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Bone Mineral Density in Adolescent Females Using Injectable or Oral Contraceptives: A 24 Month Prospective Study

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Abstract

Study Objective—To determine whether bone mineral density (BMD) is lower in hormonal contraceptive users than that in an untreated, comparison group.

Design—Observational, prospective cohort; duration: 24 months.

Setting—Adolescent clinics in a midwestern, metropolitan setting.

Patients—433 postmenarcheal girls, aged 12–18 years, on depot medroxyprogesterone acetate (DMPA) [n=58], oral contraceptives (OC) [n=187], or untreated (n=188).

Intervention—DMPA and OC containing 100 mcg levonorgestrel and 20 mcg ethinyl estradiol.

Main Outcome Measure—BMD measurements at spine and femoral neck were obtained with dual x-ray absorptiometry (DXA) at baseline and 6-month intervals.

Results—Over 24 months, mean percent change in spine BMD was: DMPA −1.5%, OC +4.2%, and untreated +6.3%. Mean percent change in femoral neck BMD was: DMPA −5.2%, OC +3.0%, untreated +3.8%. Statistical significance was found between the DMPA group and other two groups ($p<.001$). In the DMPA group, mean percent change in spine BMD over the first 12 months was −1.4%; the rate of change slowed to −0.1% over the second 12 months. No bone density loss reached the level of osteopenia.

Conclusions—Adolescent girls receiving DMPA had significant loss in BMD compared with bone gain in the OC and untreated group. However, its clinical significance is mitigated by slowed loss

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after the first year of DMPA use and general maintenance of bone density values within the normal range.

Keywords

adolescents; oral contraceptives; bone mineral density; depot medroxyprogesterone acetate

INTRODUCTION

Adolescence is a crucial period for skeletal development. Because of the dramatic effects of puberty on bone growth and consolidation, there is up to a 50% increase in total body bone mass between the ages of 12 and 18 years (1). Because sex hormones play a key role in bone mass accrual we were interested in the effects of hormonal contraception on bone in the growing adolescent (2,3).

On November 17, 2004, the U.S., Food and Drug Administration issued a “black box” warning that focused attention on young women by stating, “It is unknown if use of depot medroxyprogesterone acetate (DMPA) contraceptive injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk of osteoporotic fracture in later life”(4). Since that report, we have completed a 24 month observational study to observe the effects of DMPA on adolescent bone. Our hypothesis was that bone mineral density (BMD) would be significantly lower among DMPA users than among girls not using hormonal treatment.

Regarding OC, there has been a secular trend over the past three decades to decrease the estrogen dose toward the minimum dose that still provides contraceptive efficacy but also minimizes the risk for thromboembolic events (5). However, as such events are exceedingly rare in the adolescent population (6), a potential concern is whether these lower dose OC provide enough estrogen for optimal bone accrual in very young women. Therefore, we also examined BMD over 24 months in adolescent girls using OC containing 20 mcg ethinyl estradiol, the lowest amount of estrogen currently available in the U.S. Our hypothesis was that the gain in BMD among OC users receiving this level of exogenous estrogen would be significantly lower than in the untreated group.

MATERIALS and METHODS

Postmenarcheal girls, ranging in age from 12 to 18 years, were recruited from four general adolescent health clinics located in a Midwestern, metropolitan setting from May 2000 through January 2003. Adolescent girls initiating contraception with either DMPA or OC were eligible for enrollment. Girls who attended these clinics over the same time period who did not plan to receive hormonal contraception over the two year observation period were also eligible for enrollment. Exclusion criteria included use of DMPA, pregnancy, or abortion within the past six months, use of OC within the past three months, chronic medical condition or treatment that may have an effect on BMD, contraindications to use of sex hormones, or need for confidentiality in contraceptive management. The Institutional Review Boards of all participating institutions approved the study. Written, informed consent and assent were obtained from each custodial parent and study enrollee, respectively.

