BMC measurements show that gains in bone mass are rapid during adolescence and that up to 25% of PBM is acquired during the 2-year period across peak height velocity [32]. At peak height velocity, boys and girls have reached 90% of their adult stature but only 57% of their adult BMC [33]. At least 90% of PBM is acquired by age 18 [32] (Fig. 1).

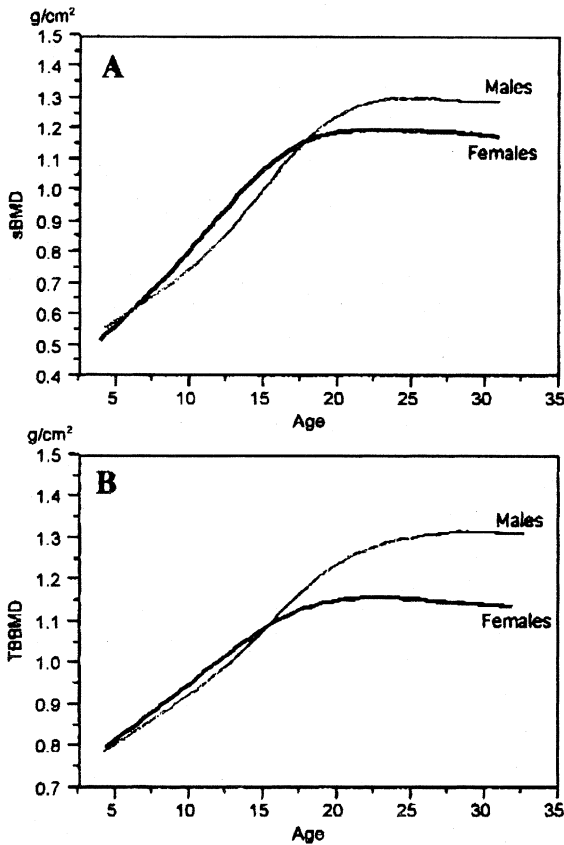


Fig. 1. Changes of BMD values of the lumbar spine (A) and whole body (B) with chronologic age. The acceleration during adolescence is followed by a plateau phase in early adulthood. DXA measurements performed in 319 healthy subjects (156 female, 163 male) from 4 to 32 years of age are shown. (Courtesy of Stefano Mora, MD, Milan, Italy.)

The human skeleton contains approximately 85% cortical bone and 15% cancellous bone, and studies have shown that the patterns of gain during growth and the rate of loss with aging differ considerably between these two skeletal compartments [34–36]. The density of cancellous bone is strongly influenced by hormonal or metabolic factors associated with sexual development during late adolescence [37]. On average, cancellous bone density in the spine increases by 13% during puberty in Caucasian boys and girls. After controlling for puberty, vertebral bone density fails to correlate significantly with age, sex, weight, height, surface area, or body mass index [37]. The increase in the density of cancellous bone during the later stages of puberty is likely a reflection of a greater thickness of the trabeculae.

The factors that account for the increase in cancellous vertebral bone density during late puberty remain to be determined. It is reasonable to suspect that many of the physical changes, such as the accelerated growth spurt and the increases in body and bone mass, are at least in part mediated by the actions of sex steroids [38]. Some of these effects may be due to changes in protein and calcium metabolism induced by sex steroids, or they may be secondary to the cascade of events triggered by the increase in growth hormone and insulin growth factor I (IGF-I) production observed after sex steroid exposure.

In the appendicular skeleton, CT values for the material density of cortical bone in children are remarkably similar and constant (2.00 ± 0.065 m/cm³) (Fig. 2) [16]. Neither puberty, age, gender, race, height, nor weight influence these measurements. These data contradict the common belief that, during the adolescent growth spurt, bone formation transiently outstrips mineral deposition and there is a temporary decrease in bone density. Because of the thickness and the relative lack of porosity of the femoral cortex, CT values for cortical bone density reflect the true density of the bone (ie, the amount of collagen and mineral in a given amount of bone) [16]. These values are eight times higher than cancellous bone density values, which is consistent with histomorphometric studies indicating an equivalent difference in the porosity of these two forms of bone [39].

Cross-sectional growth of the bones in the axial and the appendicular skeletons results from two different processes that are likely to be regulated by different means [40]. Bone growth at the midshaft of the femur is achieved by subperiosteal formation of new bone, a process that begins before birth and continues throughout life. Simultaneous to the age-specific subperiosteal bone apposition, a complex activity characterized by resorption and apposition occurs at the endosteal surface of the bone. Whereas subperiosteal activity determines the width of the bone, endosteal activity determines the width of the medullary canal. The combination of the relative activities at the two modeling surfaces over a period of time determines the thickness of the cortex. On the other hand, endochondral ossification determines the cross-sectional area of the vertebrae. Endochondral ossification begins in the central area of the cartilage anlage in the

