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Characteristics Associated with Bone Mineral Density Responses to Alendronate in Men

Erik D. Swenson¹, Karen E. Hansen², Andrea N. Jones², Zhanhai Li³, Brooke Baltz⁴, Arthur A. Schuna⁵, and Mary E. Elliott^{5,6}

¹Mercy Arthritis and Osteoporosis Center, Urbandale, IA 50322

²University of Wisconsin School of Medicine and Public Health

³University of Wisconsin Department of Biostatistics and Medical Informatics

⁴Northwestern Memorial Hospital, Chicago, IL 60611

⁵William S. Middleton Veterans Affairs Medical Center

⁶University of Wisconsin School of Pharmacy

Abstract

Background—Some patients experience reduced bone mineral density (BMD) despite bisphosphonate therapy. We performed a retrospective chart review study to detect factors associated with decreased BMD in men prescribed alendronate.

Methods—Two investigators reviewed eligible medical records and used a standardized form to record potential characteristics predicting men's response to alendronate. We analyzed patient characteristics associated with annualized change in hip and spine BMD (D-BMD).

Results—Among 115 eligible men, 19 (17%) experienced significantly decreased BMD at the hip or spine, defined as a change exceeding precision error. Eleven men (10%) fractured during therapy. Spine D-BMD was positively associated with adherence to alendronate ($R = 0.23$, $p=0.02$) and inversely associated with baseline body weight ($R = -0.21$, $p=0.03$). Hip D-BMD was positively associated with annualized weight change ($R = 0.19$, $p=0.0498$) and negatively associated with patient age and number of concomitant medications ($R = -0.21$, $p=0.03$; $R = -0.20$, $p = 0.03$, respectively). In stepwise linear models, spine D-BMD was positively associated with alendronate adherence and multivitamin use, and negatively with baseline body weight. Hip D-BMD was negatively associated with age. Fracture during treatment was associated with fracture prior to therapy ($p=0.03$)

Conclusions—In this small study of men prescribed alendronate, BMD response showed a positive association with adherence to therapy, weight gain, and use of a multivitamin. By contrast, older age, higher baseline body weight, and higher number of medications were each

associated with a decrease in BMD. Larger studies are needed to confirm and extend these findings.

Keywords

adherence; efficacy; men; osteoporosis; treatment

Introduction

An estimated two million men in the United States have osteoporosis. Men face a 20% lifetime risk of osteoporotic fracture and account for one third of older adults with hip fracture [1,2]. Evaluation and treatment of men with osteoporosis in clinical practice can be challenging and is often overlooked, even after fragility fracture [2,3].

For men with osteoporosis, providers commonly prescribe oral bisphosphonates, most often alendronate. In addition to alendronate's efficacy, safety, and cost effectiveness [4–7], a drug holiday is possible [8]. However, some patients experience a loss in bone mineral density (BMD) or a new fracture despite alendronate therapy. Indeed, a significant loss in BMD despite oral bisphosphonate prescription is a frequent reason for a new patient referral to our tertiary care osteoporosis clinic (KEH) or veterans' osteoporosis clinic (MEE).

Non-response to therapy is defined differently, depending on context. When analyzing large databases, persons who lose any amount of BMD while on therapy might be classified as nonresponders. In clinical practice, however, nonresponders are defined as those patients who experience a new fracture or significantly reduced BMD on therapy, defined as a loss greater than the precision error for measurement at that clinical center. Composite phase III clinical trials data indicate that 9% to 30% of postmenopausal women experience decreased spine or hip BMD within two years of starting alendronate [9]. Women with BMD loss are more likely to suffer incident fracture compared to patients with stable [10] or increased [9] BMD. Factors associated with poor BMD response in clinical trials of postmenopausal women include early age at menopause, family history of osteoporosis, higher baseline trochanteric BMD [11] and smaller short-term changes in markers of bone turnover after treatment is started [12]. In one randomized clinical trial of alendronate in men (n=261), BMD responses were independent of age, smoking status, free testosterone or estradiol levels, prior vertebral fracture, or T-score [13].

Similar to women, some men receiving bisphosphonates for osteoporosis suffer a significant reduction in BMD, and are thus less likely to benefit from treatment. Men with risk factors for a "poor response" might need closer monitoring in clinic, more frequent bone mineral density studies, or more intensive anabolic therapy to adequately treat their osteoporosis. We hypothesized that in men with osteoporosis, one or more patient-specific characteristics would significantly correlate with BMD responses to alendronate therapy. We used an existing Veterans' Affairs database to investigate patient variables associated with a reduction in spine and hip bone mass.