At baseline, 6, 12, 18, and 24 months, clinical and behavioral information was obtained from each study participant. Clinical information was collected by direct interview and included menstrual bleeding patterns, general medical symptoms and medication use. Height and weight were measured with the same stadiometer (Easy Glide Bearing stature board) and Mettler-Toledo scale every visit. Gynecologic age was calculated as the number of years since

menarche. Tobacco use was reported as current use or nonuse. Calcium intake was elicited with a focused 24-hour dietary recall combined with the Calcium Rapid Assessment Method (7). Girls who consumed <1300 mg/day dietary calcium were counseled by a dietician; if the level of intake did not improve after three months, the participant was given a sample of Tums 500 mg to be taken once daily for three months. Physical activity was assessed with a survey that asked each participant to classify herself as inactive, normal, or active.

At baseline, 6, 12,18, and 24 months, all study participants underwent measurement of BMD that included L1-L4 lumbar vertebrae, total hip (left), femoral neck, trochanter, and Ward's triangle. The measurement technique employed was dual energy x-ray absorptiometry (DXA) with the model QDR 4500W fan-beam densitometer (Hologic Inc., Bedford, MA). Windows 11.2 was the software, which included a low-density measurement option. In vivo intra-individual coefficients of variation were 1.2% at the spine and 1.4% at the femoral neck; inter-individual coefficients of variation were 1.3% at the spine and 2.2% at the femoral neck. All scans were obtained within four weeks of the scheduled six month intervals.

Because longitudinal growth typically does not conclude until late adolescence, we anticipated that skeletal size may change in our study participants over the observation period. As bones grow in width and length, bone thickness increases; increased bone thickness may falsely appear as increased bone density. Therefore, BMD was calculated by amount of scanned bone mineral content (BMC) within a projected area (Ap), termed areal density, and was expressed as g/cm^2. In order to correct for volumetric variations in bone, we performed an additional calculation to express bone mineral apparent density (BMAD), utilizing the following formula: spine BMAD = BMC (L_1-L_4) ÷ $Ap^{3/2}$ and femoral neck BMAD= BMC (femoral neck) ÷ Ap^2 (femoral neck) (8).

DMPA was administered every twelve weeks as a 150 mg deep intramuscular injection (gluteus or deltoids). Girls in the OC group received an OC containing 20 mcg ethinyl estradiol and 100 mcg levonorgestrel. This particular pill was chosen because it contains the lowest dose of estrogen currently available in the U.S. Compliance with DMPA injections was assessed by chart review and was calculated as number of injections divided by number of prescribed injections (total of nine injections over 24 months) x 100. Compliance rates with OC use was assessed by monthly self-report and calculated as the number of pills taken divided by the number of pills prescribed (1 pill every day from date of initiation for 24 months) x 100. Participants who elected to change contraceptive methods during the study were withdrawn.

Baseline characteristics and incidences of extreme bone loss were compared between groups with chi-square tests or Fisher exact tests for the categorical variables and analysis of variance or Kruskal-Wallis tests for the continuous variables. The association of changes in both BMD and bone mineral apparent density over time was assessed in two ways. First, repeated measures analysis of covariance (ANCOVA) was used, where the time of the visit (baseline, 6, 12, 18, and 24 months) was used as a factor in the model. ANCOVA was also utilized to examine the annual percentage change, where the time factor was incorporated into the endpoint by calculating a percentage change in BMD or bone mineral apparent density from baseline to 24 months. Prior to modeling, the distributional properties of continuous variables were examined for possible departures from normality. Multi-colinearity of predictors was also examined. The high correlation between chronological age and gynecologic age (Spearman correlation rho = 0.69, $p<.001$, $n = 370$), and between body weight and body mass index (rho = .94, $p<.001$, $n = 370$) led to the decision to use only chronological age and body weight in the multivariate models to reflect a consistent approach from a previous analysis (3).

Because three baseline characteristics, i.e., chronological age, body weight, and race are powerful predictors of BMD (2), they were treated as confounding variables and were included

in all models, whether statistically significant or not. Regarding physical activity and tobacco use, these variables were also significantly related to BMD, and, were, along with baseline bone density values, included in the models. Within each of the models, post-hoc pair-wise comparisons were done using Tukey's adjustment for multiple comparisons. Final results were considered statistically significant at the <0.025 level because of the previous interim analysis (3). All analyses were conducted with the use of SAS version 8.2.

