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Rate of bone loss is greater in young Mexican American men than women: The San Antonio Family Osteoporosis Study

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Abstract

Little is known about the progression of bone loss during young adulthood and whether it differs between men and women. As part of the San Antonio Family Osteoporosis Study we tested whether bone mineral density (BMD) changed over time in men or women, and whether the rate of BMD change differed between the sexes. BMD of the proximal femur, spine, radius, and whole body was measured in 115 men and 202 pre-menopausal women (ages 25 to 45 years; Mexican American ancestry) by dual-energy x-ray absorptiometry at two time points (5.6 years apart), from which annual percent change-in-BMD was calculated. Likelihood-based methods were used to test whether change-in-BMD differs from zero or differs between men and women. In men, percent change-in-BMD was significantly greater than zero for the 1/3 radius (i.e. indicating a gain of BMD; Bonferroni-adjusted $p < 0.01$), less than zero for the femoral neck, lumbar spine, ultradistal radius, and whole body (i.e. indicating a loss of BMD; $p < 0.01$ for all), and not different than zero for the total hip ($p = 0.24$). In women, percent change-in-BMD was greater than zero for the total hip, 1/3 radius, and whole body ($p < 0.01$ for all), less than zero for the ultradistal radius ($p < 0.01$), and not significantly different than zero for the femoral neck and lumbar spine ($p = 1.0$ for both). For all skeletal sites, men experienced greater decrease in BMD (or less increase in BMD) than women; this result was observed both with and without adjustment for age, BMI, and change-in-BMI ($p < 0.05$ for all). These results suggest that significant bone loss occurs at some skeletal sites in young men and women, and that loss of BMD is occurring significantly faster, or gain of BMD is occurring significantly slower, in young men compared to young women.

Keywords

bone mineral density; bone loss; osteoporosis; sex differences; dual-energy x-ray absorptiometry

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Introduction

The impact of bone loss on skeletal health in the elderly is widely recognized, however little is known about the progression of bone loss during the entire adult lifespan. The conventional wisdom is that medically-relevant bone loss begins at menopause in women and with advanced age in men due to a combination of hormonal and age-related factors [1,2]. Most cross-sectional studies indicate that peak bone mineral density (BMD) is achieved sometime during young adulthood and followed by a prolonged plateau phase during which BMD is maintained with little or no change [3]. Other studies show varying degrees of bone loss occurring immediately after peak attainment, particularly in the trabecular bone [1,4-7]. Further understanding of the extent and age of onset of bone loss is needed because current interventions for osteoporosis are directed only at bone loss occurring in the later years of life. Yet to be determined is whether early bone loss, and/or the cumulative loss due to moderate decline in BMD over the adult lifespan, has clinical significance or can offer new insight into disease pathogenesis or treatment. Moreover, while sex differences in onset and rates of bone loss are well known among the elderly population, it is unclear whether early bone loss differs between young men and women. Understanding sex differences in early bone loss may be important for the proper design of interventions against osteoporosis in men and women.

The San Antonio Family Osteoporosis Study (SAFOS) was designed to investigate the genetic and environmental factors on BMD and longitudinal change-in-BMD in Mexican Americans. In the current report, we investigated the differences in rates of change-in-BMD between young adult men and women, aged 25 to 45 years.

Materials and methods

Recruitment and data collection

Data collection for the baseline (calendar years 1997 to 2000) and follow-up (2003 to 2006) phases of the San Antonio Family Osteoporosis Study (SAFOS) have been previously described in detail [8-10]. Participants were recruited through a house-to-house recruitment protocol that identified probands meeting two eligibility criteria: (I) being between 40 to 60 years of age; and (II) having large families in the San Antonio area. All first, second, and third degree relatives of probands and spouses, irrespective of current health status, were invited to participate in the study. In total, 34 multigenerational families, representing a fundamentally unselected, population-based sample of Mexican Americans, were collected; this sample includes 724 participants, aged 18 to 86 on whom longitudinal measurements of bone mineral density (BMD) were obtained (i.e. those enrolled in both baseline and follow-up phases of the study). In the present study, which investigates the rates of bone loss specifically in young Mexican Americans, we limited our analysis to 325 participants (115 men, 202 pre-menopausal women) aged 25 to 45 years at baseline. This subset includes participants comprising over 1400 relative pairs, including approximately 200 siblings, 100 avuncular relationships, 500 first cousins, and over 600 other relationships.