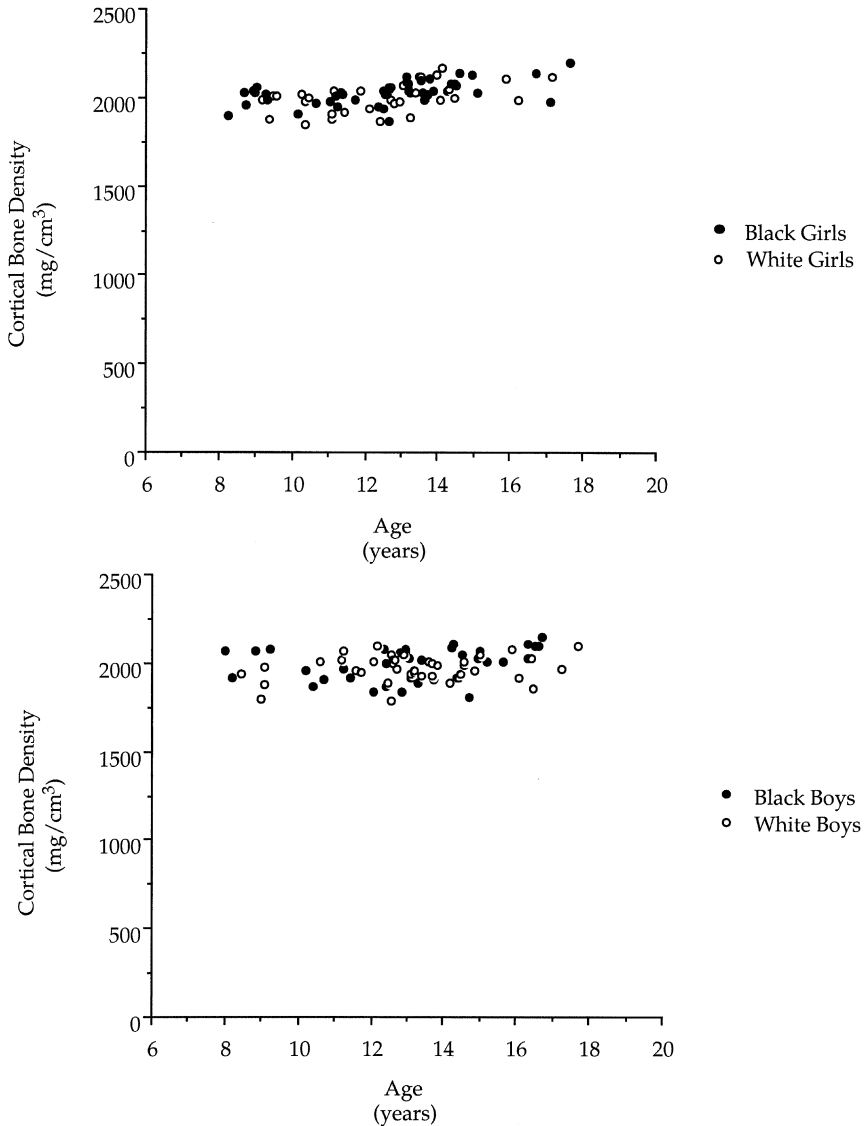


Fig. 2. Cortical bone density in 80 African American and 80 Caucasian girls and boys from 7 to 20 years of age. (Adapted from Gilsanz V, Skaggs DL, Kovanlikaya A, et al. Differential effect of race on the axial and appendicular skeletons in children. *J Clin Endocrinol Metab* 1998;83: 1420–7; with permission.)

vertebrae and, from this region, expands and progresses toward the periphery in all directions. It is generally assumed that normal development and growth of the diaphysis of the femur is mainly dependent upon mechanical loading, whereas endochondral growth and ossification may occur without mechanical stress [40].

Gender differences

Bone mass is greater and the incidence of fractures is lower in men than in women. Recent evidence indicates that neither cancellous nor cortical bone density differs between men and women; this challenges the view widely held for many years that gender differences in bone mass were due to differences in bone density [23,41].

Observations using CT indicate that, throughout life, females have smaller vertebral cross-sectional area when compared with males, even after accounting for differences in body size. On average, the cross-sectional area of the vertebral bodies is 11% smaller in prepubertal girls than in prepubertal boys matched for age, height, and weight [42]. This disparity increases with growth and is greatest at skeletal maturity, when the cross-sectional dimensions of the vertebrae are about 25% smaller in women than in men, even after taking into consideration differences in body size [41]. Thus, the phenotypic basis for the 4- to 8-fold higher incidence of vertebral fractures in women compared with that in men may lie in the smaller size of the female vertebra.

In contrast, the cross-sectional dimensions of the femur do not differ between males and females matched for age, height, and weight [43]. The cross-sectional and cortical bone areas at the midshaft of the femur are primarily related to body weight, regardless of gender; this notion is consistent with analytical models proposing that long bone cross-sectional growth is strongly driven by mechanical loads [40,44]. The reasons for the gender differences reported by some investigators in the incidence of hip fractures are unknown.

Recent evidence also indicates volumetric BMD of the long bones is similar in boys and girls. Data obtained with DXA in a large sample of healthy subjects indicated that there were no differences in BMC and BMD during the prepubertal period [45]. During puberty, BMD values in girls were higher in the pelvis and spine, whereas measures in postpubertal boys were higher in the whole skeleton. Peak BMC and BMD was achieved between the ages of 20 and 25 years and occurred much earlier in girls than in boys.

