# Age-Related Bone Mineral Density Patterns in Koreans (KNHANES IV)

Eun Young Lee, Daham Kim, Kyoung Min Kim, Kwang Joon Kim, Han Seok Choi, Yumie Rhee, and Sung-Kil Lim

Division of Endocrinology and Metabolism (E.Y.L, D.K., K.M.K., Y.R., S.K.L.), Department of Internal Medicine, Yonsei University College of Medicine, Executive Healthcare Clinic (K.J.K.), Severance Hospital, Seoul 120-752, Korea; and Division of Endocrinology and Metabolism (H.S.C.), Department of Internal Medicine, Dongguk University College of Medicine, Ilsan 410-773, Korea



**Context:** Bone loss is considered to begin with menopause in women and later in life in men; however, several recent studies have reported that bone loss began in young adults. There are still discordant results concerning age-related changes in bone mineral density (BMD), especially in nonvertebral bone.

**Objective:** The objective of the study was to investigate the age-related changes in BMD in Korean youth.

**Design and Setting:** This was a population-based, cross-sectional study from the Fourth Korea National Health and Nutrition Examination Surveys.

**Participants:** A total 10,575 Korean (4,731 males and 5,844 females) aged 10–80 yr were included.

**Main Outcome Measures:** BMD at the spine and hip was measured using dual X-ray absorptiometry.

**Results:** Age-related bone loss at the femoral neck in males occurred continuously with temporary acceleration phase after achieving peak bone mass (PBM). In contrast, age-related bone loss at total hip in both sexes and femoral neck in females showed three obvious phases: acceleration, consolidation, and then the second acceleration phase after reaching PBM. Interestingly, this pattern of bone loss was more significant in the total hip and thus showed the acceleration phase until the late 20s and the consolidation phase until the late 40s. Early accelerated loss of BMD was not observed at the lumbar spine in each sex. Although body mass index and body fat percentage were more related with BMD than other clinical parameters, they could not explain the early accelerated loss of BMD at the femur.

**Conclusions:** There was an accelerated bone loss at the femur in both sexes during early adulthood and more than 60% of the bone loss before age 50 yr occurred during this period. (***J Clin Endocrinol Metab*** **97: 3310–3318, 2012)**

Osteoporosis is the most important metabolic bone disease in an aging society, leading to mortalities and morbidities (1). It is now well established that low bone mineral density (BMD) is an important risk factor for fractures. In women, BMD dramatically decreases after menopause; however, BMD gradually decreases with age in men (1). The most evident cause of bone loss in women and men is an abrupt or gradual decline in sex hormones, respectively. Testosterone in men and estrogen in women play an important role in bone homeostasis; however, estrogen is also equally important for bone health in men, especially in the elderly (2, 3). Because estrogen treatment

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012-1488 Received February 23, 2012. Accepted May 15, 2012.
First Published Online June 14, 2012

Abbreviations: ALP, Alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; DXA, dual x-ray absorptiometry; KNHANES IV, Korea National Health and Nutrition Examination Surveys; NHANES, National Health and Nutrition Examination Survey; 25(OH)D, 25-hydroxyvitamin D; PBM, peak bone mass; QCT, quantitative computed tomography; vBMD, volumetric BMD.

in aromatase-deficient or estrogen receptor knockout men and mice stimulates bone formation (4–7), estrogen also has some anabolic effects with exclusive anticatabolic effects on bone. Failure of autophagy and nuclear pore leakage has been proposed as the putative theory of aging oxidative stress (8). Recently the critical role of Forkhead box O-1, three proteins for defending oxidative stress, was reported (9, 10). In addition to a sex hormone deficiency and aging, other factors such as genetic and environmental factors and behavioral change could contribute to osteoporosis (2). However, their contributions may be sex specific and may differ from one country to another.

Maximal bone mass at multiple skeletal sites is considered to be achieved by late adolescence (11) and then begins to decrease with age. The degree of bone loss after achieving peak bone mass (PBM) during puberty is also an important determining factor for osteoporosis. Thus, maximizing and maintaining PBM in early adulthood could offer protection against bone loss later in life, prompting some researchers to call osteoporosis a disease of childhood (12). After formation of PBM, age-related changes in BMD vary with sex and the site of bone loss. Previous studies have shown age-related bone loss in both men and women at different skeletal sites (13–15). In women, bone loss begins predominantly after menopause, and in men bone loss occurs gradually with age. In concordance with cross-sectional studies, the data from a longitudinal study showed a small bone loss before menopause or age 50 yr (16). However, several studies recently observed bone loss that began in young adult women and men (17, 18). Some studies have reported that bone loss from the hip has occurred, even in premenopausal women (19, 20). An 8-yr longitudinal study observed that early bone loss had occurred at the proximal femur in young adult men (18). More recently Khosla and colleagues (17) reported that trabecular bone loss at the distal radius and distal tibia accelerated and then decelerated, a pattern known as spooning, before 50 yr of age in men. These reports raise the possibility of an earlier onset of bone loss.

There are still many questions and discordant results regarding age-related bone loss, especially in nonvertebral bone, in both men and women. There have been few reports on the age-related changes of BMD and geometric bone structure in Asians. In addition, it is important to figure out the pattern of age-related bone loss and the precise period that bone loss begins because a comprehensive assessment of age-related bone loss could provide information on which populations may be most at risk of osteoporosis and may help elucidate the mechanisms causing osteoporosis. We thus studied population-based, age-related changes in BMD in a large cohort of 10,575 Koreans, aged 10–80 yr.

## Materials and Methods

### Study population

We recruited participants from the second (2008) and third year (2009) of the Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV). The KNHANES has been performed periodically since 1998 to investigate the health and nutritional status of Korea. The KNHANES IV was a cross-sectional and nationwide survey performed by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention. This survey used a stratified, multistage, clustered probability sampling method to select a representative sample of the noninstitutionalized, civilian Korean population. The survey was composed of a health interview survey, a nutrition survey, and a health examination survey. Data were collected by household interviews and by direct standardized physical examinations conducted in mobile examination centers. All participants in this survey signed an informed consent form.

