Timing of Peak Bone Mass in Caucasian Females and Its Implication for the Prevention of Osteoporosis

Inference from a Cross-sectional Model

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Abstract

To determine the timing of peak bone mass and density, we conducted a cross-sectional study of bone mass measurements in 265 premenopausal Caucasian females, aged 8–50 yr. Bone mass and bone mineral density were measured using dual X-ray absorptiometry and single-photon absorptiometry at the spine (anteroposterior, lateral), proximal femur, radius shaft, distal forearm, and the whole body. Bone mass parameters were analyzed using a quadratic regression model and segmented regression models with quadratic-quadratic or quadratic-linear form. The results show that most of the bone mass at multiple skeletal locations will be accumulated by late adolescence. This is particularly notable for bone mineral density of the proximal femur and the vertebral body. Bone mass of the other regions of interest is either no different in women between the age of 18 yr and the menopause or it is maximal in 50-yr-old women, indicating slow but permanent bone accumulation continuing at some sites up to the time of menopause. This gain in bone mass in premenopausal adult women is probably the result of continuous periosteal expansion with age. Since rapid skeletal mineral acquisition at all sites occurs relatively early in life, the exogenous factors which might optimize peak bone mass need to be more precisely identified and characterized. (J. Clin. Invest. 1994. 93:799–808.) Key words: bone loss • bone mass • osteoporosis • peak bone mass • skeletal growth

Introduction

Osteoporosis is characterized by a deficiency of bone tissue relative to the volume of anatomical bone. This reduced density increases susceptibility to fracture. Such a reduction reflects either the inadequate accumulation of bone tissue during skeletal growth and consolidation, excessive losses thereafter, or both (1). Since residual bone mineral at the age of 60–90 yr is the net result of these factors (2–5), and since there are no safe, effective ways to rebuild the osteoporotic skeleton, pre-vention by maximizing bone mass (BM)[1] during skeletal growth and development and minimizing postmenopausal bone losses, emerges as the crucial strategy (1). Consequently, a knowledge of appropriate timing of peak BM and bone mineral density (BMD) is essential if preventive measures are to be adequately implemented (6, 7).

Peak bone mass (PBM) is probably the result of interaction between endogenous (heredity, endocrine) and exogenous (nutrition, physical activity) factors (5, 8). It has been shown that by the age of 14 yr, values for bone size, mass, and density of adolescent girls were similar to the corresponding values of their mothers (8). In this respect, those findings agree with other reports indicating early attainment of trabecular PBM (9–11), and presumably cortical PBM, as determined by a variety of techniques. Such an early attainment of PBM is supported by the observation that from age of 14 yr, longitudinal bone growth diminishes, although consolidation continues. By the age of 16 yr most epiphyses are closed, and endosteal bone apposition is ceasing as well (8). Most of the cross sectional studies which have related BM to age either ended by the late adolescence or early 20s (12–25) or started by the beginning of third decade (26–48), thereby perhaps missing an important phase of the timing of PBM. There is also no study where multiple skeletal sites were measured in the same individuals between childhood and adulthood. Some older radiogrammetry studies of the second metacarpal (3) as well as single-photon absorptiometry technique of the forearm (49, 50) indicate BM to peak by the late 20s or early 30s. This belief is widely accepted in the published literature although those changes might not be representative of the entire skeleton or different bones within the skeleton.

We therefore decided to determine the timing of PBM and BMD of the whole skeleton and at different skeletal locations (spine, anteroposterior [AP] and lateral; proximal femur; neck; Ward's triangle; trochanter; and forearm, proximal and distal) in premenopausal Caucasian females of different age, covering the time period between childhood and menopause. Skeletal locations were selected based on the prevalence of bone fractures in postmenopausal women.

Methods

Subjects. 265 premenopausal Caucasian females aged 8–50 yr from Columbus, OH, participated in this study. The subjects were recruited

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1. *Abbreviations used in this paper:* AP, anteroposterior; BM, bone mass; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; PBM, peak bone mass; ROI, region of interest.

through advertisements in the local newspapers as well as at The Ohio State University. They were representative of the middle class Americans. All subjects were ambulatory and free of any acute or chronic disease and not taking medications known to affect BM. Four girls were scanned with orthodontic bracing. All females, except those in early puberty ($n = 40$), were menstruating (average onset of menarche 12.7 ± 1.2 yr). Most of the women in reproductive age reported regular menstrual cycles. Only 12 women reported irregularity in menstrual cycle. Menopause was defined as absence of menses for at least 6 mo. 58% of the subjects were mother-daughter pairs. The age range of mothers was 32–50 yr. Their body mass index (BMI), BMD, and bone mineral content (BMC) of the whole body, as well as BM measurements of the other regions of interest (ROI) were the same ($P < 0.1$ to $P < 0.9$) as in the comparable age group of nonrelated adult women so that both groups were combined into one. All participants gave informed consent according to guidelines of the Human Subjects Committee at The Ohio State University.

Anthropometry. The subject's weight was determined in kilograms to the nearest 10th, in normal indoor clothing without shoes. Standing height was recorded without shoes on a portable stadiometer to the nearest 10th of a centimeter with mandible plane parallel to the floor. The pubertal stage based on breast development and pubic hair distribution were obtained by self-assessment and by marking corresponding illustrations of sexual development (51, 52).

BM measurements. Each participant had a BM measurement of the whole body, forearm, spine, and the femur. BM measurements of the whole body, lumbar spine in AP and lateral projections, and proximal femur were done by the dual X-ray absorptiometry (DXA) technique with a Lunar DPX machine (Lunar, Madison, WI). Forearm measurements were done using single-photon absorptiometry (SPA) on the Lunar SP2 scanner. The BMC for every skeletal location was expressed in grams and divided by the projected area of the bone to derive the bone mineral areal density (BMD) in grams per square centimeter. The whole-body scan was taken in a standard position using a medium speed scan. Segmental analysis of the skull was done from the whole-body scan. For AP spine measurements, hips and knees were flexed at 90° to minimize lumbar lordosis. The lateral spine was measured in a left lateral position using back and lumbar supports with hips and knees flexed to prevent spine rotation and lordosis. A foot support was used to maintain a 20° internal rotation of the leg for hip measurements to compensate for femoral neck anteversion. The neck of the femur, Ward's triangle, and intertrochanteric regions were recorded separately. The radius shaft was measured at one-third of the forearm length proximal to the ulna styloid process and both radius and ulna were measured at the ultradistal location. The precision error (%CV) in our laboratory was 0.7% for the whole body, 1.0% for AP spine, 3.1% lateral spine, 2.0% radius shaft, 3.0% for ultradistal forearm, 0.7% neck of the femur, 3.2% Ward's triangle, and 2.1% trochanter.