Tracking of bone mass

The amount of bone that is gained during adolescence is the main contributor to PBM, which, in turn, is a major determinant of osteoporosis and fracture risk in elderly persons. Recent evidence seems to indicate that the morphologic traits that contribute to the strength of the bone track throughout life; values remain in the same position relative to population percentiles [45–47]. In one study, DXA bone mineral measurements of premenopausal mothers and prepubertal daughters showed considerable familial resemblance at all skeletal sites [47]. Moreover, DXA values in the

daughters 2 years later correlated strongly with baseline values. Similarly, longitudinal CT measurements of cross-sectional areas of the vertebrae and femurs and of cancellous bone density in healthy children indicated that measures at early puberty predicted values at sexual maturity [46]. When baseline values were divided into quartiles, a linear relation across pubertal stages was observed for each quartile. The regression lines differed among quartiles, paralleled each other, and did not overlap (Fig. 3). Therefore, individual volumetric BMD and bone size tracked through growth and maintained the same position in the normal distribution at the end of puberty as was present in the prepubertal period. Thus, we are now in a position to identify children who are genetically prone to develop low values for peak bone mass and toward whom osteoporosis prevention trials should be geared.

Determinants of bone mass

Studies on various sample populations show that about three fourths of the variance in peak bone mass is attributable to hereditary factors. The remaining fraction of the variance in peak bone mass is caused by environmental factors, such as nutrition and physical activity behaviors.

Heredity and bone mass

Genetics

The obvious application of genetic studies to osteoporosis and bone mass is the discovery of genetic markers that consistently predict osteoporotic fractures and allow the early identification of subjects at high risk. Understanding the role played by genetic factors may also facilitate the prediction of response to treatment. As an example, the response of bone mass to dietary supplementation with vitamin D and calcium is partly dependent on the vitamin D receptor (VDR) genotype [48–50]. It is possible that other genes may aid in identifying subjects who would benefit from treatments such as hormone replacement therapy, bisphosphonates, or exercise.

Heredity is an important determinant of bone mass, as measured with absorptiometric techniques. Convergent data from mother-daughter pairs, sib pairs, and twin studies have estimated the heritability of bone mass to account for 60% to 80% of its variance [51–53]. The magnitude of the genetic effect varies with age and between skeletal sites; it is higher in young than in elderly persons and in the spine than in the extremities [54]. Further support for this genetic influence comes from studies showing reduced bone mass in daughters of osteoporotic women when compared with control subjects [53], in men and women with first-degree relatives who have osteoporosis [55], and, more recently, in investigations reporting a link between several “candidate” genes and bone mass [56].

Two approaches are usually used to determine the genetic contribution to complex diseases: linkage and association studies. Linkage studies are expensive, time consuming, and require sophisticated technology and a detailed understanding of the complex phenotype of osteoporosis. As our knowledge of phenotypes increases and we are able to unambiguously identify this disease before it clinically manifests, linkage studies searching for the genotypes of osteoporosis will become more feasible.

Few linkage studies have been conducted to date, probably because of the difficulty in obtaining suitable multigenerational families. In a Chinese cohort selected for hypertension, forearm bone density was modestly linked to chromosomes 2p21 and 13q34 [57]. However, the most extensive genome screens published to date present evidence of linkage of lumbar spine BMD to chromosomes 1q21-q23 and 6p11-12 and femoral neck BMD to chromosome 5q33-q35 [58]. In another study, the linkage approach was used to test a number of candidate genes known to be implicated in the control of bone density and bone metabolism in a large number of probands and relatives [58]. A suggestive linkage was found in this study only with the gene encoding for the parathyroid receptor type 1. Moreover, an initial genome screen in seven large pedigrees suggested that a candidate region conferring susceptibility to low BMD of the femoral neck was located on chromosome 1p36 [59]. Extended analysis confirmed these data and showed that a major quantitative trait locus controlling femoral neck BMD is located on chromosome 1p36.2-p36.3 [60].

The results of these studies are heterogeneous. The main limitation of all linkage studies lies in selection bias; in some studies, the presence of a proband with osteoporosis was sought, whereas in others the linkage was examined on the basis of low BMD values. Unfortunately, the phenotype of the probands is far from homogeneous, and cases of secondary osteoporosis were not excluded, which jeopardizes the possibility of significant results.

Association studies examine specific genomic regions at or near candidate genes and, in osteoporosis research, are facilitated by our knowledge of the factors that regulate bone turnover and the proteins that make up normal bone matrix. Given the wide range of factors involved in bone metabolism, there is a seemingly unlimited supply of candidate genes for osteoporosis, although relatively few have been studied. Studied candidate genes are presented in Table 1, and the list is continuously expanding. The search is challenging because multiple genes are likely to interact with each other and with environmental factors to produce disease.