Anthropometric, medical, and body composition data were collected during baseline and follow-up exams (3.5 to 8.9 years apart, mean = 5.6 years). Demographic, lifestyle, medical history, and reproductive history data were concurrently assessed at both phases via questionnaire. Women who reported an absence of any menstrual periods within the previous 12 months at either the baseline or follow-up exam were excluded from analysis. Covariates considered in our analysis include: age (years), body mass index (BMI, kg/m²), and interim change in BMI (kg/m²/year) calculated as difference between follow-up and baseline BMI divided by the exact elapsed time between exams. Details regarding covariate data collection have been previously described by Mitchell et al. [8]. Additional covariates assessed by questionnaire were initially investigated but not included in the analyses presented herein due

to lack of statistically significant effects on change-in-BMD. These covariates include diabetes mellitus (yes/no; assessed by glucose tolerance test or current use of anti-diabetic medication), cigarette smoking (current smoker/not), alcohol consumption (current drinker/not), dietary calcium intake (mg/deciliter), supplemental calcium consumption (yes/no), use of oral contraceptives (women only; current user/not), parity (women only; number of live births), age at first menses (women only; years), and lactation history (women only; months breastfeeding). Approximately 81% of the original study participants were re-enrolled for follow-up. No differences in baseline covariates were observed between participants returning and not returning for the follow-up phase (results not shown).

BMD (g/cm^2) measurements of the femoral neck, total hip, total lumbar spine (L1 to L4), ultradistal radius, 1/3 radius (measured at one third of the total radius length from the distal end), and whole body (excluding skull) were obtained by dual-energy x-ray absorptiometry (DXA) at both baseline and follow-up. During the interim between baseline and follow-up phases of the study, DXA equipment was upgraded from the Hologic 1500W to Hologic 4500W densitometer (Hologic Inc., Bedford, MA). A concurrent update in software was applied to ensure comparability of scoring algorithms between models. Extensive cross-calibration of equipment has been previously described [10]. In brief, duplicate measures of a sample of subjects recorded from the two densitometers showed near-perfect agreement ($R^2 > 99.8\%$, $p < 10^{-13}$) and no mean differences (paired t-test $p > 0.1$) for several bone sites of the proximal femur and spine. Precision of the Hologic 1500W model for BMD was $0.009 \text{ g}/\text{cm}^2$ for total lumbar spine, $0.007 \text{ g}/\text{cm}^2$ for total hip, and $0.002 \text{ g}/\text{cm}^2$ for the manufacturer's spine phantom. Precision of the Hologic 4500W model for BMD was $0.006 \text{ g}/\text{cm}^2$ for total lumbar spine, $0.007 \text{ g}/\text{cm}^2$ for total hip, and $0.002 \text{ g}/\text{cm}^2$ for radius. All DXA readings were performed by the same trained technician. Measurement drift was prevented by daily equipment calibration on the phantom, and the same reviewer evaluated baseline and follow-up scans to ensure comparability of regions of interest.

Statistical analyses

Distributions of BMD and covariates were assessed at baseline and follow-up and outliers greater than 4 SD from trait means were excluded (0 to 4 observations removed per trait). Annual percent change in BMD was calculated as the difference between follow-up and baseline measurements divided by baseline measurements, divided by exact elapsed time in years, with positive values indicating a yearly gain, and negative values indicating a yearly loss.

Statistical tests were performed to examine three specific hypotheses regarding annual percent change in BMD at each bone site: (I) does sex-specific change-in-BMD differ from zero?; (II) does change-in-BMD differ between men and women?; and (III) does change-in-BMD differ between men and women while adjusting for age, BMI, and change-in-BMI? Because the sample contains related individuals from multigenerational families, classic statistical methods (i.e. t-tests and linear regression), which assume independent observations, would underestimate the variances around parameter estimates and were therefore not utilized to test these hypotheses. Instead we employed analogous methods in a variance components framework, conditional on the pedigree structure of the data to provide accurate variance estimates and thus allows sound statistical testing of our hypotheses among related participants.