True density (g/cm³) of the body of the third lumbar vertebra (L₃) was estimated using AP and lateral spine projections from which volume parameters were derived. Body of L₃ in a cross section has a shape of a ellipse (53) and its volume was estimated using: $V = \pi \cdot l/2 \cdot w/2 \cdot h$, where l = diameter of vertebral body in AP projection (length), w = diameter of vertebral body in lateral projection (width), and h = height of vertebral body in lateral projection. The estimate of true density was obtained by dividing BMC of lateral projection by this calculated volume.

Statistics. To evaluate the appropriate timing of PBM and/or the age of the cessation of rapid accumulation of skeletal minerals, at different skeletal ROI (inflection point), in this cross-sectional study, we applied several mathematical models, one of which has been previously described (54).

First, with two components linear regression model (split regression) we fit the bone size and bone density parameters of the entire sample as functions of age. For each dataset, a coefficient of correlation was computed both for the simple linear model (r), and for the split regression model (R). The value of R for the split-regression model was derived from the sum of the squared deviations of the data points from

the two computed components of the model, i.e., from the sloping segment below the threshold and from the mean of the suprathreshold values. It is thus the counterpart of a multiple R computed in a multiple-linear-regression routine, and, as with a multiple-regression model, R^2 is equal to the fraction of the original variance explainable by the model. The location of the inflection point of the two component regression was determined from the split that gave the highest value for R^2. However, due to the inability of this method to determine SE of the estimated age at the inflection point, the same set of data was further analyzed by applying different mathematical models specifically designed for this purpose.

In the second analysis, data for the individual variables were initially smoothed by using a cubic spline (55) (making no a priori assumptions about the model), using the S-Plus package (56) running on the DEC station 5000 (Digital Equipment Corp., Marlboro, MA) to assess the overall shape of the plots. These plots indicated that the variables of interest fell into one of the three segmented regression model categories: (*a*) two quadratic equations; (*b*) a quadratic and a linear equation; (*c*) a single quadratic equation. For each model we determined both the age of the transition point between the curves and the age of maximal bone mass.

For quadratic-quadratic models equations are of the form:

$$y = a_l + b_l * \text{age} + c_l * \text{age}^2 \quad \text{for ages below the transition point}$$

$$y = a_u + b_u * \text{age} + c_u * \text{age}^2$$

for ages above or/equal to the transition point

The age of the transition point (TP$_t$) was calculated using the equation TP$_t = [-(b_u - b_l)/2(c_u - c_l)]$ and the age of overall maximum (PBM$_t$) from the equation PBM$_t = [-b_l/2c_l]$. In quadratic-quadratic models and in quadratic-linear models with negative slopes of the second segment, the timing of PBM was considered to be the age of the inflection point as well. In quadratic-linear models with a positive slope of the linear component, PBM was set at the maximum year of observation. In this case, the inflection point was considered coincident with the transition point.

SAS Proc NLIN (SAS Institute Inc., Cary, NC) was used to fit each of these segmented models assuming an unknown inflection point running on the IBM 3090/600J mainframe computer. The fitted models provide the highest R-squared values within the appropriate model category. Estimates and standard errors of the inflection points were obtained by the multivariate delta method on Excel running on the Macintosh. The data for femoral neck, Ward's triangle, trochanter, L₃ body lateral, and L₃ body-mid were fitted by a quadratic-quadratic model; data for height, total body, skull, lumbar spine L_{2-4}, L₃ body volume/BMC, radius shaft and wrist were fitted by a quadratic-linear model; and a single quadratic model was applied to fit data for the true density of the body of L₃ vertebra.

Other calculations were performed using the Crunch statistics package (Crunch Software Corp., Oakland, CA) running on a personal computer. Percent difference in various bone variables between prepubertal children (aged 8 yr) and their older counterparts who reached PBM and/or are at the age of the inflection point was calculated to estimate the average rate of accretion of skeletal minerals along the left segment of each model. The same was done for the quadratic right segments comparing BM at the peak and/or at the inflection point with bone mass of women of age range 45–50 yr. Percent difference along linear segments was calculated from the slopes. Boxplot diagram of the effect of pubertal stage on total body BMC and BMD was constructed using Data Desk Professional statistics software (Data Description Inc., Ithaca, NY) running on a Macintosh.

Results

Variation in body weight was more pronounced in individuals above the age of 18 yr, primarily because there was a larger proportion of obese individuals among adults. To assess therefore the potential effect of weight on the timing of PBM and

slope of the curve after the inflection point, we analyzed the data set with and without subjects with BMI above 29.9. The regression coefficient of the biphasic linear model improved significantly for almost every skeletal site when we excluded overweight women, as presented in Table I. Based on this evaluation all subsequent mathematical modeling was done in subjects with BMI < 29.9 ($n = 234$).

Fig. 1 represents cubic splines with 95% pointwise confidence intervals for three types of relationships between the bone variables and age; these are best described by quadratic-quadratic, quadratic-linear, and single quadratic equations in the models.

Figs. 2–7 show graphically BMD/BMC profiles over time for total body, forearm, femur, spine AP, spine lateral, and head, respectively.

Table II presents number of subjects, R^2 of the model, age of the inflection point of particular bone variable with standard error, and the estimate of bone variable at the inflection point. The estimated slopes of linear part of all quadratic-linear models with corresponding standard errors are presented in Table III.