Among those who participated in the survey, bone mineral density was measured in 10,575 participants (4,731 males and 5,844 females) aged 10–80 yr from all 16 administrative districts of Korea. Dual x-ray absorptiometry (DXA) examinations were conducted on subjects over 10 yr of age. Pregnant women were excluded. Subjects whose weight or height exceeded the limit of the DXA scan table (136 kg for weight and 196 cm for height) were also excluded. All subjects underwent a thorough physical examination. Age, body weight, height, smoking and drinking history, exercise, and calcium (Ca) and phosphorus (P) intakes were recorded. Smoking and drinking alcohol were indicated as yes when the subject had ever smoked tobacco or consumed alcohol, respectively. Dietary intakes of Ca and P were estimated using a 24-h dietary recall method. Exercise was indicated as yes when the subject exercised regularly at moderate or vigorous levels (for more than 30 min at a time and more than five times a week in the case of moderate physical activity and for more than 20 min at a time and more than three times a week in the case of vigorous physical activity). Blood samples were obtained for biochemical analysis from all participants during the survey. These samples were immediately refrigerated, transported to the Central Testing Institute in Seoul, Korea, and then were analyzed within 24 h.

### Body composition and BMD

Body weight, anthropometrics, and BMD were measured in light clothing without shoes or jewelry. Percentage body fat (fat mass/total mass $\times$ 100) as well as BMD at the lumbar spine (L1–4) and proximal femur (total hip region) were measured using DXA (QDR 4500A; Hologic Inc., Waltham, MA) equipment located in the mobile examination centers. We analyzed the results of the DXA using industry standard techniques at the Korean Society of Osteoporosis and performed analysis using Hologic Discovery software (version 13.1) in its default configuration. Objects that may affect the accuracy of the DXA results, such as prosthetic devices or implants, were considered missing data for regional and global DXA results. The precision of the DXA has been previously reported. In the National Health and Nutrition Examination Survey (NHANES) survey, the DXA instruments were calibrated using the methods in a previous report (21). We obtained the reference values of the NHANES using this calibration method (22). The NHANES calibrations were applied for appropriate comparisons between the present and pre-

vious data. We maintained DXA calibrations via an internal referencing system and periodically measured bone and soft tissue equivalent reference standards during the examination.

We further analyzed geometric bone structure properties using the Hip Structure Analysis program included in APEX software (Hologic Inc.), as previously described (23, 24). The Hip Structure Analysis program yielded data for mean cortical thickness (millimeters) and buckling ratio in each of the narrow neck regions.

### Statistical analysis

A generalized additive model with a cubic B-spline was used to explore age-related changes in BMD and other clinical parameters. Pearson's correlation analyses were used to evaluate the association between BMD and variable parameters. The SAS program (version 9.1; SAS Institute, Cary, NC) was used to analyze age-related changes in BMD and other variable markers. Other statistical analyses were carried out using the SPSS program (version 15.0; SPSS, Chicago, IL). A $P < 0.05$ was considered significant.

## Results

### Age-related changes in BMD and geometry

Age-related changes in BMD at the femoral neck and total hip are shown in Fig. 1, A–D. PBM was achieved by age 21 and 19 yr in males and females, respectively. In males, age-related bone loss at the femoral neck occurred gradually, with a temporary acceleration phase after reaching PBM. The pattern of bone loss in the total hip was similar to the changes in the femoral neck except that there was a consolidation phase (maintaining bone mass) after the acceleration phase. In women, age-related bone loss at the femoral neck showed three obvious phases: acceleration, consolidation, and then a second acceleration phase after reaching PBM. This pattern of bone loss was more significant in the total hip. Therefore, there was an acceleration phase until the late 20s and a consolidation phase until the late 40s. In geometric analysis, the femoral neck cortical thickness showed similar changes to the femoral neck BMD in both males and females (Fig. 2, A and B). As expected, the buckling ratio increased with age in both sexes (Fig. 2, C and D).