RESULTS

Table 1 presents baseline data for the study population which comprised 433 adolescent girls who selected either DMPA (n = 58) or OCs (n = 187), or represented the untreated comparison group (n = 188). The untreated group was significantly younger, reported a more active lifestyle as well as lower prevalence of tobacco use than the two contraceptive groups. The OC group had significantly higher body weight and higher spine and femoral neck BMD than the other two groups at baseline. No statistically significant differences were identified among the groups regarding racial background, height, body mass index, menstrual history and serum vitamin D levels. Group compliance with DMPA injections was 99.4% (95% CI 98.2%–100%); group compliance with OCs was 86.3% (95% CI 86.26%–86.34%).

A total of 184 girls completed their 24 month study visit as follows by group: DMPA (n = 27, 46.5%), OC (n = 62, 33%) and untreated group (n = 95, 51%). The major reasons for attrition were appointment noncompliance (30%) or discontinuation of the method (25%). No statistically significant differences were found in baseline characteristics between these study participants and those who completed their 24 month observation. Table 2 presents lumbar spine and femoral neck bone mineral density in mean absolute values at baseline, 12, and 24 months, along with percent change values from baseline to 24 months.

Over the first 12 months, the mean percent changes in BMD were at the spine: DMPA −1.4% (95% CI −2.73, −0.10); OC +2.3% (95% CI +1.49, +3.18); untreated +3.8% (95% CI +3.11, +4.57). At the femoral neck, the mean percent changes were: DMPA −2.2% (95% CI −3.95, −0.39); OC +0.3% (95% CI – 0.87, +1.41); untreated +2.3% (95% CI +1.29, +3.27). The majority decrease in BMD of the spine occurred in the first year: 12 months −1.4%; 12–24 months −0.1%. However, at the femoral neck, there was accelerated loss in the second year: −2.2% 12 months; 12–24 months −3.0%. At 24 months, the mean BMD values were significantly lower in the DMPA group than in the OC group at both lumbar spine ($p < .001$) and femoral neck BMD ($p < .001$) and significantly lower in the DMPA group than in the untreated group at both lumbar spine ($p < .001$) and femoral neck BMD ($p = .003$). Percent change (depicted also in Table 2) in BMD at the lumbar spine over 24 months was – 1.5% in the DMPA group, + 4.2% in the OC group and +6.3% in the untreated group. Post-hoc testing revealed statistical significance between the DMPA versus the OC group ($p < .001$) and DMPA versus the untreated group ($p <.001$). At the femoral neck, percent change in BMD over 24 months was –5.2% in the DMPA group, +3.0% in the OC group and +3.8% in the untreated group. Post-hoc testing revealed statistical significance for the DMPA group versus the OC group ($p <.001$) and the DMPA group versus the untreated group ($p <.001$).

BMD results were recalculated correcting for possible volumetric changes in bone and were expressed as bone mineral apparent density (data not shown). The mean absolute value in bone mineral apparent density at the lumbar spine was significantly lower in the DMPA group than in either the OC group ($p = .002$) or the untreated group ($p <.001$). The percentage change decreased in the DMPA group compared with increases in the OC ($p = .007$) and untreated groups ($p < .001$). One comparison between the OC group and untreated group reached marginal statistical significance: bone mineral apparent density at the lumbar spine was lower in mean absolute value among the OC users than among the untreated group ($p = .03$). At the

femoral neck, the only statistical difference in bone mineral apparent density at the femoral neck was in absolute value (p=.02) between the DMPA and the OC group.

Seven of 21 (33%) DMPA users who completed the study had a greater than 5% loss in BMD of the lumbar spine from baseline to any follow-up measurement over 24 months, compared with only one of the OC users (2%) and none in the untreated group ($p < .001$). Moreover, none of the DMPA users gained more than 5% bone density versus 5 (10%) of the oral contraceptive users and 48 (57%) of controls ($p < .001$). Of note is that none of the participants who lost >5% BMD during the observation period reached the level of BMD defined as osteopenia (defined here as a lumber spine BMD of more than 2 standard deviations below the mean of the entire group at baseline). A detailed description of salient attributes in the study participants who lost >5% bone density is listed in Table 3. No statistically significant differences were found in demographic background, anthropometry, or clinical characteristics in this group versus those participants who either lost less than 5% or who gained BMD over the same observation period.