Skeletal height, in this cross-sectional study, reaches its maximum 1–7 yr earlier in comparison to the rapid cessation of the accumulation of bone minerals (age of the inflection point) at the several sites measured. As the figures show, there is a strong positive relationship between BM and age throughout adolescence. Rapid cessation of accumulation of BM at most of the skeletal locations will be by late adolescence (except for the distal forearm and the true density of the body of the third lumbar vertebra, which is by the age of 22 and 27 yr, respectively). After the age of 18 yr there are no significant differences in BM or BMD between younger and older premenopausal women for most of the skeletal sites except for the skull. BMC/BMD of the whole body and the lumbar spine in AP projection as well as the BMD of the forearm have the age of PBM set up by 50 yr, which is due to weak positive slopes of
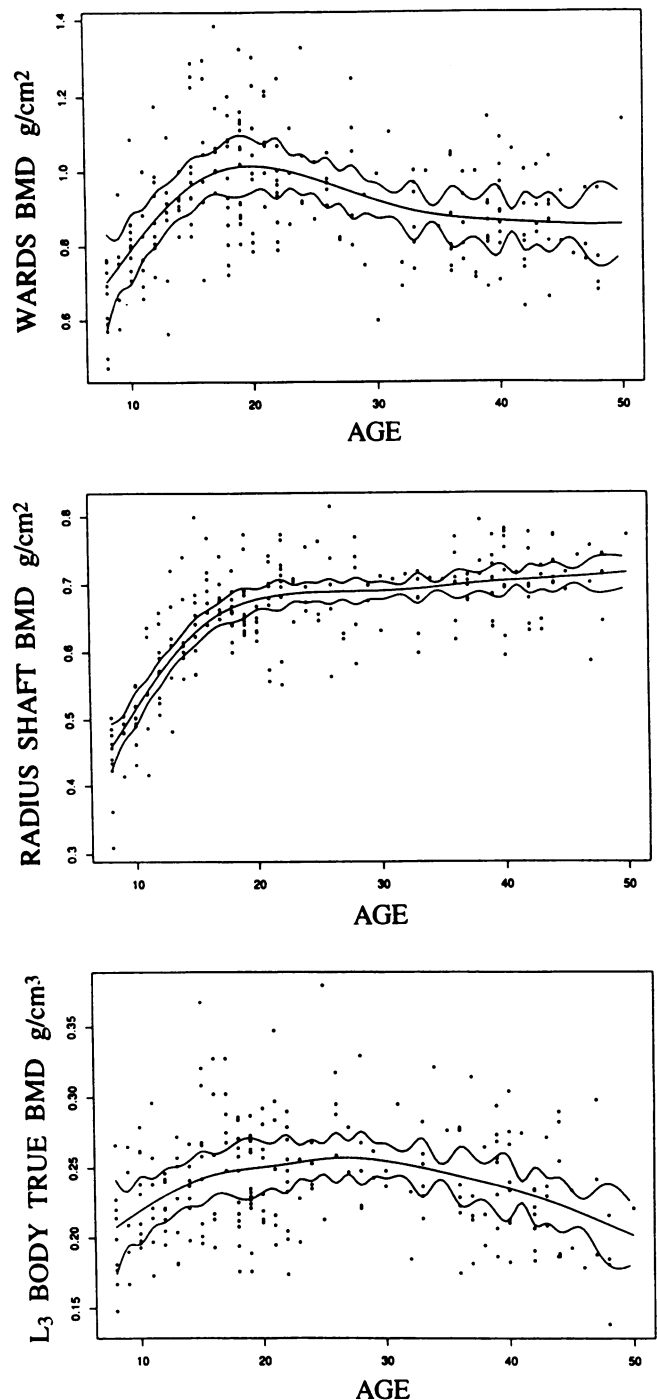

Figure 1. Cubic splines with 95% pointwise confidence interval for various BM-age profiles. From top to bottom: Ward's BMD profile over time representative of quadratic-quadratic model; BMD of the radius representing quadratic-linear model; and true density of the vertebral body representing single quadratic model.

the linear segments. Volume of the body of L_3 is also larger in older than younger premenopausal women, based on the degree of the slope of the linear part of the quadratic-linear model. This indicates continuation of vertebral modeling beyond adolescence, although at a much slower rate than before. BMC of the body of L_3 vertebra practically was no different in 20- (age at peak) and 50-yr-old women, probably as the end result of the gain in bone volume balanced with the loss of
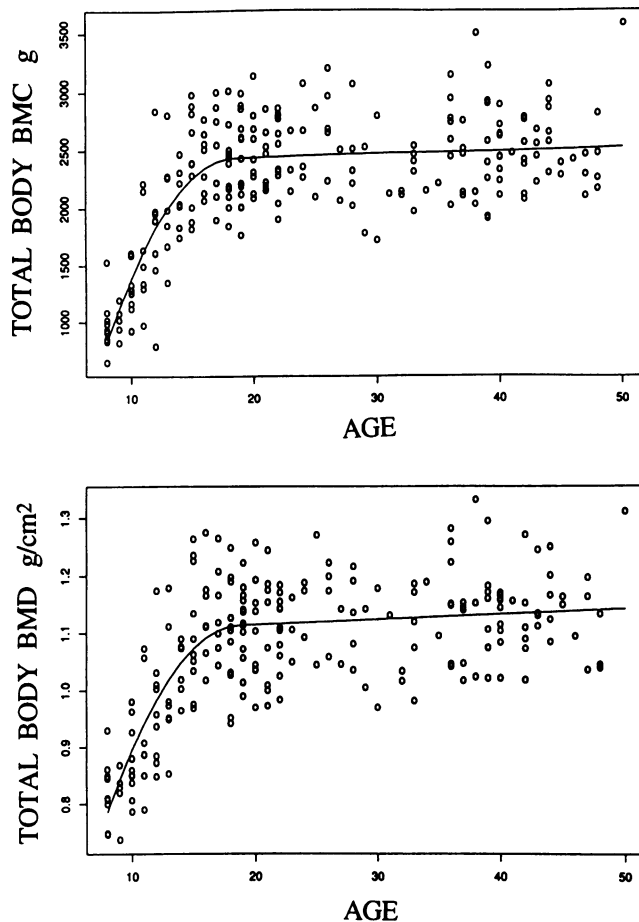
Table I. Effect of Excluding Extremes of Weight on Regression Parameters