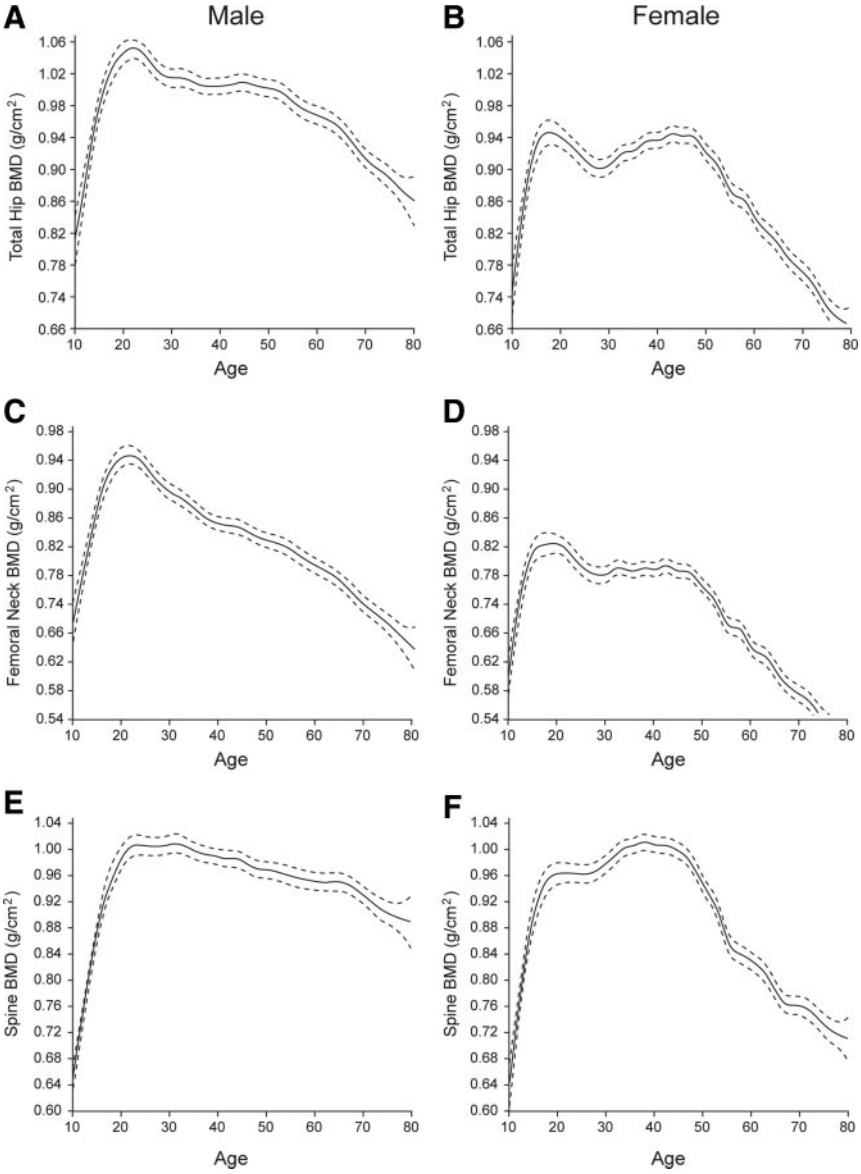


**FIG. 1.** Age-related changes in BMD at femoral neck (A and B), total hip (C and D), and lumbar spine (E and F) in males and females. Data are shown with a smoothing spline and 95% confidence interval.

Unlike in the femur, age-related bone loss at the lumbar spine did not show any significant acceleration phase in early adulthood in both sexes (Fig. 1, E and F). BMD at the lumbar spine was maintained until around 35 yr of age and then declined very slowly in men. In women, BMD at the lumbar spine was maintained until around 30 yr of age and then increased slightly until menopause. After menopause, lumbar BMD in women decreased abruptly.

### Annual rates of bone loss by age group

We categorized age by four patterns of BMD changes, bone acquisition phase and three phases of bone loss as follows: first acceleration phase, consolidation or deceleration phase, and second acceleration phase (menopause

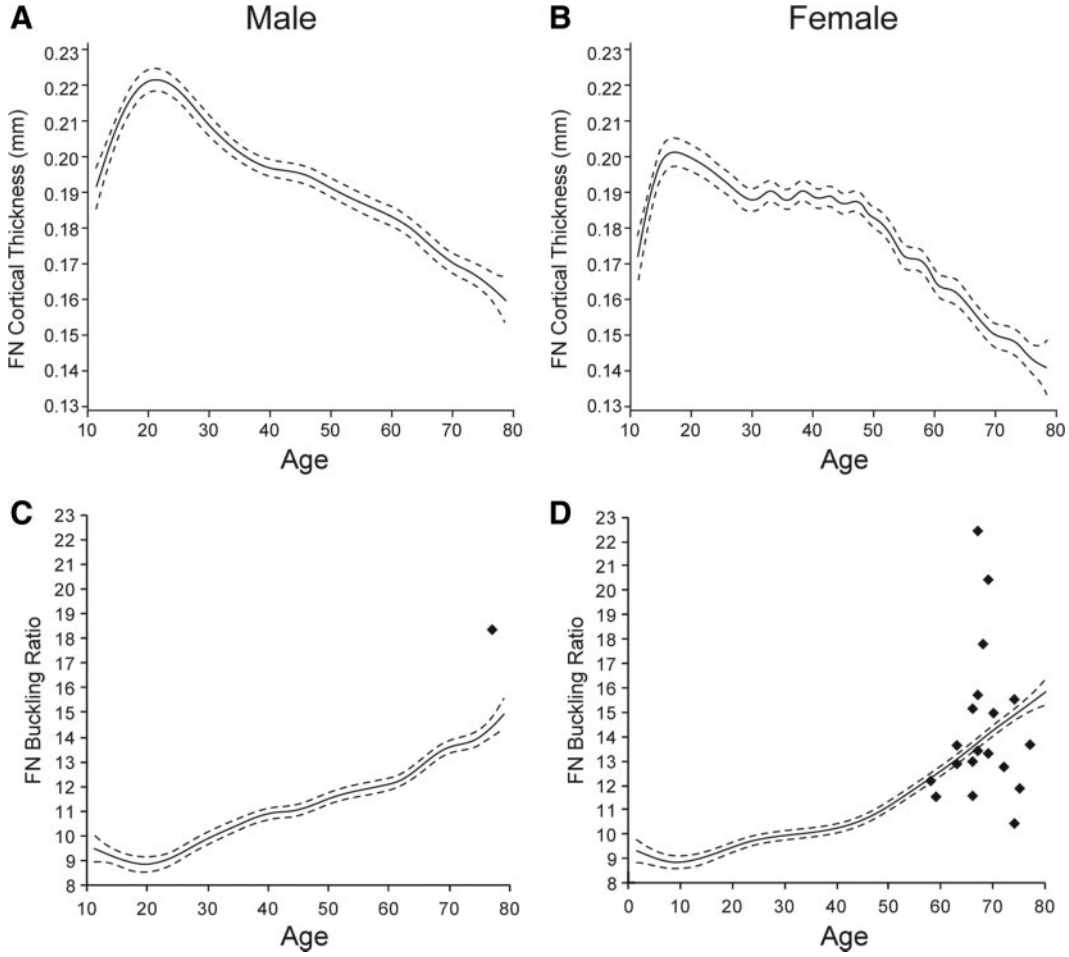


**FIG. 2.** Age-related changes in femoral neck (FN) cortical thickness (A and B) and buckling ratio (C and D) in males and females. *Dot* (◆) signifies buckling ratios in subjects with fractures. Data are shown with a smoothing spline and 95% confidence interval.