The general form of our model is:
$$y_i = \mu + \sum_j \beta_j X_{ji} + g_i + e_i$$
, where y_i is change-in-BMD for the i th individual, μ is the sample mean change-in-BMD, j is the set of predictors including sex, age, BMI, change-in-BMI, and menopause, β_j are the regression coefficients corresponding to each predictor, X_{ji} are the values of the predictors for the i th individual, g_i is the additive polygenic effect (based on expected genetic sharing due to the familial relationship between

relative pairs), and e_i is the residual error effect. Detailed discussion of the polygenic effect, which for the purpose of this study may be considered a nuisance parameter, is available elsewhere [9,11]. Model parameters were estimated using pedigree-based maximum likelihood methods. Hypotheses I, II, and III, above, were tested by comparing constrained and unconstrained models via the likelihood ratio test, which follows a χ^2 distribution with 1 degree of freedom. For example, to test hypothesis I, likelihoods were compared between the constrained model in which μ was set equal to zero and the unconstrained model in which μ was estimated. To test models II and III, likelihood comparisons were made between the constrained model in which β_{sex} was set equal to zero and the unconstrained model in which β_{sex} was estimated. For hypothesis I and II, additional covariates (i.e. age, BMI, change-in-BMI, and menopause) were not considered, so parameters corresponding to these variables are not included in the models. Significance of covariates was assessed by the likelihood ratio test comparing models including and excluding the covariate being tested (which, again, follows the χ^2 distribution with 1 degree of freedom). To be conservative, covariates with statistical significance at $\alpha < 0.1$ were included in our models. To correct for multiple testing (of the 12 parameters estimated and tested in this study), we present the statistical significance of all tests as Bonferroni-adjusted p-values (i.e. nominal p-values each multiplied by 12). Because change-in-BMD across the different skeletal sites is correlated, these tests are not independent and therefore Bonferroni-adjusted p-values are likely to be conservative. Modeling was performed using the Sequential Oligogenic Linkage Analysis Routines software [11]. The R suite was used for summary statistics, data manipulation, and creation of figures including plotting LOWESS curves (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the SAFOS participants aged 25 and 45 years (115 men, 202 women) who were included in this study are presented in Table 1. Mean BMI at baseline was $> 30 \text{ kg/m}^2$ in both men and women and mean weight gain was 0.45 kg/year in men and 0.82 kg/year in women over 5.6 years of follow-up (range = 3.5 to 8.9 years; mean in men = 5.6 years; mean in women = 5.5 years). Baseline BMD is indicated in g/cm^2 , rather than T- or Z-scores, due to lack of an appropriate ethnically- and weight-matched reference population. However, for both men and women, mean baseline BMD of the femoral neck and total hip were nearly identical to those reported in Mexican Americans aged 20 to 50 years in the NHANES III study, which included 1406 men and 1227 women [12]. The distributions of change-in-BMD (% change/year) are shown in Figure 1. Change-in-BMD was approximately normally distributed and exhibited substantial variation in this population.

Results addressing tests of hypotheses I, II and III are summarized in Table 2:

Hypothesis I: does BMD change over time in men or women?

Mean percent change-in-BMD for each skeletal site is shown in columns 1 and 2 (mean change and p-value for change different from zero) for the total sample, and in columns 3-4 and 5-6 for men and women, respectively. BMD at the 1/3 radius increased in both men and women ($p < 0.001$ for both), whereas BMD of the ultradistal radius decreased in both men and women ($p < 0.001$ for both). Femoral neck and lumbar spine BMD decreased in men ($p < 0.001$ for both) but did not exhibit significant change in women. Total hip BMD did not change in men ($p = 0.24$) but increased in women ($p < 0.001$). Whole body BMD decreased in men ($p < 0.001$) and increased in women ($p < 0.001$).

Hypothesis II: does the magnitude of change-in-BMD differ by sex?

Column 7 in Table 2 presents the p-values for a test of the hypothesis of equality of the change-in-BMD between men and women. For all skeletal sites, mean percent change-in-BMD in men

was more negative or less positive than in women (i.e. men experienced greater loss or less gain in BMD; $p < 0.001$ for all).

Hypothesis III: do sex differences in change-in-BMD persist after adjustment for covariates (i.e. age, BMI, and change-in-BMI)?