Genetic studies in adults outnumber those in children and adolescents, despite the likelihood that genetic influences have a greater effect on bone mineral acquisition than on loss [56]. In a study of a large group of female subjects, polymorphisms of the VDR gene at a *BsmI* restriction site were associated with BMD in prepubertal and adolescent girls [61]. Girls with BB genotype had significantly lower spinal BMD standard deviation scores than girls with Bb and bb genotypes [61]. In contrast, polymorphisms at the start

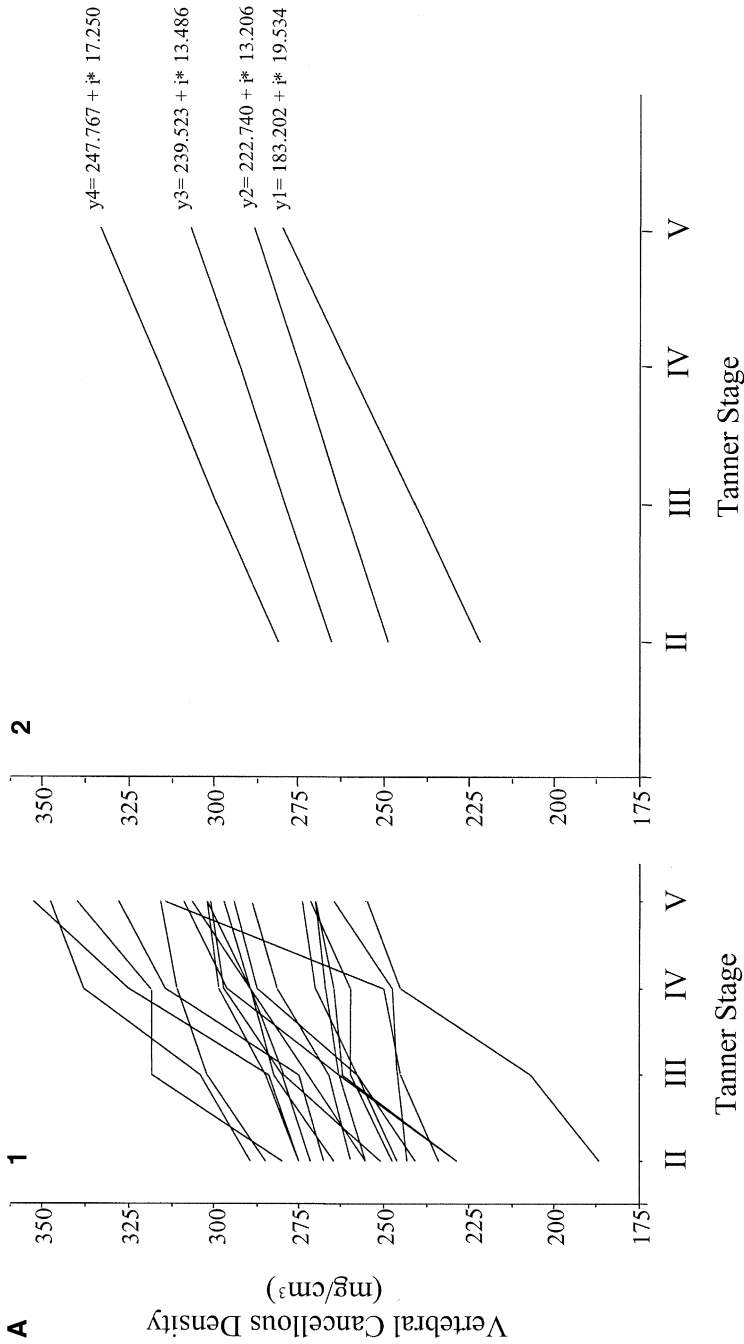


Fig. 3. Longitudinal measurements of vertebral cancellous bone density (A) and vertebral cross-sectional area (B) in 20 girls from Tanner stages 2 to 5 of sexual development. Values are shown for each quartile (1) and for each quartile (2). (Adapted from Loro ML, Sayre J, Roe TF, et al. Early identification of children predisposed to low peak bone mass and osteoporosis later in life. *J Clin Endocrinol Metab* 2000;85:3908–18; with permission.)