or age over 50 yr in males). Mean changes in BMD per year (percentage) revealed bone loss in all phases except in the bone acquisition phase (Table 1). As shown in Fig. 1, annual rates of bone loss were significant in the first acceleration phase. In the first acceleration phase, mean changes in BMD were −1.29%/yr at the femoral neck and −1.20%/yr at the total hip in males. In females, the annual rates of bone loss in the first acceleration phase were −0.66%/yr at the femoral neck and −0.49%/yr at the total hip. Although this was lower than the annual rate of bone loss in women over 50 yr, it showed an obvious aggravation of bone loss in early adulthood. Of significance, the annual rates of bone loss in males in the first acceleration phase were higher (almost 2-fold) than in those over 50 yr. It appears that more than 60–80% of bone loss before age 50 yr occurred during early adult-

**TABLE 1.** Mean annual changes (percentage) in BMD at the femoral neck, total hip, and lumbar spine in males and females

| | Femoral neck | | Total hip | | Lumbar spine | |
|---|---|---|---|---|---|---|
| | Mean %/yr (R) | *P* value | Mean %/yr (R) | *P* value | Mean %/yr (R) | *P* value |
| Males | | | | | | |
| 10–22 (n = 469) | 3.55 (0.473) | <0.001 | 3.19 (0.510) | <0.001 | 5.44 (0.711) | <0.001 |
| 23–29 (n = 474) | −1.29 (−0.162) | <0.001 | −1.20 (−0.177) | <0.001 | −0.33 (−0.020) | 0.667 |
| 30–49 (n = 1781) | −0.32 (−0.165) | <0.001 | −0.02 (−0.025) | 0.287 | −0.16 (−0.098) | <0.001 |
| 50–80 (n = 2007) | −0.59 (−0.371) | <0.001 | −0.43 (−0.337) | <0.001 | −0.20 (−0.130) | <0.001 |
| Females | | | | | | |
| 10–19 (n = 327) | 4.65 (0.486) | <0.001 | 3.84 (0.492) | <0.001 | 6.12 (0.665) | <0.001 |
| 20–28 (n = 646) | −0.66 (−0.171) | <0.001 | −0.49 (−0.145) | <0.001 | 0.28 (0.015) | 0.708 |
| 29–49 (n = 2466) | −0.11 (−0.008) | 0.677 | 0.13 (0.102) | <0.001 | −0.10 (−0.022) | 0.279 |
| 50–80 (n = 2405) | −1.08 (−0.591) | <0.001 | −0.87 (−0.568) | <0.001 | −0.81 (−0.461) | <0.001 |

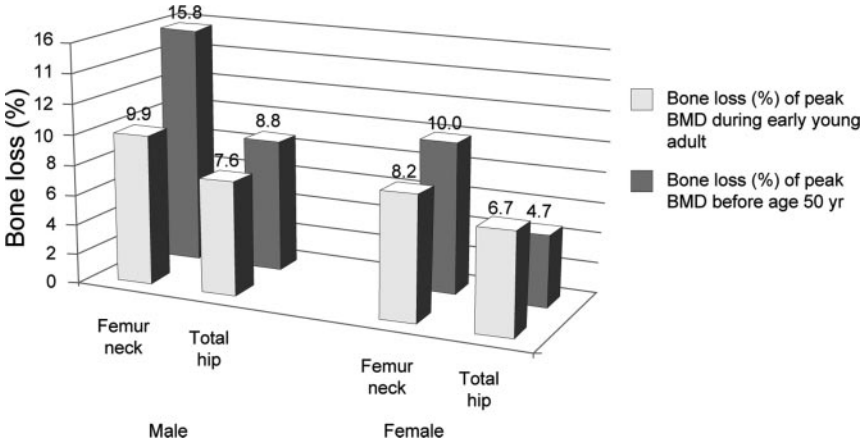


**FIG. 3.** The percentage of bone loss before age 50 yr.

hood (Fig. 3). In both sexes, this was not observed in the lumbar spine (Table 1).

### Age-related changes for other clinical parameters

Age-related changes in body mass index (BMI), body fat percentage, and alkaline phosphatase (ALP) and 25-hydroxyvitamin D [25(OH)D] levels are shown in Fig. 4. BMI increased during adolescence, was maintained during adulthood, and decreased slowly after the age of 50 yr in men. In women, an increase in BMI was relatively constant until the age of 70 yr. Sex differences were observed in body fat percentage. In men, body fat percentage decreased during puberty, increased slightly in the 20s, and was then maintained for life. In women, body fat percentage increased during puberty, decreased slightly in the 20s, and again increased gradually for life. As expected, ALP levels decreased abruptly after puberty in both males and females. In both sexes, 25(OH)D levels decreased during puberty and then increased throughout life with some variation.

### Correlations between BMD and variable parameters according to age group

To determine the factors related to BMD changes, we investigated the correlations between BMD and various parameters according to the four age groups described previously (Table 2). Age showed negative correlations with BMD in most age groups. BMI also had negative correlations with BMD, and the correlation was still significant after adjusting for age. Because age and BMI are important determining factors of BMD, we analyzed other parameters after adjusting for age and BMI. Among the clinical parameters, such as 25(OH)D and ALP levels, Ca and P intake, body fat percentage, and alcohol, smoking, and exercise habits, body fat percentage showed significant negative correlations with BMD in most age groups.

## Discussion

Our findings in this cross-sectional study indicate an accelerated phase of bone loss at the femur in both sexes during early adulthood. These findings may aid in developing a better understanding of the age-related early bone loss and a prevention strategy for osteoporosis in later life.