We examined potential clinical correlates of osteopenia of study participants who, at any measurement point, fulfilled this criterion for osteopenia, as described in Table 4. One girl in the DMPA group, no girl in the OC group, and four in the untreated group at some point during the observation period had BMD values reach into the osteopenic range. In comparison to those who had BMD values above the mean for the entire cohort at baseline, these participants had significantly lower body weight, body mass index, and younger gynecologic age.

DISCUSSION

In this observational study, adolescent girls who received DMPA contraceptive injections for 24 months experienced a significant decrease in BMD at both the lumbar spine and femoral neck (−1.5%, −5.2% respectively) compared to concurrent increases in the OC and untreated groups. The data on bone loss with DMPA are consistent with previous longitudinal studies of adolescent DMPA users that decreased an average of −3.1% (range −1.5 to −6.0%) at the lumber spine for up to two years (9–13).

With our data, combining the percent loss in BMD in the DMPA users with percent gain in the untreated group resulted in a discrepancy of 7.8%. As previous statistical analysis has yielded a clinically significant increased risk for fracture with a discrepancy of 7% among postmenopausal women (14), our observed magnitude of difference in BMD among adolescent DMPA users, if irreversible, may increase eventual risk for fractures. No studies to date have evaluated DMPA use and fracture risk in adolescent girls. However, in premenopausal adult women, two studies reported no difference in bone density in past DMPA users versus never-users (15–16). The inference from these data would be no increased risk for fracture in adult women who had used DMPA at a younger age. Other findings in our study underscore the concern regarding protection of bone in the adolescent girl who is using DMPA. For example, whereas none of the DMPA users experienced at least a 5% gain in bone density, almost 60% of the controls did. In summary, some of our data lend support to the recent FDA warning that use of DMPA may interfere with achievement of optimal peak bone mass in the adolescent.

One reassuring finding in our study was the low number of girls in either contraceptive group who reached a clinically significant level of osteopenia during the observation period. Thus, it is unlikely that a healthy adolescent would reach a level of osteopenia that would incur increased current risk for fracture exposed to hormonal contraception during a two-year duration. A second reassuring finding was that the loss in BMD at the spine in the DMPA users did not seem to increase between 12 and 24 months (−0.1%) beyond that seen from 0 to 12 months (−1.4%). Providing further support for decreasing degree of loss in bone density over

time with use of DMPA, Scholes et al, found that prevalent users of DMPA had less bone loss than those who were recent new users of DMPA (13).

Given the convincing evidence for loss of BMD in the adolescent receiving DMPA and the potential ill effect in the future, a crucial question for the clinician is what to do on behalf of the adolescent requesting or using DMPA in the present. First, it must be stated that DMPA contraception is a very highly effective method that obviates the need for use of insertable spermicidal jelly, foam or sponge, or for remembering to take a pill every day or attach a patch once a week (17). For example, we had a 15% pregnancy rate in our adolescent oral contraceptive users compared to 0% in our DMPA users. Thus, with its very high efficacy and low need for patient involvement for that efficacy, DMPA would seem to be an ideal contraceptive for this age group (18).

Second, although data are sparse, the scant literature that does exist suggests that pregnancy has a negative impact on an adolescent's bone mass (19). This impact probably derives from the sacrifice of mother's bone calcium to the large calcium needs of the fetus, especially given the typically low levels of calcium dietary intake in this patient population (20). Third, the few data available indicate at least partial recovery of the bone loss after discontinuation of DMPA (13,21). Thus, a cautionary note is recommended in a clinician's decision to stop prescription of DMPA for an adolescent in need of a highly effective contraceptive (22).

We did not determine any clinical predictors of bone loss that would help guide the provider in deciding when to proceed with or when to discontinue DMPA in the adolescent; however, we did find that low body weight and low body mass index were associated with osteopenia. Previous research also indicates that genetic predisposition to osteopenia, certain chronic health conditions and medications and physical immobility predispose to low bone density (23). Although a clinician may consider obtaining DXA testing in an adolescent with these risk factors prior to initiating DMPA, there is no indication to obtain DXA testing before or during DMPA use in the healthy adolescent (22). Each decision must be made balancing the overall risks and benefits of using DMPA over time and discussed fully with the patient (and her parent, given no issues of confidentiality) (24). Anticipatory guidance for every adolescent receiving DMPA should also include advice on boosting calcium dietary intake and regular physical exercise.