Site code	All subjects		Weight excluded	
	Inflection point (age)	R^2	Inflection point (age)	R^2
	yr		yr	
Height	17	0.678	17	0.686
Total body BMC	17	0.587	19	0.639
Total body BMD	18	0.573	18	0.605
Skull	20	0.643	20	0.648
Fem. neck	18	0.375	18	0.412
Ward's	18	0.275	18	0.328
Trochanter	18	0.195	18	0.227
L_{2-4} BMC	18	0.553	18	0.666
L_{2-4} BMD	18	0.616	18	0.640
L_3 body vol.	19	0.540	19	0.594
L_3 body-lat.	18	0.253	18	0.287
L_3 body-mid.	18	0.218	18	0.245
L_3 body dens.	25	0.123	18	0.125
Radius	18	0.663	18	0.680
Wrist	20	0.421	20	0.425

Figure 2. Total body BMC and BMD versus age.

determines timing of peak bone mass, nor the slope of the regression lines which determine the rate of bone gain or bone loss. To pursue this question further Dr. Christopher Cann (University of California, San Francisco) kindly provided us with the data for the density of the body of L_1 vertebrae as assessed by the single-energy quantitative computed tomography. The average density for 14 vertebrae of women aged 21–40 yr was 0.204 ± 0.019 g/cm^3. An additional 0.0166 g/cm^3 was added to approximate for the trabecular density error introduced by the technique, which underestimates true BMD of an ash weight measurement (60). Corrected as such, the density of the vertebrae should be about 0.220 g/cm^3. Our analysis of L_3 vertebrae in 86 premenopausal women of the same age range yields an estimate for true density of 0.248 ± 0.040 g/cm^3. In a similar study Gomez et al. (unpublished observations in 1991) determined volumetric density of the body of excised lumbar vertebrae (n = 15, location unknown) applying dual X-ray absorptiometry measurements and Archimedes principle for volume determination. They found true density from lateral and apical projections being 0.277 ± 0.085 and 0.288 ± 0.095 g/cm^3, respectively. Those comparisons indicate that our estimates of the true density could be close to the real values.

Although the segmented models for BM and BMD versus age describe skeletal development as a quadratic function rather than exponential, bone growth is accelerated during puberty. Fig. 8 shows a boxplot diagram for the BMC and BMD of
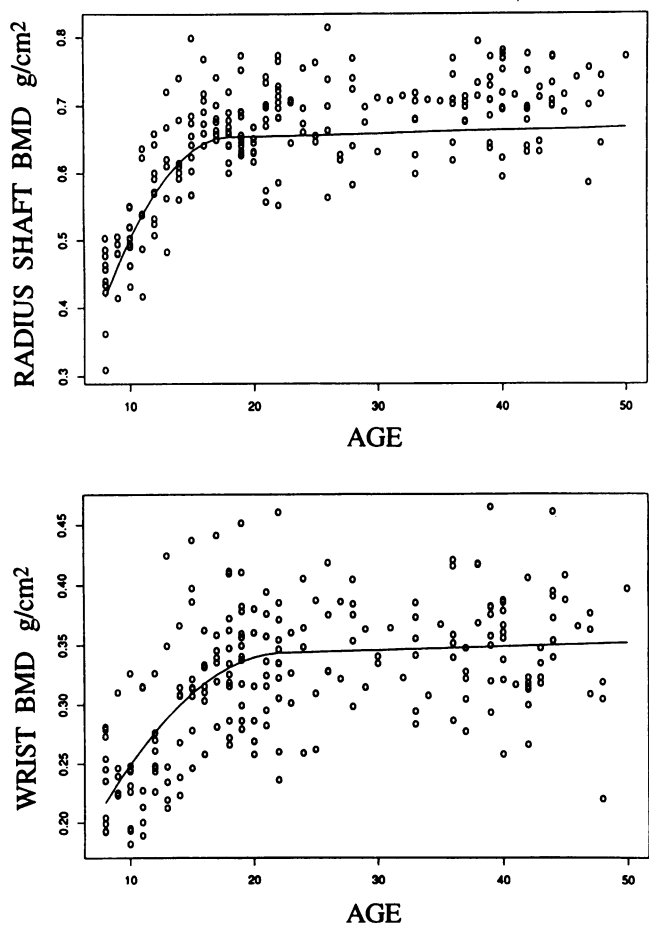
trabecular bone mass as evidenced by the difference in the areal density and volumetric density of the body of L_3 vertebra between the young and old premenopausal females (Fig. 6). Of particular interest is significantly lower BMD of the proximal femur and the trabecular portion of the body of L_3 in older than in younger premenopausal women. This was immediately apparent after maximal BM accumulation in 17- and 23-yr-old females. Similar observation was recently reported in a short-term longitudinal study conducted in children in Geneva who showed zero increment change in the hip and the spine region by the age of 17–19 (57). There is practically no plateau for those skeletal sites and bone loss proceeds immediately after the peak as indicated by the lower BMD in young adults. Maximal true bone density of the vertebral body of L_3 vertebra was established in 27-yr-old females although this could be even as early as the age of 18 yr. The problems of getting a good fit (R^2 = 0.131) were probably due to minimal difference in true density of the vertebra between children and adults.