Skeletal growth involves changes in size, shape, and material properties, and these changes vary in tempo and magnitude within different regions of the skeleton. Skeletal mass is also accrued throughout childhood and adolescence. Genetic factors are known to determine 60–80% of the variability in skeletal development and acquisition; however, modifiable factors related to nutrition, lifestyle, exercise, and hormonal imbalance can also influence bone growth, modeling, and remodeling (12). There is evidence that some bone loss begins in the third decade, particularly for trabecular bone, but is then accelerated (25). Understanding the change of bone mass and geometry during adolescence and early adulthood is essential to unraveling the determinants of bone fragility and for development of a prevention strategy against fragility fractures.

In this study, the acquisition of PBM was achieved at the end of adolescence in women and was delayed several years in men, as previously reported (11). Compared with the Caucasian population (11, 26, 27), PBM appeared to be reached a little later in the Korean population. Although we could not determine whether there were ethnic differences in the acquisition of PBM with ages, the genetic factors and lifestyle factors such as daily calcium/protein intake, consumption of dairy products, prevalence of vitamin D insufficiency, and frequency/intensity of weight-bearing physical activity between Korean and Caucasian population may contribute to this difference. Interestingly, we observed an early loss in BMD at the femoral neck and total hip. After reaching PBM, BMD decreased rapidly until the age of 28 or 29 yr and then increased slightly or remained constant. In men, age-related bone loss at the femur occurred continuously, with an obvious temporal acceleration phase after achieving PBM. After reaching PBM, age-related bone loss at the femur in women revealed three obvious phases: first acceleration, consolidation or deceleration, and second acceleration. About 5–16% of peak BMD at the femur was lost by the age of 50 yr. In addition, more than 60% of bone loss in males and 80% in females that took place

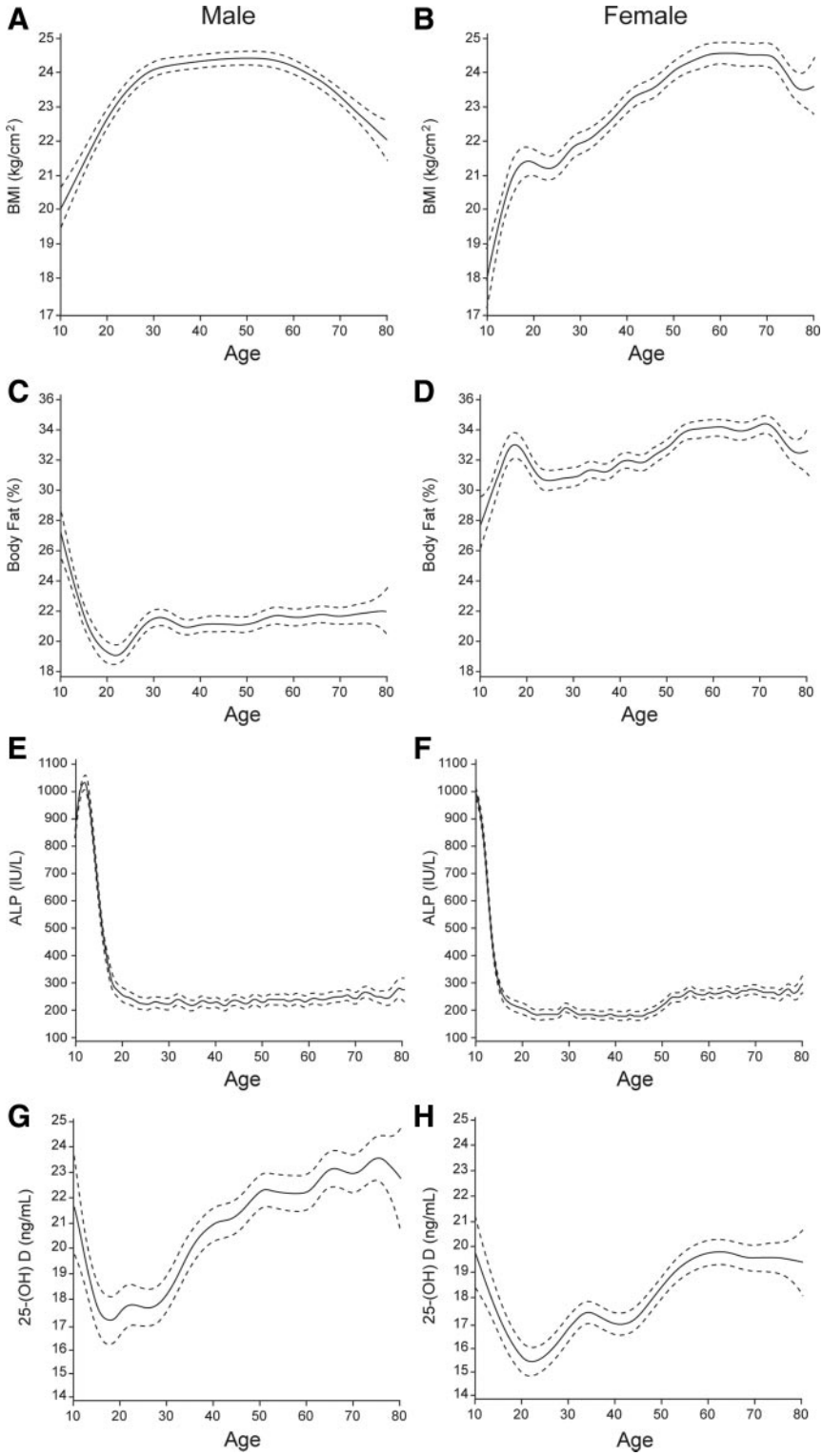


**FIG. 4.** Age-related changes in BMI (A and B), body fat percentage (C and D), ALP levels (E and F), and 25(OH) D levels (G and H) in males and females. Data are shown with a smoothing spline and 95% confidence interval.

before age 50 yr occurred during young adulthood. Accelerated bone loss was observed in males between the age of 23 and 29 yr and from 20 to 28 yr in females. In this age group, changes in skeletal size are not expected to be significant.