Our results showed marginal statistical significance between the OC group and the untreated group in bone mineral apparent density at the lumbar spine. This is in contrast to significant findings in BMD at both spine and femoral neck from the statistical analysis conducted after 12 months observation (3). Power analysis indicates that given our results, we would have needed an increase of 60 subjects to confer statistical significance. The important question that arises from our study is whether the amount of estrogen in some of the currently available OC is sufficient to promote optimal skeletal development in the very young woman. Previous research indicates that it may not be sufficient (25). As the estrogen in an OC essentially supplants estrogen produced by the ovary, further research should be directed toward establishing that optimal dose for bone accrual in the adolescent who is treated with OC.

Our study had potential sources of bias. As with all observational studies, confounding influences on BMD may be unevenly distributed among the treatment groups as was the case in our study with attributes such as body weight. However, we adjusted our findings for those attributes that were significantly related to BMD, thus minimizing their influence on the results. In addition, we had a high attrition rate, especially in the OC group. As there were no differences identified between those who finished and did not finish the study, we do not think this was a significant source of bias.

In conclusion, we found statistically significant decreases in spinal and femoral neck BMD in adolescent DMPA users over 24 months, when compared with increases in BMD in controls. These data support the focus of the recent “black box” warning by the FDA regarding bone loss in adolescents using DMPA. However, the amount of loss does not confer clinically significant osteopenia and the bone loss appears to slow down after one year of use. The presence of known risk factors for osteopenia, such as very low body weight and prolonged physical immobility, may prompt earlier bone density assessment and possible discontinuation of the drug. Regarding OC and bone, it is unclear whether the currently available low-dose pills, containing 20 mcg ethinyl estradiol, are adequate for bone development in the adolescent; further research is needed to define the level of exogenous estrogen required to achieve optimal bone mass accrual during this important period of skeletal growth. Finally, the risks of these two contraceptive methods to bone need to be balanced against the expected adverse effects on bone resulting from pregnancy at this age. Patient and parent education and treatment should be individualized to ensure effective contraception while maximizing bone development during adolescence.

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Table 1

Baseline descriptive data of study participants.

Characteristics		Untreated (n=188)	DMPA (n=58)	OC (n=187)	P-Value
Chronological Age (yrs)		14.8 ± 1.9	15.8 ± 1.6	16.0 ± 1.4	<.001
Gynecologic Age (yrs)		2.7 ± 1.8	3.9 ± 1.8	4.0 ± 1.7	<.001
Race, n (% black)		119 (63)	37 (64)	114 (61)	.87
Body Weight (kg)		63.5 ± 16.5	60.5 ± 12.8	68.9 ± 17.1	<.001
Height in (cm)		160.2 ± 9.7	161.7 ± 6.9	161.7 ± 6.6	.15
Body Mass Index		25.8 ± 9.6	23.0 ± 4.1	26.3 ± 6.2	.27
Spine BMD		0.98 ± 0.11	0.98 ± 0.09	1.03 ± 0.11	<.001
Femoral Neck BMD		0.92 ± 0.15	0.92 ± 0.14	0.97 ± 0.14	.007
Vitamin D (IU/d)		53.5 ± 36.5	66.0 ± 24.7	59.3 ± 33.9	.61
Regular Menses, n (%)		167 (89)	45 (78)	149 (80)	.03
Smoker, n (%)		10 (8)	14 (33)	37 (29)	<.001
Physical Activity n(%)	Active	99 (53)	78 (42)	22 (38)	.009
	Normal	66 (35)	12 (6)	7 (12)	
	Inactive	23 (12)	97 (52)	29 (50)	

All numbers represent mean ± SD except race, regular menses, smoker and physical activity which are reported as counts and percents.

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Table 2

Absolute and percent change in bone mineral density (BMD) at L1-L4 spine and femoral neck. DMPA=depot medroxyprogesterone acetate, OC=oral contraceptive (20 mcg ethinyl estradiol + 0.1mg levonorgestrel).