The estimated values for true density of the body of L_3 are slightly higher than values for volumetric density previously reported for the trabecular portion of the spine using in vitro ashing (26, 27), quantitative computed tomography, and other techniques (58). This could be partially due to inclusion of cortical bone of terminal plates (59) and/or systematic error which underestimated the volume of the body of L_3 vertebrae. Such error will distort the location of the relationship between BMD and age along the y-axis (bone volume or density) but not the location of the inflection point along the x-axis, which

Figure 3. BMD (areal) of the radius shaft and ultradistal forearm (wrist) versus age.
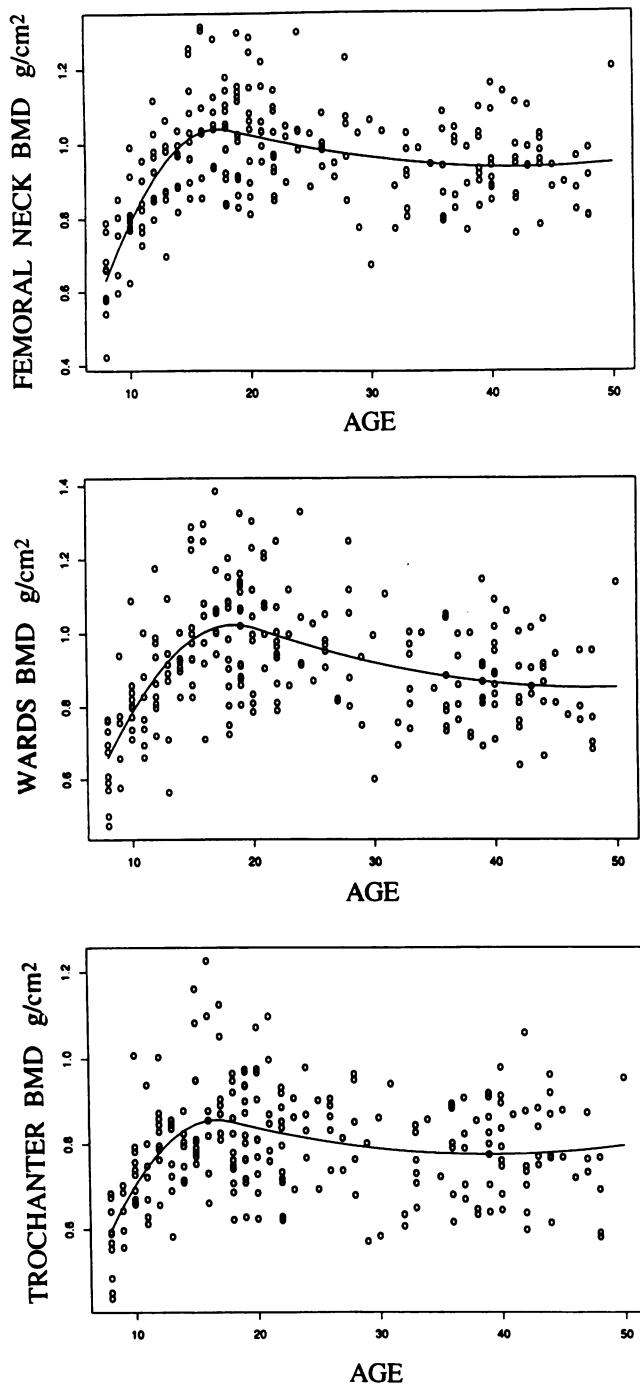
Figure 4. BMD (areal) of the femoral neck, Ward's triangle, and trochanteric region versus age.

tors determining resistance or susceptibility to fracture) (2–5, 61). The timing of PBM has been considered by various authors to occur from ages early as 17–18 to as late as 35 yr. In some reports, it is considered to last for only a brief moment before the decline or age-related loss begins, while in others the peak seems to a plateau lasting several years. As we have shown here, both patterns are correct, but for different skeletal regions.

Almost all skeletal sites we measured in this cross-sectional study attained most of the BM and BMD by late adolescence or young adulthood, indicating an early timing of PBM for the hip and the trabecular bone of the spine. This is supported by the studies which compared BM of teenage daughters with the BM of their mothers, as well as studies of trabecular BM measured either by histomorphometry or computerized tomography of the spine (8–11). Based on this cross-sectional study, peak adult height was attained by the average age of 16, indicating cessation of longitudinal bone growth by late adolescence. The timing of the cessation of longitudinal bone growth was 1–7 yr earlier than the cessation of the rapid accumulation of BM at various skeletal sites. This time discrepancy indicates ongoing rapid consolidation of skeletal density after the bulk of bone modeling has been completed. A similar phenomenon was previously documented in our longitudinal study of skeletal mineralization and growth during late adolescence (8).

From the preadolescent years (8 yr) up to the end of second
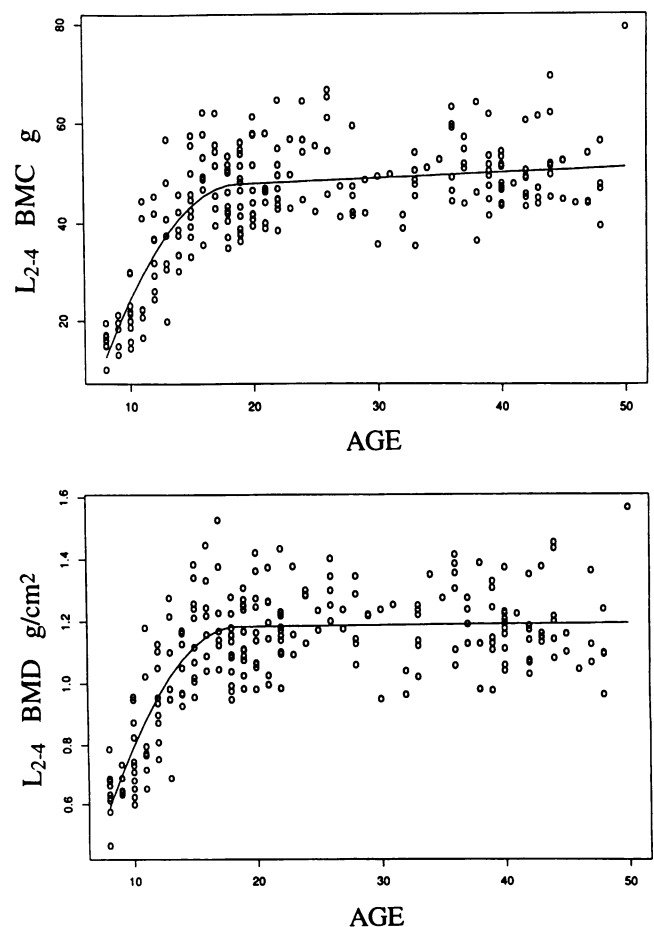
Figure 5. BMC of the lumbar spine (L_{2-4}) in AP projection and areal density of the same region versus age.

the total body of female participants aged 8–17 yr (n = 83) as related to the pubertal stage. It is evident that a substantial proportion of the total skeletal mass (37%) has been accumulated between pubertal stage 2 (mean age 11 yr) and 5 (mean age 15 yr).