Age-related changes in the femoral neck cortical thickness revealed a similar pattern of age-related changes in BMD at the femoral neck. Accordingly, the buckling ratio increased gradually in an oblique J-shape pattern. However, the low sensitivity for measuring cortical thickness by the DXA technique should be considered. Khosla *et al.* (17) also observed the so-called spooning pattern of age-related changes in BMD by quantitative computed tomography (QCT). They observed accelerated bone loss followed by deceleration at the distal radius and distal tibia before 50 yr of age, but this change was found only in young adult men (17). In the current study, we found a similar pattern of bone loss at the femur in both sexes but especially in women. An accelerated phase of bone loss at the femur during early adulthood has also been observed in other ethnic groups (19, 20). In previous studies, cortical bone volumetric BMD (vBMD) in the long bone, midshaft of the femur and radius, as measured by QCT, did not show any changes during childhood and adolescence (28, 29). Other studies using peripheral QCT have observed an increase in cortical vBMD of the long bone during puberty (30, 31). Regarding the change of femoral neck BMD, estimates of vBMD did not change with age in some studies (27, 32). Discrepant results obtained using DXA, QCT, and peripheral QCT may reflect methodological differences between the techniques, variability in the specific subregion of bone studied, the total number of subjects, or ethnicity. Another observation in this study was that age-related changes in BMD were quite different at different skeletal sites. The early loss in femoral BMD was not observed at the lumbar spine in either sex. This suggests that bone remodeling may be regulated differently at different skeletal sites.

The next question was on how early loss of femoral BMD may be reconciled. Because bone loss in the femur begins as early as the third decade of life in both men and women, aging *per se* was considered first. Reactive oxygen

**TABLE 2.** Correlations between changes in BMD and various markers in males and females

| | Femoral neck | | | | Total hip | | | | Lumbar spine | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Males** | **10–22** | **23–29** | **30–49** | **50–80** | **10–22** | **23–29** | **30–49** | **50–80** | **10–22** | **23–29** | **30–49** | **50–80** |
| Age | 0.473[a] | −0.162[a] | −0.165[a] | −0.371[b] | 0.510[b] | −0.177[a] | −0.025 | −0.337[a] | 0.711[c] | −0.020 | −0.098[c] | −0.130[c] |
| BMI[d] | 0.455[a] | 0.360[a] | 0.328[a] | 0.365[a] | 0.485[b] | 0.403[a] | 0.385[a] | 0.425[a] | 0.376[c] | 0.322[c] | 0.246[c] | 0.352[c] |
| 25(OH)D[e] | 0.106[c] | 0.154[b] | 0.093[a] | 0.073[a] | 0.124[b] | 0.121[b] | 0.116[a] | 0.083[a] | 0.066 | 0.082 | 0.044 | 0.024 |
| ALP[e] | −0.156[b] | −0.137[c] | −0.162[a] | −0.162[a] | −0.161[b] | −0.167[b] | −0.168[a] | −0.181[a] | −0.227[c] | −0.148[a] | −0.154[c] | −0.151[c] |
| Ca intake[e] | 0.057 | 0.005 | 0.092[b] | 0.132[a] | 0.049 | 0.030 | 0.091[b] | 0.106[a] | 0.065 | −0.026 | 0.063[b] | 0.040 |
| P intake[e] | 0.032 | −0.007 | 0.106[a] | 0.151[a] | 0.046 | 0.028 | 0.099[a] | 0.128[a] | 0.024 | −0.029 | 0.021 | 0.037 |
| Body fat (%)[e] | −0.430[a] | −0.292[a] | −0.284[a] | −0.180[a] | −0.434[a] | −0.306[b] | −0.274[a] | −0.178[a] | −0.513[c] | −0.209[c] | −0.182[c] | −0.064[a] |
| Alcohol[e] | −0.041 | 0.104[c] | 0.014 | 0.002 | −0.012 | 0.064 | | 0.007 | −0.081 | 0.056 | 0.024 | |
| Smoking[e] | −0.031 | −0.014 | −0.017 | −0.020 | −0.064 | 0.008 | −0.003 | −0.011 | −0.095 | 0.027 | −0.034 | −0.011 |
| Exercise[e] | 0.161[c] | 0.087 | 0.086[a] | 0.064[b] | 0.139 | 0.089 | 0.087[a] | 0.080[a] | 0.220[a] | 0.072 | −0.023 | 0.024 |
| | **Femoral neck** | | | | **Total hip** | | | | **Lumbar spine** | | | |
| **Females** | **10–19** | **20–28** | **29–49** | **50–80** | **10–19** | **20–28** | **29–49** | **50–80** | **10–19** | **20–28** | **29–49** | **50–80** |
| Age | 0.486[a] | −0.171[a] | −0.008 | −0.591[a] | 0.492[c] | −0.145[a] | 0.102[a] | −0.568[a] | 0.665[a] | 0.015 | −0.022 | −0.461[a] |
| BMI[d] | 0.475[a] | 0.304[a] | 0.374[a] | 0.323[a] | 0.544[c] | 0.410[a] | 0.448[a] | 0.360[a] | 0.475[a] | 0.340[a] | 0.329[a] | 0.310[a] |
| 25(OH)D[e] | 0.048 | 0.083[a] | 0.041[c] | 0.091[a] | 0.096 | 0.083[c] | 0.073[a] | 0.085[a] | 0.060 | 0.048 | 0.026 | 0.016 |
| ALP[e] | −0.302[a] | −0.264[a] | −0.165[a] | −0.160[a] | −0.335[c] | −0.284[a] | −0.159[a] | −0.194[a] | −0.372[a] | −0.189[a] | −0.181[a] | −0.211[a] |
| Ca intake[e] | 0.012 | 0.062 | 0.065[b] | 0.053[b] | 0.023 | 0.007 | 0.053[a] | 0.068[b] | 0.066 | 0.025 | −0.028 | 0.058[c] |
| P intake[e] | 0.050 | 0.066 | 0.060[b] | 0.060[b] | 0.034 | 0.029 | 0.047[b] | 0.067[b] | 0.034 | 0.061 | 0.028 | 0.036 |
| Body fat (%)[e] | −0.207[a] | −0.143[a] | −0.179[a] | −0.095[a] | −0.163[c] | −0.178[a] | −0.180[a] | −0.100[a] | −0.185[c] | −0.150[a] | −0.127[a] | −0.020 |
| Alcohol[e] | −0.106 | 0.028 | 0.013 | −0.008 | −0.131[b] | 0.015 | −0.002 | −0.018 | −0.050 | −0.012 | −0.001 | |
| Smoking[e] | | 0.060 | −0.034 | −0.049[b] | | 0.032 | −0.028 | −0.055[b] | | 0.026 | −0.043[b] | −0.055[d] |
| Exercise[e] | | 0.008 | 0.011 | 0.056[b] | | −0.007 | 0.004 | 0.088[a] | | | −0.001 | 0.024 |
| Age of menarche (yr)[e] | −0.137[c] | 0.008 | −0.025 | −0.044[b] | −0.221[b] | −0.029 | −0.022 | −0.051[b] | −0.310[a] | −0.002 | −0.056[c] | −0.110[a] |