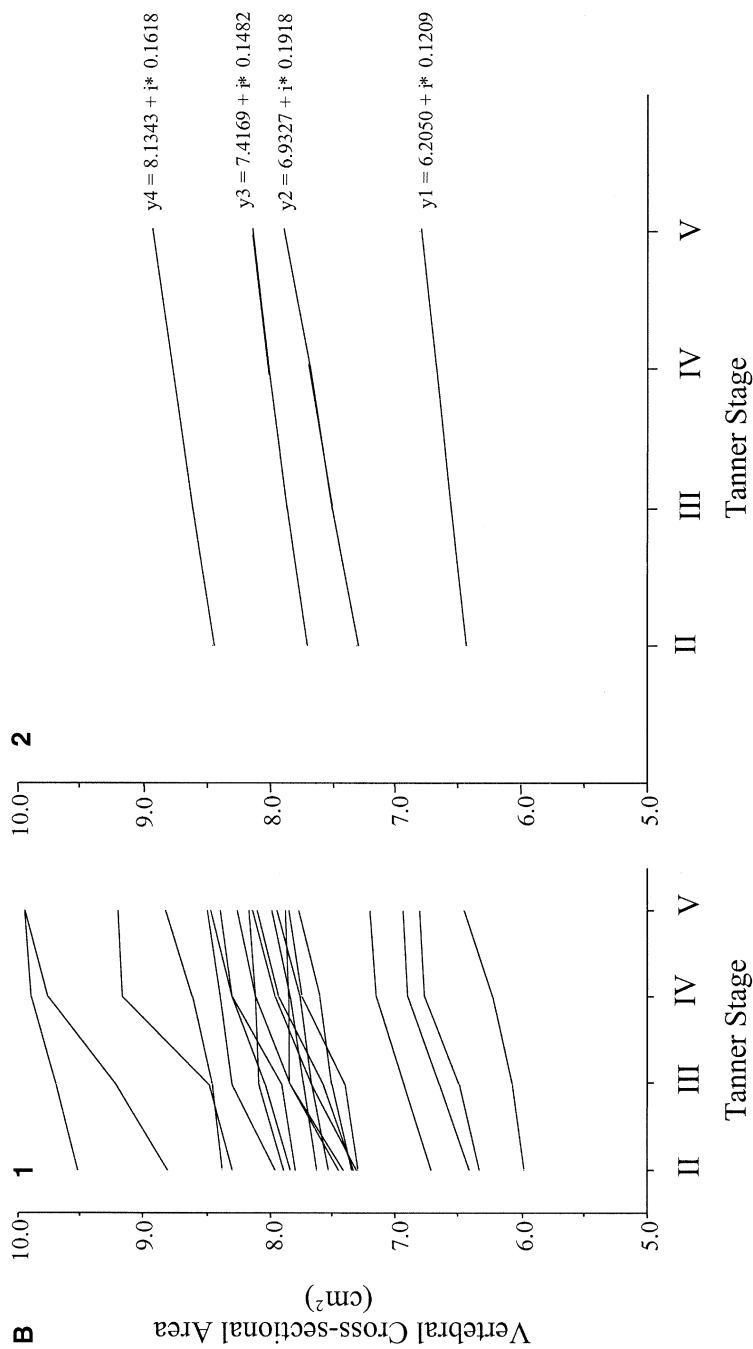


Fig. 3 (continued)

Table 1
Candidate genes in the general population

Gene name	Gene symbol	OMIM entry number
Vitamin D receptor	VDR	601769
Estrogen receptor 1	ESR1	133430
Estrogen receptor 2	ESR2	601663
Calcitonin receptor	CALCR	114131
Parathyroid hormone receptor 1	PTHRI	168468
Collagen type I alfa1	COLIA1	120150
Collagen type I alfa2	COLIA2	120160
Interleukin-6	IL6	147620
Transforming growth factor beta 1	TGFb1	190180
Apolipoprotein E	APOE	107741
Calcium sensing receptor	CASR	601199
Tumor necrosis factor receptor 2	TNFR2	191191
Aromatase	ARO	107910

codon site of the VDR gene, detected with the *FokI* restriction enzyme, were not associated with BMD at any skeletal site in prepubertal girls [62]. An association between femoral and spinal BMD and the VDR genotype at the *ApaI* and *BsmI* restriction sites has been shown using QCT in prepubertal American girls of Hispanic descent [63]. In this study, girls with aa and bb genotypes showed significantly higher volumetric BMD values than girls with the other genotypes at the spine and the femur. A polymorphism in the Sp1-binding site of the gene encoding for collagen type I $\alpha 1$ was also found to explain some of the variability in vertebral BMD in this cohort of prepubertal girls [64]. In contrast, no relationship between the VDR genotype at *BsaMI* site and forearm BMD, rate of gains of BMD, was found in Norwegian boys and girls [65].

Ethnic differences

The prevalence of osteoporosis and the incidence of fractures are substantially lower in black than in white persons, a finding generally attributed to racial differences in adult bone mass [66]. Whether these racial differences are present in childhood has been the subject of considerable interest. Several reports have suggested a greater skeletal size in black children, and most studies with single photon absorptiometry have indicated radial bone mass to be greater in black subjects [67]. More recent investigations using dual x-ray or photon absorptiometry techniques have yielded conflicting results. Some studies found the bone mass of black children to be greater than that of white children [68], whereas others detected no racial differences in bone mass in the axial or appendicular skeleton [13,69].

Studies using CT indicate that, regardless of gender, race has significant and differential effects on the density and the size of the bones in the

axial and appendicular skeletons [70]. In the axial skeleton, the density of cancellous bone in the vertebral bodies is greater in black than in white adolescents, regardless of gender. This difference becomes apparent during the late stages of puberty and persists throughout life. Before puberty, cancellous bone density is similar in black and white children; during puberty, it increases in all adolescents. The magnitude of the increase from prepubertal to postpubertal values is substantially greater in black than in white subjects (34% versus 11%, respectively) (Fig. 4) [70]. Histomorphometric data indicate that the higher cancellous bone density in black subjects is due to greater trabecular thickness and that there are no racial differences in the number of trabeculae or their degree of mineralization [71]. The cross-sectional areas of the vertebral bodies, however, do not differ between black and white children [70]. Thus, theoretically, the structural basis for the lower vertebral bone strength and the greater incidence of fractures in the axial skeleton of white subjects resides in their lower cancellous bone density.