Discussion

PBM is generally defined as the highest level of BM achieved as a result of normal growth. PBM is important because, together with age-related loss later on, it is one of the two principal factors determining BM late in life (and hence one of the fac-

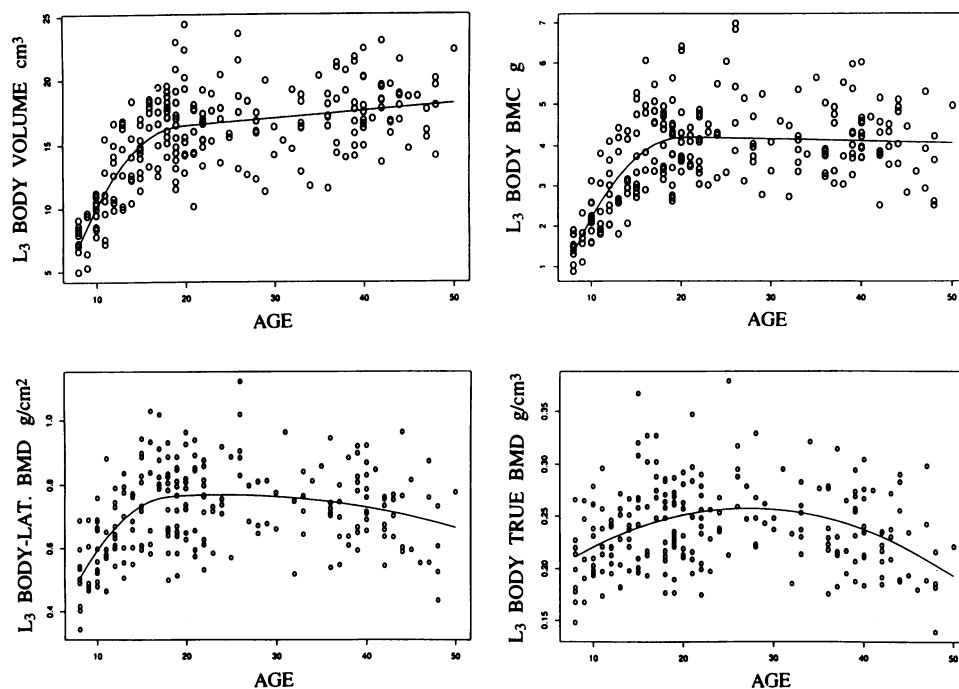Figure 6. Volume of the body of L₃ vertebrea, BMC of the body of L₃ vertebrea, areal density of the lateral projection of the body of L₃ vertebra, and true BMD of the body of L₃ vertebra versus age.

decade of life, bone size and BM increase rapidly. The average annual gain in height between the ages of 8 and 16 yr is 3.9 cm, which is 2.4% of the peak adult height for women in this study. The accumulation of total bone mineral between the age of 8 and 18 yr is about 146 g/yr, or 6% of the total body mineral of 2,432 g. When this is translated into total body calcium (assuming 39% Ca in hydroxyapatite crystal), 58 g of calcium is required for annual accretion, or 160 mg/d, to reach an average maximal total body calcium content of 949 g.

Females begin puberty at about age 10 and will reach maximum velocity in their height growth around 12 yr of age. Cessation of linear growth in girls occurs at about age 16 (51). A substantial proportion of skeletal mass (37%) has been accumulated over the 4-yr period between pubertal stage 2 and pubertal stage 5, as previously noted (13, 15–21, 24, 62). Calculated average daily skeletal calcium accretion during this age period could be as high as 300–400 mg/d.

Based on this cross-sectional model, bone size, BM, and BMD of the regional skeletal sites increased on average by

about 4%/yr between preadolescent period (age 8 yr) and late adolescence when most of the BM will be accumulated. This ranged from 1.2% for the estimate of true density of the body of L₃ to 6.6% for the femoral neck. The relatively smaller increments in true density (mass/volume ratio in g/cm³) are of interest, indicating that most of the changes we measure during growth using either single photon or dual X-ray absorptiometry are predominantly due to the change in bone volume, and to a much lesser extent to increases in BMD. A similar

Table II. Age of the Inflection Point for Various Bone Parameters with Estimates of Bone Variable at the Inflection Point and R^2 of Each Model

| ROI	n	R^2	Inflection point age	Estimate of bone variable
			yr	
Height	234	0.692	16.25±0.04*	162.8 cm
Total body BMC	231	0.624	18.33±0.07	2432 g
Total body BMD	231	0.587	18.70±0.08	1.11 g/cm²
Skull	231	0.642	21.77±0.12	2.29 g/cm²
Fem. neck	232	0.425	17.23±0.07	1.04 g/cm²
Ward's	232	0.328	18.49±0.09	1.02 g/cm²
Trochanter	232	0.229	16.72±0.12	0.86 g/cm²
L₂₋₄ BMC	231	0.657	18.79±0.07	48.05 g
L₂₋₄ BMD	231	0.630	18.45±0.07	1.18 g/cm²
L₃ body vol.	228	0.583	19.18±0.10	16.46 cm³
L₃ body BMC	229	0.482	20.02±0.10	4.20 g
L₃ body-lat.	229	0.274	23.97±0.19	0.77 g/cm²
L₃ body-mid	229	0.237	23.15±0.24	0.73 g/cm²
L₃ body dens.	227	0.131	27.18±0.06	0.257 g/cm³
Radius	223	0.673	17.82±0.07	0.65 g/cm²
Wrist	222	0.407	22.32±0.18	0.34 g/cm²
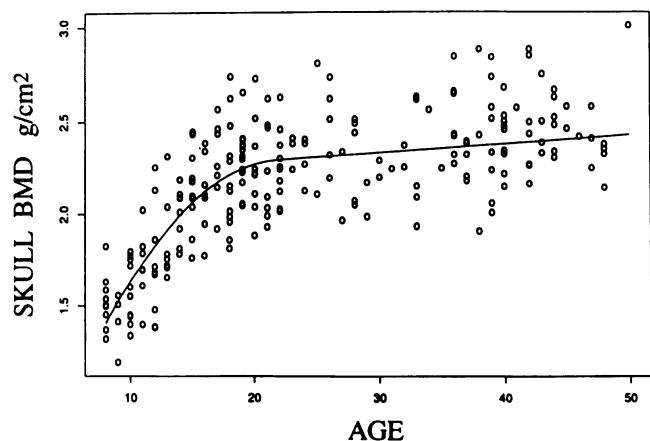
Figure 7. BMD (areal) of the skull versus age.