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

[d] Adjusted for age.

[e] Adjusted for age and BMI.

species play a significant role in the pathogenesis of age-associated human disease and are also important for bone loss with aging (8). The pattern we observed also may be explained by a transient adjustment phenomenon that occurs during the transitional period between the modeling and remodeling phase, after completion of lineal growth. Robust secretion of GH and IGF-I is tapering down significantly at this age, and enormously elevated serum ALP levels dropped abruptly in our study. The secretory pattern of many other hormones, growth factors, and cytokines could have changed tremendously during this period. Less likely, the decline of free estradiol associated with aging in men was also considered because the decline pattern reveals similar trends to the changes in femoral BMD and structure (33, 34). In the correlation analysis, BMI and body fat percentage showed greater correlation with BMD than other clinical parameters. However, habitual and lifestyle changes, such as Ca intake, alcohol, smoking, and exercise habits, could not explain the spooning pattern. Although causality cannot be established between these variables, this result suggests that habitual or environmental factors might affect bone loss less than hormonal, aging, or genetic factors in young adults.

Several studies have reported on age-related changes in BMD; however, most of these studies have been confined to a specific sex, a certain age group, or a specific site for BMD measurement. The major strength of our study is that we analyzed data collected from a nationwide survey that included more than 4000 participants from each sex, aged 10–80 yr, in Korea. Despite this strength, our study has some limitations. First, DXA measures total bone and cannot distinguish cortical bone from trabecular bone is a concern. Thus, the changes we observed here are integrated changes in both compartments of the femur. Previous QCT data revealed that cortical bone mass remained relatively stable in both sexes until midlife and trabecular bone loss began in young adult life (35). Although the proximal femur consists of predominantly cortical bone (36), the early life changes in bone mass we observed may be due largely to the previously described changes in young adulthood in trabecular, but not cortical, bone. Second, this is a cross-sectional study, and therefore, secular changes in skeletal size and other confounders may bias the rate of bone loss estimated from this study. Furthermore, a causal relationship cannot be established based on the cross-sectional nature. Third, we could not measure hormonal levels, such as estradiol, testosterone, GH, and IGF-I. We also could not obtain qualitative information about smoking and alcohol use. Lastly, despite statistical significance, the clinical significance of some of

the findings is questionable because of low correlation coefficients.

In conclusion, we observed an accelerated phase of bone loss at the femur in both sexes during early adulthood. Further studies to identify the factors that accelerate bone loss in young adults may be helpful to reduce the occurrence of fractures later in life. Longitudinal studies are also needed to verify the early bone loss in various ethnic groups.

## Acknowledgments

The authors alone are responsible for the content and writing of the paper.

Address all correspondence and requests for reprints to: Sung-Kil Lim, M.D., Ph.D., Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea. E-mail: lsk@yuhs.ac.

This work was supported by the National Research Foundation of Korea Grant 20110001024 funded by the Korean government (Ministry of Education, Science and Technology).

Disclosure Summary: The authors report no conflicts of interest.