Column 8 in Table 2 presents the p-values for a test of the hypothesis of equality of the change-in-BMD between men and women following adjustment for covariates. The greater loss of BMD (or lesser gain of BMD) in men was observed even while simultaneously adjusting for the effects of age, BMI, and change-in-BMI, indicating that this sex difference is not fully explained by the covariates included in our models. Other covariates, including history of diabetes, smoking, alcohol consumption, dietary and supplemental calcium, parity, age of first menses, and history of breastfeeding were not significantly related to change-in-BMD and did not account for the sex difference in change-in-BMD. Women taking oral contraceptives experienced less loss of BMD or more gain of BMD than women not taking oral contraceptives, though use of oral contraceptives did not account for the sex difference.

The sex differences are illustrated in Figure 2, which shows unadjusted percent change-in-BMD by age for men and women with LOWESS curves depicting the sex-specific trends. Trend lines indicated that the sex differences in rates of change-in-BMD were evident across the entire age range, 25 to 45 years (rather than driven by differences limited to a narrower age range).

Because BMD, as measured by DXA, was calculated as the ratio of bone mineral content (BMC) to the 2-dimensional areal projection of the bone, we conducted a further analysis to determine whether the observed BMD associations might be due primarily to changes in either BMC or bone area. We therefore calculated annual percent change-in-BMC and change-in-bone area and tested hypotheses I, II, III just as we did for change-in-BMD. These results (not shown) indicated that both BMC and bone area are changing, and in the same direction, for all skeletal sites. Moreover, change-in-BMC differed significantly between men and women for all skeletal sites ($p = 0.03$ to 10^{-21}) except lumbar spine (which exhibited modest, but not statistically significant, sex differences; $p = 0.09$), and in all cases, men experienced greater decline or less increase in BMC than women. Conversely, change-in-bone area did not differ between sexes ($p > 0.1$) except for whole body ($p < 0.001$). Therefore, while significant change is occurring in the same direction in both BMC and bone area, it is the change-in-BMC, and not the change-in-area, that appears to drive the greater bone loss observed in the young men compared to women.

Discussion

To date, studies of bone loss have primarily been conducted in older cohorts for whom osteoporosis is a greater risk. However recent work has indicated that bone loss, particularly that of trabecular bone, may begin much earlier in life [1,4-7,13]. In the present study we report two important findings: first, that significant decrease in BMD is occurring in men and women aged 25-45 at several skeletal sites, and second, that loss of BMD is occurring significantly faster, or gain of BMD is occurring significantly slower, in young men compared to young women (Figures 1-2, Table 2). Though our study sample is modest in size, our findings are highly significant even after Bonferroni adjustment for multiple testing. Moreover, the sex difference was observed even after adjustment for age, BMI, and change-in-BMI. Similar results were observed when height, weight, change-in-height and change-in-weight were modeled in place of BMI and change-in-BMI (results not shown).

These findings are consistent with previous studies of bone loss in younger populations, although others have not explicitly addressed sex differences. Riggs et al. showed significant

decrease in trabecular volumetric BMD of the radius and tibia among 100 white men aged 30 to 49 and 97 women aged 20 to 49, and although they did not test for sex differences, men experienced qualitatively greater loss of both trabecular and cortical volumetric BMD than did women [1]. They estimated that the substantial trabecular bone loss occurring during young adulthood accounted for 33% to 50% of total trabecular bone loss over the entire lifespan in both sexes [1]. Other studies reported significant bone loss of the hip among 96 pre-menopausal women aged 30 to 48 [6], and that onset of hip and spine bone loss in women occurred between ages 20 and 42, and 39 and 50, respectively [4]. An investigation of 107 young male athletes (ages 17 to 25 years) reported significant hip bone loss after age 19 [5].