Endpoint	Time	Adjusted Group Mean(SE)*			P-Values
		Untreated	DMPA	OC	
Spine-Absolute Values g/cm^2	0	0.98(0.007)	0.97(0.013)	1.01(0.007)	
	6	1.00(0.007)	0.96(0.013)	1.02(0.007)	DMPA vs. OC (p=.005)
	12	1.02(0.008)	0.95(0.013)	1.03(0.008)	DMPA vs. OC (p<.001), DMPA vs. Control (p=.003)
	18	1.03(0.008)	0.95(0.013)	1.03(0.008)	DMPA vs. OC (p<.001), DMPA vs. Control (p<.001)
	24	1.04(0.008)	0.94(0.014)	1.03(0.008)	DMPA vs. OC (p<.001), DMPA vs. Control (p<.001)
					Significant Increase in Controls (p<.001)
					Significant Increase in OCs (p<.001)
Spine-%Change (0–24 mos.)	-	6.3% (0.53%)	−1.5% (1.01%)	4.2% (0.70%)	DMPA vs. OC (p<.001), DMPA vs. Control (p<.001),
Femoral Neck-Absolute Values g/cm^2	0	0.92(0.010)	0.92(0.017)	0.96(0.010)	
	6	0.93(0.010)	0.90(0.017)	0.96(0.010)	
	12	0.94(0.011)	0.90(0.018)	0.96(0.011)	
	18	0.95(0.011)	0.86(0.019)	0.97(0.011)	DMPA vs. OC (p<.001)
	24	0.96(0.012)	0.86(0.020)	0.97(0.012)	DMPA vs. OC (p<.001), DMPA vs. Control (p=.003)
					Significant Increase in Controls (p=.006)
					Significant Decrease in DMPAs (p<.001)
Femoral Neck-%Change (0–24 mos.)	-	3.8% (0.80%)	−5.2% (1.57%)	3.0% (1.02%)	DMPA vs. OC (p<.001), DMPA vs. Control (p<.001)

*Values adjusted for age, race, body weight, tobacco use, physical activity and baseline BMD.

Table 3

Description of study participants who lost more than 5% BMD at lumbar spine from baseline to any measurement interval over 24 months. (Characteristics measured at baseline except change in body mass index (BMI) and amenorrhea both measured from baseline to last observation.)

Subject	Contraceptive Group	Chronological Age (yrs)	Gynecologic Age (yrs)	Race	Body Weight (kg)	BMI	Menstrual History	Level of Physical Activity	Change in BMI (%)	# Months to Amenorrhea
1	DMPA	14.6	3.4	Black	61	21.4	Irregular	Active	3.3	10
2	DMPA	15.6	3.4	Black	59	21.7	Irregular	Normal	5.1	9
3	DMPA	15.2	2.2	Black	72	26.4	Regular	Inactive	37.1	7
4	DMPA	14.7	4.3	White	46	19.1	Regular	Normal	−6.6	0
5	DMPA	18.5	3.8	Black	53	19.5	Irregular	Active	4.4	1
6	DMPA	15.5	4.1	White	61	25.1	Regular	Normal	−1.9	3
7	DMPA	15.0	5.0	Black	85	31.2	Regular	Active	19.1	3
8	OC	15.5	2.4	Black	105	40.0	Irregular	Active	8.0	-

Table 4

Description of study participants who, at any measurement point over 24 months, had lumbar spine BMD values greater than 2 SD below the mean values of the entire group at baseline 15. (Characteristics measured at baseline except change in body mass index (BMI) measured from baseline to last observation.)

Subject	Treatment Group	Chronological Age (yrs)	Gynecologic Age (yrs)*	Race	Body Weight (kg)*	BMI*	Menstrual History	Level of Physical Activity	Change in BMI (%)
1	untreated	14.9	0.07	White	51	21	Regular	Active	3.2
2	untreated	14.8	0.73	White	42	17	Regular	Active	5.8
3	untreated	16.5	0.56	White	44	16	Irregular	Normal	9.1
4	untreated	13.0	0.28	Black	45	19	Regular	Active	5.4
5	DMPA	15.7	4.00	White	58	25	Regular	Normal	−7.6

*p < .01 for group means in comparison with those in the rest of the study sample with bone density values above the mean at baseline.

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