## References

1. **Riggs BL, Melton Iii 3rd LJ, Robb RA, Camp JJ, Atkinson EJ, Peterson JM, Rouleau PA, McCollough CH, Bouxsein ML, Khosla S** 2004 Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res 19:1945–1954
2. **Riggs BL, Khosla S, Melton 3rd LJ** 2002 Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev 23: 279–302
3. **Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM** 2001 Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 86: 3555–3561
4. **Bilezikian JP, Morishima A, Bell J, Grumbach MM** 1998 Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. N Engl J Med 339:599–603
5. **Rochira V, Carani C** 2009 Aromatase deficiency in men: a clinical perspective. Nat Rev Endocrinol 5:559–568
6. **Vandenput L, Ederveen AG, Erben RG, Stahr K, Swinnen JV, Van Herck E, Verstuyf A, Boonen S, Bouillon R, Vanderschueren D** 2001 Testosterone prevents orchidectomy-induced bone loss in estrogen receptor-$\alpha$ knockout mice. Biochem Biophys Res Commun 285: 70–76
7. **Parikka V, Peng Z, Hentunen T, Risteli J, Elo T, Väänänen HK, Härkönen P** 2005 Estrogen responsiveness of bone formation in vitro and altered bone phenotype in aged estrogen receptor-$\alpha$-deficient male and female mice. Eur J Endocrinol 152:301–314
8. **Manolagas SC, Parfitt AM** 2010 What old means to bone. Trends Endocrinol Metab 21:369–374
9. **Ambrogini E, Almeida M, Martin-Millan M, Paik JH, Depinho RA, Han L, Goellner J, Weinstein RS, Jilka RL, O'Brien CA, Manolagas SC** 2010 FoxO-mediated defense against oxidative stress in osteoblasts is indispensable for skeletal homeostasis in mice. Cell Metab 11:136–146
10. **Rached MT, Kode A, Xu L, Yoshikawa Y, Paik JH, Depinho RA, Kousteni S** 2010 FoxO1 is a positive regulator of bone formation by favoring protein synthesis and resistance to oxidative stress in osteoblasts. Cell Metab 11:147–160
11. **Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R** 1991 Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab 73:555–563
12. **Rizzoli R, Bianchi ML, Garabédian M, McKay HA, Moreno LA** 2010 Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone 46: 294–305
13. **Szulc P, Marchand F, Duboeuf F, Delmas PD** 2000 Cross-sectional assessment of age-related bone loss in men: the MINOS study. Bone 26:123–129
14. **Arlot ME, Sornay-Rendu E, Garnero P, Vey-Marty B, Delmas PD** 1997 Apparent pre- and postmenopausal bone loss evaluated by DXA at different skeletal sites in women: the OFELY cohort. J Bone Miner Res 12:683–690
15. **Ertungealp E, Seyisoglu H, Erel CT, Senturk LM, Gezer A** 1999 Changes in bone mineral density with age, menopausal status and body mass index in Turkish women. Climacteric 2:45–51
16. **Warming L, Hassager C, Christiansen C** 2002 Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int 13:105–112
17. **Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S** 2008 A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res 23:205–214
18. **Nordström P, Neovius M, Nordström A** 2007 Early and rapid bone mineral density loss of the proximal femur in men. J Clin Endocrinol Metab 92:1902–1908
19. **Slemenda C, Longcope C, Peacock M, Hui S, Johnston CC** 1996 Sex steroids, bone mass, and bone loss. A prospective study of pre-, peri-, and postmenopausal women. J Clin Invest 97:14–21
20. **Kröger H, Heikkinen J, Laitinen K, Kotaniemi A** 1992 Dual-energy X-ray absorptiometry in normal women: a cross-sectional study of 717 Finnish volunteers. Osteoporos Int 2:135–140
21. **Schoeller DA, Tylavsky FA, Baer DJ, Chumlea WC, Earthman CP, Fuerst T, Harris TB, Heymsfield SB, Horlick M, Lohman TG, Lukaski HC, Shepherd J, Siervogel RM, Borrud LG** 2005 QDR 4500A dual-energy X-ray absorptiometer underestimates fat mass in comparison with criterion methods in adults. Am J Clin Nutr 81:1018–1025
22. **Kelly TL, Wilson KE, Heymsfield SB** 2009 Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS ONE 4:e7038–e7038
23. **Uusi-Rasi K, Semanick LM, Zanchetta JR, Bogado CE, Eriksen EF, Sato M, Beck TJ** 2005 Effects of teriparatide [rhPTH (1–34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone 36:948–958
24. **Beck TJ, Looker AC, Ruff CB, Sievanen H, Wahner HW** 2000 Structural trends in the aging femoral neck and proximal shaft: analysis of the Third National Health and Nutrition Examination Survey dual-energy X-ray absorptiometry data. J Bone Miner Res 15:2297–2304
25. **Khosla S, Riggs BL, Atkinson EJ, Oberg AL, McDaniel LJ, Holets M, Peterson JM, Melton 3rd LJ** 2006 Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. J Bone Miner Res 21:124–131
26. **Bonjour JP, Theintz G, Law F, Slosman D, Rizzoli R** 1994 Peak bone mass. Osteoporos Int 4(Suppl 1):7–13
27. **Lu PW, Cowell CT, Lloyd-Jones SA, Briody JN, Howman-Giles R** 1996 Volumetric bone mineral density in normal subjects, aged 5–27 years. J Clin Endocrinol Metab 81:1586–1590
28. **Gilsanz V, Skaggs DL, Kovanlikaya A, Sayre J, Loro ML, Kaufman**

**F, Korenman SG** 1998 Differential effect of race on the axial and appendicular skeletons of children. J Clin Endocrinol Metab 83: 1420–1427
29. **Skaggs DL, Loro ML, Pitukcheewanont P, Tolo V, Gilsanz V** 2001 Increased body weight and decreased radial cross-sectional dimensions in girls with forearm fractures. J Bone Miner Res 16:1337–1342
30. **Kontulainen SA, Macdonald HM, McKay HA** 2006 Change in cortical bone density and its distribution differs between boys and girls during puberty. J Clin Endocrinol Metab 91:2555–2561
31. **Neu CM, Rauch F, Manz F, Schoenau E** 2001 Modeling of cross-sectional bone size, mass and geometry at the proximal radius: a study of normal bone development using peripheral quantitative computed tomography. Osteoporos Int 12:538–547
32. **Bachrach LK, Hastie T, Wang MC, Narasimhan B, Marcus R** 1999 Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. J Clin Endocrinol Metab 84:4702–4712
33. **Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL** 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 83: 2266–2274
34. **Khosla S, Melton 3rd LJ, Achenbach SJ, Oberg AL, Riggs BL** 2006 Hormonal and biochemical determinants of trabecular microstructure at the ultradistal radius in women and men. J Clin Endocrinol Metab 91:885–891
35. **Khosla S, Melton 3rd LJ, Riggs BL** 2011 The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? J Bone Miner Res 26:441–451
36. **Eastell R, Mosekilde L, Hodgson SF, Riggs BL** 1990 Proportion of human vertebral body bone that is cancellous. J Bone Miner Res 5:1237–1241