In contrast, in the appendicular skeleton, race influences the cross-sectional areas of the femurs but not the cortical bone area or the material

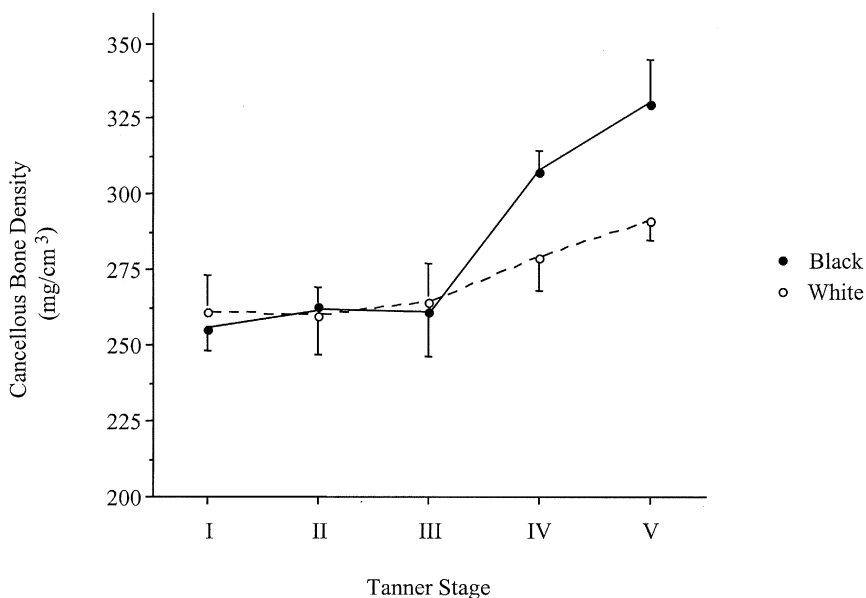


Fig. 4. Vertebral cancellous bone density in African American and Caucasian girls at each stage of pubertal development. Although values are similar before puberty and in early puberty and although they increase during puberty, the increases are greater in African American than in Caucasian children. (Adapted from Gilsanz V, Roe TF, Mora S, et al. Changes in vertebral bone density in black girls and white girls during childhood and puberty. *N Engl J Med* 1991;325:1597–600; with permission.)

density of cortical bone [70]. Although values for femoral cross-sectional area increase with height, weight, and other anthropometric parameters in all children, this measurement is substantially greater in black children [70]. Because the same amount of cortical bone placed further from the center of the bone results in greater bone strength, the skeletal advantage for black persons in the appendicular skeleton is likely the consequence of the greater cross-sectional size of the bones [44].

Limited data from Asian and Hispanic youth suggest that their bone mass is similar to that of Caucasian children but much lower than that of African American children [72,73]. Differences in bone and body size account for much of the apparent observed ethnic differences in BMD among non-Hispanic, Hispanic, and Asian children [72,73].

Influence of environment and behavior on bone mass

Physical activity

The impact of exercise and physical activity on skeletal integrity has generated considerable interest over the last two decades. The theoretical foundation for a direct effect of exercise on bone mass is based on the relationship between the intensity of bend or strain on bone and the adaptation of bone to that stimulus (the mechanostat theory) [44]. According to this model, whenever activity falls below the physiologic minimal effective strain threshold, bone resorption exceeds bone formation. In contrast, net gains of bone occur only when the intensity of loading is increased above the physiologic loading zone. This model accounts for the bone loss observed during immobilization and the increased bone mass of elite athletes.

The beneficial effects of exercise on bone mass are well documented through multiple observational and retrospective studies that indicate that weight-bearing activities increase bone mass. The earliest studies were comparisons of bone structure in tennis players. In these studies, long-term players were found to have 10% to 35% greater cortical thickness and higher bone mass in the playing arm than in the nonplaying arm [74,75]. In addition, other investigators have reported that the bilateral difference in bone mass was two to four times greater in players who started training before menarche [76]. Studies of prepubertal female gymnasts showed a larger cross-sectional area of the forearm despite a shorter stature [77] and that areal BMD values expressed as standard deviation scores were significantly greater than zero (the predicted mean of the controls) in the arms, legs, and spine, which are all weight-bearing sites [77]. In other studies, children and adolescents who were physically active accrued more bone mineral than their sedentary peers [32,78], and a more recent study demonstrated that physical activity levels measured by accelerometry and parental report were positively associated with total body BMC and BMD measurements in preschool children [79].

Studies comparing the effects of different physical exercises on bone indicated that high-impact exercises resulted in the greatest increases in bone mass in adolescents [80]. Similarly, gymnasts had higher spine and femur BMD than swimmers or sedentary girls [81]. Amateur athletes involved in weight-bearing sports (eg, rugby, soccer, endurance running, fighting sports, and bodybuilding) had higher values for total body and leg BMD than amateur sportsmen involved in active loading activities (eg, swimming and rowing) [82].

Several randomized trials involving weight-bearing activity interventions for bone mass gains have been conducted in children and adolescents (Table 2) [83–89]. Exercise session attendance ranged from 50% to 97%; exercise adherence is therefore a potentially serious threat to the internal validity of the results. However, the most recent studies showed very high rates of adherence. With one exception at 36+ months [83], the duration of the interventions was 6 to 12 months. All studies reported significant changes in femoral BMD, and four studies indicated increases in lumbar spine BMD and BMC in the intervention groups.