Methods

Identification of subjects and eligibility criteria

We used VA Pharmacy Service records to identify all male veterans 50 years old who received their first prescription for alendronate (Fosamax®) between July 2000 and May 2004. We excluded men receiving alendronate for Paget disease or glucocorticoid-induced osteoporosis, receipt of other bisphosphonates before initial alendronate therapy, receipt of primary care elsewhere and death or nursing home admission within two years of beginning alendronate. We further excluded men who did not have two DXA scans bracketing therapy and men for whom there was an extended gap (≥ 12 months) between baseline DXA and onset of alendronate. We also excluded men with less than 6 months or more than 36 months between alendronate onset and follow up DXA. The University of Wisconsin Human Subjects and William S. Middleton Veterans Affairs Research and Development Committees approved the study and waived written consent from subjects.

Chart review and data collection

Two investigators separately reviewed each subject's medical record using the Veterans Affairs Computerized Patient Record System and recorded patient characteristics using a standardized chart review form. Discrepancies in data obtained from chart review were resolved by a third inspection of the medical record. For each veteran, we recorded the number of medications taken when alendronate was initiated, including calcium, vitamin D and multivitamin prescriptions. We noted whether a co-payment (\$8 per month per prescription except for POW's or combat-injured veterans) was required for alendronate. We calculated adherence using a modification of the medication possession ratio, which we defined as the number of actual alendronate fills divided by the number of potential fills over the study interval [14]. Subjects were defined as adherent if their medication possession ratio was ≥ 80%, a threshold commonly used in other studies of adherence to medications including bisphosphonates [14]. We recorded bone mineral density (BMD) measurements (g/cm^2) and corresponding T-scores obtained at the L1–L4 spine and total proximal femur before and after initiation of alendronate. At the time of each bone density test, a radiology technician recorded height and weight using a wall-mounted stadiometer and balance beam scale. A single radiology technician performed all measurements of height and weight at the time of the BMD test. All BMD measurements were performed by the same technician using the same densitometer and were interpreted by a single physician.

Statistical Analysis

We calculated changes in BMD between DXAs bracketing alendronate use for lumbar spine and hip. We then calculated annualized change in BMD using the total change in BMD and the time between DXA scans. Such changes are subsequently referred to as spine D-BMD or hip D-BMD. Change in BMD at a skeletal site was considered significant if it exceeded the least significant change for that site for the densitometer used [15]. The least significant changes (precision errors) for BMD at the VA Medical Center at the time of the study were 0.053 (0.019) g/cm^2 for the lumbar spine and 0.027 (0.010) g/cm^2 for the total hip. We conducted all analyses of data using R version 2.13.11 [16].

We used three approaches to assess characteristics associated with change in BMD. For continuous variables, we calculated the Pearson correlation coefficient between the characteristic and the annualized change in BMD at a given site [17]. For all variables, we compared the characteristics of subjects with any decrease in BMD ($D-BMD < 0$) at a given site to those with stable or increased BMD at that site. We also compared the characteristics of subjects with an increase or decrease in BMD that exceeded the precision error at that site to subjects without a significant change in BMD. For proportions, 95% confidence intervals (95% CI's) were calculated using the small sample approximation for binomial variables [17].

We used univariate correlation analysis and stepwise linear models in predicting changes in annualized bone mineral density as a function of demographic, medication-related, and osteoporosis variables. Demographic variables included subjects' age, race (white or other), current tobacco use (yes/no), current alcohol use (yes/no), and subjects' baseline, final, and annualized change in height, weight, and body mass index. Medication variables included adherence to alendronate, co-pay requirement, number of concomitant medications, and prescription of calcium, vitamin D and multivitamins through the VA Medical Center. Osteoporosis variables included presence of a fracture before or during alendronate therapy and baseline BMD. In this analysis, variables were considered statistically significant if the p value for their beta coefficient was < 0.05 [17]. In constructing a model for annualized changes in BMD, the partial F test was used, and a variable was considered to add significantly to the model if the partial regression coefficient had a p value < 0.05 . We used one-way analysis of variance and Student's two-sided t-test to determine the relationship between annualized changes in bone density and categorical variables [17].

Results

Figure 1 summarizes our sequential approach to identify 115 men for study inclusion. The pharmacy identified 1283 veterans who had received alendronate from July 2000 to May 2004. From this group, we excluded 530 veterans based on gender, use of glucocorticoids and use of another bisphosphonate prior to alendronate. An additional 392 veterans were excluded due to age < 50 years, receipt of primary care elsewhere, death or nursing home admission. Receipt of alendronate for indications other than low bone mass and onset of alendronate outside the stipulated dates prompted exclusion of an additional 163 veterans. We excluded another 83 men due to lack of paired bone density studies bracketing alendronate therapy. The remaining 115 veterans met all eligibility criteria allowing study inclusion.