* Mean±SE.

Table III. Estimated Slope of Linear Part of All Quadratic-Linear Models and Its Estimated Standard Error

ROI	Estimate of slope	SE
Height	−0.0121	0.0422
Total body BMC	2.8777	2.8969
Total body BMD	0.0009	0.0007
Skull	0.0049	0.0022
L_{2-4} BMC	0.1086	0.0632
L_{2-4} BMD	0.0004	0.0010
L_3 body vol.	0.0559	0.0218
L_3 body BMC	−0.0049	0.0078
Radius	0.0005	0.0004
Wrist	0.0003	0.0005

observation was previously documented using ash weight/volume ratio of the human radii in vitro in a study by Trotter and Hixon (63) and by calculating BM apparent density in the study of Katzman et al. (19) Trotter and Hixon also studied skeletal weights throughout the lifespan and found maximal skeletal weight to be apparently at age twenty, with relatively rapid decline thereafter. However, there were only a few subjects in the third and fourth decades in their study, making the assessment of precise timing difficult (63).

Developmental processes or changes in skeletal morphology continue after puberty although at a much slower rate. The analysis of the right segment of the biphasic models reveals interesting differences in behavior of various skeletal regions of interest during adulthood up to the age of 50 yr.

Whole body BMC and BMD changed only slightly between 18 and 50 yr. This change amounted to an overall increase in total skeletal mass of about 4%, and of total skeletal density of about 2.6%, but was not statistically significant. These changes are, however, congruent with the data of Recker et al. (64), who showed recently in a longitudinal study conducted among college-age women an annual gain in total body bone mineral, of about 1.2% during the third decade of life, confirming some of the findings of the previous cross-sectional studies, although with a greater change. They also indicated that mineral acquisition ceased by the age of 29 yr (64). In a similar cross-sectional study, using a sexually mixed cohort of young individuals, Mazess et al. (41) showed the same trend, although their sample was substantially smaller than this one. However, if we accept obese women in the model, there was a significant positive slope from the age of 18 to the age of 50 for total body bone mineral, reflecting either increased prevalence of obesity with age, or the slow osteotrophic effect of obesity, or both.

It is worth noting that the older premenopausal women had lower BMD in the hip region (neck of the femur, Ward's triangle, and trochanter) than the younger women, and that the maximal values were found in the ~ 17-yr-old females. This suggested that the decline in the BMD of the proximal end of the femur begins immediately after the acquisition of PBM. The cross-sectional, apparent decrease was about −0.3%/yr for the trochanteric region, −0.4%/yr for the femoral neck, and −0.6%/yr for Ward's triangle. A disproportionally higher decline in the BMD at Ward's triangle corresponds to the early disappearance of trabecular architecture in the region visible on standard skeletal radiographs of the hip (65). A difference of about 15.5% is found in the proximal femur between the

ages of 17 and 50 yr. The same phenomenon has been very well documented in similar cross sectional studies conducted previously (33, 34, 37–39, 42–44, 46–48). The significance of this finding needs to be further clarified, probably through longitudinal studies, particularly focusing on its contribution to the development of hip fractures later on in life.

A similar trend for the same cohort of women, age range 23–50 yr, was observed in the central vertebral trabecular bone of the spine, where the decrease in BMD of about −0.5%/yr was found. This loss of trabecular bone was previously documented by different techniques: compressive strength (26) and ash (27) measurements of the vertebrae in vitro, by iliac crest bone histomorphometric analysis (9, 10), as well as by the use of the computerized tomography of the vertebrae (11, 35). However, our studies show the importance of looking at total BM, and not BMD alone. Despite the fall in true density of the body of the L_3 vertebra, the BMC of AP L_{2-4} was steadily increasing, and at a rate of about 0.23%/yr (total of 7% between the age of 19 and 50 yr). This is probably due to the increase in
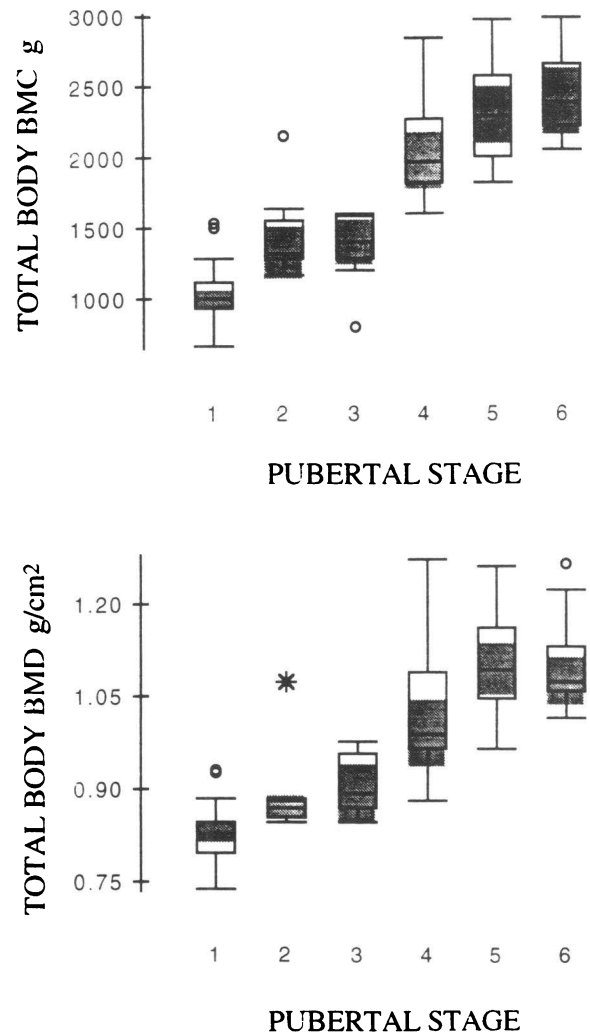