Whether the beneficial effect of physical activity on the growing skeleton is maintained in adulthood is unknown because no prospective study has been designed to address this question. However, the results of most, but not all, retrospective analyses indicate that the enhancement of bone acquisition during growth due to exercise interventions may be long lasting. Lifetime tennis players, playing at a lower level of intensity than during their youth, have remarkably higher forearm mineral content than control subjects [74]. Retired soccer players have high BMD during the first 10 to 20 years after cessation of the sport, but their BMD is lower compared with active players [90]. Other studies suggest that BMD values are maintained at about 0.5 to 1.0 SD above the age-predicted mean in athletes who have been retired for 10 to 20 years [77,91–94]. Peri- and postmenopausal women who participated in sport activities during adolescence showed BMD measurements at the lumbar spine and femur that were remarkably higher than those of women who did not participate in physical activities during youth [95]. In a recent follow-up study of 27 years, lifetime physical activity was related to adult BMD, indicating the importance of continuing exercise after growth [96]. In contrast, a decrease in spinal BMD has been reported in runners who ceased exercising [97]. Similarly, cessation of exercise led to the return of BMD values to pre-training levels in 12 women who performed unilateral leg press for a year [98].

Calcium and bone mass gains

The earliest data suggesting an influence of dietary calcium on PBM come from a study of two Croatian populations with substantially different calcium intakes [99]. The differences seen in bone mass were present at 30 years of age, which suggests that the effects of dietary calcium probably occurred during growth rather than in adulthood. Moreover, some

Table 2

Physical activity intervention studies and bone outcomes in children and adolescents

Study	Sample	Intervention duration and frequency	Results: significant differences in bone outcomes
Blimkie et al [88]	14- to 18-yr-old girls (n = 36)	Duration: 6 mo Frequency: 3 times per wk	NS
Morris et al [21]	9- to 10-yr-old girls (n = 73)	Duration: 10 mo Frequency: 30 min, 3 times per wk	BMD, BMC Total body Lumbar spine Proximal femur Femoral neck
Bradney et al [85]	8- to 11-yr-old boys (n = 40)	Duration: 8 mo Frequency: 30 min, 3 times per wk	BMD Total body Lumbar spine Legs
Heinonen et al [90]	10- to 15-yr-old girls (n = 73)	Duration = 9 months Frequency = 50 min, 2 times per wk	BMD, BMC Lumbar spine Femoral neck
Fuchs et al [86]	7- to 9-yr-old boys and girls (n = 41)	Duration: 7 mo Frequency: 15 min, 3 times per wk	BMD, BMC Femoral neck
Sundberg et al [27]	15- to 16-yr-old boys and girls (n = 80)	Duration: 3–4 yr Frequency: 40 min, 4 times per wk	BMD, BMC Total body Lumbar spine Femoral neck In boys
Petit et al [50]	9- to 12-yr-old girls (n = 87)	Duration: 7 mo Frequency: 10–12 min, 3 times per wk	BMD Femoral neck

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; NS, not significant.

epidemiologic studies have shown an increased prevalence of osteoporosis in regions where dietary calcium intake is extremely low [100].

The most convincing evidence that calcium consumption influences rates of bone mineral accrual comes from controlled supplementation trials in young healthy subjects (Table 3). These studies showed that subjects given additional calcium for 1 to 3 years had greater gains than did control subjects [101–108]. Although bone size increased as a result of added dietary calcium in two studies [102,106], the response to calcium varied with skeletal site, pretreatment calcium consumption, and pubertal stage. Greater bone mineral gains have been generally reported at cortical skeletal sites in prepubertal subjects and in girls whose habitual dietary intake was less than 850 mg per day [106].

Whether short-term increases in bone mineral observed in these trials will translate into a clinically relevant reduction in osteoporosis risk is unknown. The magnitude of gains in BMC or BMD in most studies was modest (less than 5%). Moreover, the beneficial effect of calcium supplementation

Table 3

Calcium supplement intervention studies and bone outcomes in children and adolescents

Study	Sample	Intervention duration and calcium supplement	Results: significant difference in bone outcomes
Johnston et al [76]	6- to 14-yr-old boys and girls; identical twins (n = 70)	Duration: 36 mo Supplement: calcium citrate (1000 mg)	BMD Lumbar spine Radius Prepubertal subject
Lloyd et al [45]	11- to 12-yr-old girls (n = 94)	Duration: 18 mo Supplement: calcium citrate (500 mg)	BMD Total body Lumbar spine
Chan et al (1994)	9- to 13-yr-old girls (n = 48)	Duration: 12 mo Supplement: dairy products (1200 mg)	BMD, BMC Total body Lumbar spine
Lee et al (1995)	7- yr-old boys and girls (n = 84)	Duration: 18 mo Supplement: calcium carbonate (300 mg)	BMD, BMC Lumbar spine Radius
Bonjour et al [107]	7- to 9-yr-old girls (n = 144)	Duration: 12 mo Supplement: milk extract (850 mg)	BMD Femur Radius
Nowson et al [132]	10- to 17-yr-old girls; twin pairs (n = 84)	Duration: 18 mo Supplement: calcium (1000 mg)	BMD, BMC Lumbar spine
Slemenda et al [118]	6- to 14-yr-old boys and girls; twin pairs (n = 90)	Duration: 3-yr follow-up of Johnston et al [76] Supplement: calcium (1000 mg)	NS
Lee et al [111]	8.7-yr-old boys and girls (n = 162)	Duration: 12 mo Frequency: calcium (300 mg)	BMD, BMC Distal radius