In a cross-sectional study of Afro-Caribbean 188 men and 283 women aged 18 to 49 years, Wang et al. observed an inverse correlation between age and BMD of the radius and tibia (i.e., a decrease in BMD across age cohorts). Moreover, the correlation was stronger in men than women, suggesting that for those under 50 years of age, men may lose BMD at a faster rate than women [7]. Sheu et al. reported in a large longitudinal study of Afro-Caribbean men aged 40 to 92 years that the youngest cohorts (237 men aged 40 to 44, and 298 men aged 45 to 49 years) experienced the greatest decline in trabecular volumetric BMD of the radius and tibia (compared to older cohorts) [13]. Overall, among studies investigating bone loss using methods capable of separately measuring trabecular and cortical BMD, all show evidence that onset of trabecular bone loss may occur up to decades before that of cortical bone [1,7,13]. In the present study, BMD was measured using DXA, a technology that cannot separately distinguish trabecular and cortical bone. Nevertheless, analysis of disparate skeletal sites, which differ substantially in trabecular vs. cortical content, lends some insight into rate and timing of trabecular and cortical bone loss. For example, BMD of trabecular-rich sites, including lumbar spine and ultradistal radius declined in our Mexican American sample, especially in men, but also to a lesser degree in women. In contrast, BMD at other skeletal sites comprised of greater proportions of cortical bone, such as the total hip and 1/3 radius, did not decline (and in fact increased) in young Mexican Americans. This finding is consistent with the significant increase in cortical BMD of the tibia observed by Riggs et al. in women aged 20-30 years, as well as non-significant positive changes for cortical BMD of the tibia in men aged 20-30 years and for cortical BMD of the radius in women aged 20-40 years. Taken together, these observations are consistent with the notion that trabecular bone loss may temporally precede cortical loss. However, caution is warranted in the interpretation of negative percent change-in-BMD as an indicator of “bone loss” because negative values of change-in-BMD are possible when both BMC and bone area are increasing with age, if bone area is increasing at a faster rate relative to BMC. In this sense, BMD (and possibly bone strength) may decline without concurrent loss of bone.

The positive percent change-in-BMD observed in this study, particularly for cortical-rich skeletal sites, is of particular interest. Very few studies have looked at skeletal changes during this period of life, and it is currently unclear why BMD should increase at these sites in young adults. We speculate that part of this apparent increase in BMD may be due to concurrent weight gain in our sample. The Mexican Americans in our study are, in general, overweight (mean BMI > 30 kg/m²), and exhibit considerable weight gain between the ages of 25 and 45 years (0.68 kg/year). Increases in BMD may indicate a skeletal response to changes in adiposity and musculature. Part of the observed increase in BMD may also be due to measurement artifact, because as mentioned above, changes in DXA-assessed BMD may not entirely reflect biological bone loss/gain. We speculate that measurement artifact of this nature would not account for the observed sex difference in rates of BMD change.

It is unclear whether the significant differences in change-in-BMD observed between men and women in this study is specific to Mexican Americans or can be generalized to other ethnic groups and/or to the wider U.S. or world populations. In particular, the study sample size is

relatively small, (although similar in size to other reports on change-in-BMD in young adults), and, as mentioned, the SAFOS cohort is largely overweight and is experiencing weight gain, both of which may affect change-in-BMD. Also, differences in exposure to environmental risk factors may be responsible for the observed greater decline in BMD in young men compared to young women. Smoking was similar between the sexes, whereas alcohol consumption was greater in men; however, neither of these risk factors explained the differing rates of bone loss among men and women. Other, non-measured lifestyle risk factors, including vocation, physical activity, diet, and adolescent environment may be involved. Likewise, studies in this population [9,10] and others [14,15] indicate that genetics plays a large role in bone loss, and gene-by-sex interactions may contribute to the observed differences between young men and women.

In summary, this study identified interesting observations that challenge the conventional wisdom regarding bone loss: first, that significant decrease in BMD occurs in young adults at several skeletal sites, and second, that unlike in older cohorts, young men may experience more rapid decline in BMD than young women. These findings suggest that bone loss in younger individuals may be important for future risk of osteoporosis and that skeletal health may be of concern across the adult lifespan, rather than only with advanced age. Moreover, the sex-specific patterns of change-in-BMD, particularly the greater decline in BMD in men than women at some skeletal sites, suggests that sex-specific strategies for prevention of osteoporosis, possibly beginning in young adulthood, may be warranted to improve long-term skeletal health.

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Figure 1. Distributions of percent change-in-BMD for (A) femoral neck, (B) total hip, (C) lumbar spine, (D) 1/3 radius, (E) ultradistal radius, and (F) whole body. Gray bars represent the total sample. Black bars representing women illustrate that women contribute disproportionately to the right side, and men disproportionately to the left side, of the total distribution.