Figure 8. Boxplots of total body BMC and total body BMD and pubertal stage. The outlined central box depicts the middle half of the data between 25th and 75th percentiles. Median = horizontal line across with 95% confidence interval (*shaded area*). Whiskers = highest and lowest connected data value. Open circle = outlier. Star = extreme outlier.

the volume of the entire vertebra including the spinal processes. It has previously been documented that the bodies of the lumbar vertebrae become significantly broader with age (66–68). This is most likely the explanation for third decade bone gain (0.6%/yr) in the lumbar spine in women, as assessed by dual-photon absorptiometry (64). Several studies previously reported either decline in areal density (69–72) or no change during premenopausal years (73–75) as assessed by dual-photon absorptiometry.

BMD of the radial shaft was slightly higher in older than in younger adult premenopausal women indicating increase at the rate of ~ 0.2%/yr after the rapid cessation of accumulation of bone minerals at the age of 18 yr. This increase, though small, is probably responsible for the general assumption in the published literature of the late timing of PBM (late 20s and 30s). A similar increase was noticed recently in a cross-sectional study among premenopausal black females (0.4%/yr) (75) and definitely confirmed in a longitudinal study among college-age women during third decade of life (0.5%/yr) (64). Areal BMD of the distal forearm (mixed cortical and trabecular bone) was practically the same in women of that age range.

Radiogrammetric methods were extensively used in epidemiological studies in the early 50s and 70s. The technique evaluates periosteal and endosteal envelope changes in tubular bones according to age. Garn (3) has suggested that the external diameter of the second metacarpal bone, as an indicator of periosteal growth, reaches a plateau by the age of 20 yr in males and a few years earlier in females. Medullary area is constantly increasing in males after the age of 20. In females, however, during this adolescent growth spurt, there is an endosteal apposition of cortical bone which marks the beginning of the consolidation of skeletal mass (3, 8, 19). Cortical BM, as represented by cortical width and cortical area of the second metacarpal, is at its maximum by the age of 30 (3).

Older premenopausal women had significantly higher BMD of the skull than younger adult women in the study. The difference was steadily increasing (0.1%/yr) up to the age of 50, again indicating continuing periosteal apposition with age. The enlargement of head in breadth and length after puberty has been previously observed in cross-sectional and longitudinal anthropometric studies. Israel (76) reported cranial thickening at the frontal region and increases in skull size from adulthood to senescence. In a longitudinal study between age of 32 and 54 yr Susanne (77) found a mean increase of about 3 mm in head length and about 5 mm in head breadth.

Periosteal apposition has previously been described for tubular bones as well, including ribs (78), shaft of the femur (79, 80), and second metacarpal (81, 82). In a study of human ribs, Epker and Frost (78) used tetracycline labeling in vivo to reveal continued apposition of periosteal bone after the age of 20. All the above studies indicate that periosteal bone surface remains active throughout life and is probably responsible for the positive net bone tissue balance resulting in the increase in BM with age seen at various skeletal sites measured in this study.

Because data for most of the studies previously mentioned, including this one, are cross-sectional, involving different age cohorts, it is necessary to separate the changes due to secular trends from those resulting from continuing growth and aging. It is very well known that the lengths of the long bones are highly correlated with stature and are influenced by secular changes but not by age-associated factors (77). The same probably applies to the BM measurements as well (83). Secular

changes will therefore tend to overestimate bone loss or underestimate bone gain as reported for the periosteal apposition on the skull (77). As the height of the participants in this study did not change with age after maximal growth we assume that the influence of those factors was minimal.

In conclusion, the results of our study clearly show that most of the skeletal mass/density of multiple skeletal sites including the whole body will be accumulated by late adolescence, or by the average age of 18 yr. The same is true for the type of bone as well, cortical or trabecular. This model particularly applies to the trabecular bone of the spine and proximal part of the femur, which start to decline immediately after PBM formation at the age of 18 yr. This does not necessarily mean a decrease in strength, since bony expansion and maintenance or even increase of BM at these sites may adequately compensate for trabecular density changes. If the relationship between BM and BMD is driven by a feedback loop with a mechanostat, then the decrease in trabecular volume may reflect this increase in BM that results from periosteal expansion of the vertebrae (84). The other regions of interest show minimal change or slight gain in BM, when adult premenopausal women were compared, indicating ultimate timing of PBM by late forties. This estimated gain in BM and BMD is probably the consequence of continuous periosteal expansion with age.

These differences between the skeletal sites established during the period between adolescence and menopause, in both positive and negative directions, probably combined to eliminate any significant change in the skeleton as a whole. Internal losses could contribute to the net skeletal gains and vice versa as a part of mineral redistribution. To what extent mild elevations of parathyroid activity induced by either low calcium intake and/or the obligatory bony expansions with age are responsible for internal restructuring remains to be determined. There are some indications that exogenous factors could contribute to PBM or prevent premenopausal bone losses at various skeletal sites. This primarily applies to nutritional factors (64, 85–87) and exercise (64, 88, 89), independently or in combination. It would be therefore of considerable importance to conduct clinical intervention studies during skeletal formation and up to the menopause, with specially monitoring the hip region. The same is true for endogenous factors as well (hormonal) which might influence skeletal growth and PBM (90, 91). Small gains during attainment of PBM could have a profound effect on the prevention of osteoporotic fractures later in life.

Acknowledgments

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