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; NS, not significant.

does not seem to last, and most studies reported that the benefits of intervention disappeared once the treatment was stopped. However, in other studies, the benefits persisted 12 months after discontinuation of calcium supplementation.

Hormonal status and bone mass

Completion of normal skeletal growth and development and bone mineral accrual require adequate interaction of several hormones (sex steroids, growth hormone, insulin-like growth factors, and thyroid hormone). The importance of normal endocrine function for the attainment of a normal PBM is apparent from several clinical states of altered hormonal secretion. The presence of osteopenia in patients with abnormal pubertal development demonstrates the critical role that pubertal hormone changes

have on mineral acquisition. Adult patients with hypogonadotropic hypogonadism commonly have low BMD values resulting from inadequate bone mineral accrual during puberty [109]. Androgen receptors mediate the effects of testosterone in bone, but their function is generally exerted after conversion to estrogen by a specific aromatase present in osteoblastic cells [110]. Thus, the more important sex steroid involved in skeletal maturation is estrogen [111]. Amenorrheic teenage girls have lower lumbar bone density than girls with normal menses [112]. In addition, male patients with aromatase deficiency or estrogen receptor defects resulting in complete resistance have a phenotype that includes tall stature, normal secondary sexual characteristics, severe osteoporosis, and skeletal immaturity (delayed physal closure), despite normal serum levels of testosterone [113–115]. Idiopathic delayed puberty has also been implicated as a cause of reduced peak bone mass [116].

Reduced bone density is commonly seen in growth hormone (GH)-deficient children who fail to acquire bone mineral at the expected rate [117,118]. Part of the bone mass deficit in these patients is caused by reduced bone size. Much of the GH action on bone is mediated through IGF-I, which functions as a bone trophic hormone that positively affects osteoblasts and stimulates collagen synthesis [119]. In humans, IGF-I serum levels have been found to be positively correlated to bone size measured at the midshaft of the femur [120].

Excessive production of thyroid hormone impairs bone mineralization during growth and therefore does not allow for a normal bone mineral accrual. A study of hyperthyroid girls demonstrated significantly reduced whole body and lumbar spine bone density at diagnosis compared with healthy girls matched for age and body size [121].

Lifestyle factors

Even healthy children and adolescents might fall short of optimal bone health because of current lifestyle trends. A few trends are likely to manifest during adolescence. First, inactivity poses a great threat to bone mineral gains. Television viewing and computer use continue to increase, and the time spent in physical activities is declining. This habit seems to be more frequent in selected groups of youths [122].

A second trend is the increasing use of tobacco among adolescents [123]. Tobacco use generally begins during adolescence and is variably associated with a reduced BMD [124–127]. The decrement of bone mass observed in young smokers is generally modest. However, because those who begin smoking at an early age are more likely to continue and to be heavy users [128], they are more likely to experience the increasing, cumulative decrements in bone density [129].

Although little is known about the effect of alcohol use and abuse on bone gains in adolescents, in adult men and women, excess alcohol intake seems to have an adverse effect on the preservation of bone mass, mainly by

suppressing bone formation [130]. For this reason, alcohol abuse may have an adverse affect on skeletal development in adolescents.

Finally, the effect that pregnancy and lactation have on bone acquisition in teenagers is yet to be fully defined. Normal pregnancy places a demand on calcium homeostasis because the fetus and the placenta draw calcium from the maternal circulation to mineralize the fetal skeleton, and low BMD has been reported during pregnancy. Whether pregnancy during adolescence negatively influences bone density and PBM is the subject of great interest.

Summary

Among the main areas of progress in osteoporosis research during the last decade or so are the general recognition that this condition, which is the cause of so much pain in the elderly population, has its antecedents in childhood and the identification of the structural basis accounting for much of the differences in bone strength among humans. Nevertheless, current understanding of the bone mineral accrual process is far from complete. The search for genes that regulate bone mass acquisition is ongoing, and current results are not sufficient to identify subjects at risk. However, there is solid evidence that BMD measurements can be helpful for the selection of subjects that presumably would benefit from preventive interventions.

The questions regarding the type of preventive interventions, their magnitude, and duration remain unanswered. Carefully designed controlled trials are needed. Nevertheless, previous experience indicates that weight-bearing activity and possibly calcium supplements are beneficial if they are begun during childhood and preferably before the onset of puberty. Modification of unhealthy lifestyles and increments in exercise or calcium assumption are logical interventions that should be implemented to improve bone mass gains in all children and adolescents who are at risk of failing to achieve an optimal peak bone mass.

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