Figure 2.

LOWESS curve showing change-in-BMD by baseline age in men (x's and solid line) and women (o's and dashed line) for (A) femoral neck, (B) total hip, (C) lumbar spine, (D) 1/3 radius, (E) ultradistal radius, and (F) whole body. Across all age ranges, men show greater loss (or lesser gain) of BMD than women.

Table 1

Characteristics of the SAFOS sample 25 to 45 years of age

variable	total sample		men		women	
	mean	(SD)	mean	(SD)	mean	(SD)
sample size, n	317		115		202	
follow-up (years)	5.6	(0.7)	5.6	(0.7)	5.5	(0.7)
age (years)	34.3	(5.9)	34.2	(6.1)	34.3	(5.7)
anthropometrics						
height (cm)	162.3	(8.9)	170.8	(6.2)	157.5	(6.1)
weight (kg)	80.6	(20.9)	88.6	(20.9)	76.0	(19.5)
BMI (kg/m ²)	30.5	(7.1)	30.3	(6.3)	30.6	(7.5)
annual weight gain (kg/year)	0.68	(1.41)	0.45	(1.35)	0.82	(1.42)
annual change in BMI (kg/m ² /year)	0.26	(0.53)	0.15	(0.45)	0.32	(0.56)
medical						
diabetes (%)	11.0	-	11.2	-	10.9	-
pre-menopausal (%)	-	-	-	-	100.0	-
oral contraceptives (%)	-	-	-	-	21.9	-
lifestyle						
alcohol consumption (%)	49.1	-	62.1	-	41.3	-
smoking history (%)	20.5	-	23.3	-	18.9	-
baseline BMD (g/cm ²)						
femoral neck	0.89	(0.13)	0.92	(0.13)	0.87	(0.12)
total hip	0.99	(0.15)	1.05	(0.15)	0.96	(0.14)
lumbar spine	1.05	(0.12)	1.04	(0.13)	1.05	(0.12)
1/3 radius	0.72	(0.07)	0.79	(0.05)	0.68	(0.04)
ultradistal radius	0.50	(0.07)	0.55	(0.06)	0.47	(0.05)
whole body	1.14	(0.10)	1.20	(0.10)	1.11	(0.08)

Table 2

Mean percent change-in-BMD for total sample, men, and women ages 25-45

	total sample		men		women		sex difference	
	n=317	n=115	n=202	n=202	n=202	n=202	n=202	n=202
annual % change	mean ^a	p-value	mean	p-value ^b	mean	p-value ^b	base model	covariate model
femoral neck	-0.16	< 10 ⁻⁴	-0.47	< 10 ⁻⁴	0.02	1.000	< 10 ⁻³	0.024
total hip	0.52	0.108	0.21	0.240	0.70	< 10 ⁻¹⁵	< 10 ⁻⁵	< 10 ⁻⁴
lumbar spine	-0.17	< 10 ⁻⁵	-0.41	< 10 ⁻⁵	-0.03	1.000	< 10 ⁻³	< 10 ⁻³
1/3 radius	0.53	< 10 ⁻⁴	0.28	< 10 ⁻⁴	0.68	< 10 ⁻²¹	< 10 ⁻⁵	< 10 ⁻⁶
ultradistal radius	-0.51	< 10 ⁻¹⁸	-0.90	< 10 ⁻¹³	-0.29	< 10 ⁻³	< 10 ⁻⁷	< 10 ⁻⁷
whole body	0.06	< 10 ⁻⁸	-0.41	< 10 ⁻⁸	0.32	< 10 ⁻⁶	< 10 ⁻²⁰	< 10 ⁻²¹

statistical significance presented as Bonferroni-adjusted p-values

^a positive values indicate increase in BMD; negative values indicate decrease in BMD^b p-values for test of null hypothesis I (i.e. that sex-specific mean change-in-BMD is zero)^c p-values for test of null hypothesis II (that change-in-BMD is equal between sexes)^d p-values for test of null hypothesis III (that change-in-BMD is equal between sexes while adjusting for age, BMI, and change-in-BMD)