Subjects' mean (SD) age was 69 (9) years and mean (SD) body weight was 80 (15.7) kg (Table 1). Mean (SD) number of medications was 9 (5). Fifty-nine percent of subjects had a clinical fracture before beginning alendronate therapy. Forty-one percent of men had osteoporosis based on a T score -2.5 at the spine or hip. Eighty-five men (74%) had osteoporosis by DXA, a baseline fracture, or both. During the study interval, 73 of the 115 men (63%, 95% CI 54%, 72%) were adherent to therapy based on a medication possession ratio 80%. All subjects received brand name Fosamax® throughout the study interval.

Subjects' mean interval between bone density tests was 1.6 years (SD 0.6, median 1.4, range 0.6 to 3.2 years). Hardware or technical issues precluded the ability to collect paired BMD tests for 1 and 2 men for the spine and hip, respectively. Thus, 114 men had paired spine BMD values and 113 had paired hip BMD values. Based on precision errors for BMD measurement, 76 subjects (66%) experienced significantly increased BMD at the spine (n=38, 33%), hip (n=13, 11%), or at both sites (n=25, 22%). Mean (SD) annualized percent changes in BMD (D-BMD) at the lumbar spine and total hip were 4.2% (5.0%) and 0.8% (2.9%), respectively. Baseline spine and hip BMD were each significantly associated with baseline body weight ($R = 0.30$, $p = 0.001$ and $R = 0.27$, $p = 0.004$, respectively). Any loss in bone density at the lumbar spine and/or hip occurred in 53 (46%) of men. This included 30 (26%) of men who lost only hip BMD, 10 (9%) who lost only spine BMD, and 13 (11%) with loss at both spine and hip. Based on precision errors for BMD measurement, significant reduction in BMD between subsequent DXAs at the spine, hip, or both sites were seen for two, 15, and two men respectively, a total of 19 subjects (17%). Nine of the 19 veterans with significant loss in BMD in fact showed significant loss over one year. Eleven subjects (10%) experienced a fracture during therapy. Figure 2 depicts the number of responders (no significant bone loss and no fracture on therapy) and non-responders, who are further characterized.

Characteristics associated with Spine D-BMD

The primary factor associated with spine D-BMD was adherence to alendronate. We found a significant correlation between adherence and D-BMD ($R = 0.23$, $p = 0.02$, Table 2). Similarly, spine D-BMD was significantly higher for men who were adherent to therapy (medication possession ratio = 80%) compared to non-adherent men ($p = 0.02$, Figure 3). We found an inverse association between baseline body weight and change in spine BMD ($R = -0.21$, $p = 0.03$, Table 2). Race, age, number of concomitant medications, required co-pay for alendronate, fracture before or during alendronate therapy, and use of tobacco, calcium and vitamin D were not associated with changes in spine BMD in univariate analyses. In stepwise linear models, spine D-BMD was positively associated with alendronate adherence ($p = 0.02$) and multivitamin use ($p = 0.04$), and negatively associated with baseline body weight ($p = 0.046$) (Table 3). Subjects who experienced any loss in spine BMD were significantly less likely to be prescribed multivitamins, compared to those with stable or increased spine BMD (multivitamin prescription in 52% versus 79% respectively, $p = 0.009$). Baseline body weight and multivitamin use each improved a spine D-BMD model based on adherence.

Characteristics associated with Hip D-BMD

Three factors were significantly associated with hip D-BMD. Age was inversely correlated to change in hip BMD ($R = -0.21$, $p = 0.03$, Table 2). Hip D-BMD was significantly lower among men within the oldest age group (75 years or older), compared to men in the youngest age group, age 50–64 ($p = 0.02$, Figure 4). The annualized change in body weight was positively associated with change in hip BMD ($R = 0.19$, $p = 0.0498$, Table 2). Finally, the number of concomitant medications was inversely associated with change in hip BMD ($R = -0.20$, $p = 0.03$). Adherence correlated with change in hip BMD, though the p -value did not

reach significance ($R=0.17$, $p=0.07$). Adherence was higher in subjects with stable or increased hip BMD compared to subjects with any loss in hip BMD (medication possession ratio 87% versus 72%, $p=0.01$). Race, required co-pay for alendronate, fracture before or during alendronate therapy, and use of tobacco, calcium, vitamin D and multivitamins were not associated with changes in hip BMD. Compared to subjects who experienced either a significant decrease in hip BMD or fractured on therapy, those who did not fracture or lose significant hip BMD were marginally more likely to use vitamin D supplements ($p=0.071$, odds ratio 2.43, 95% CI 0.84, 6.90).

In stepwise linear models, age was a significant negative predictor ($p=0.01$) of hip D-BMD and adherence was marginally and positively predictive ($p=0.07$). Age, baseline body weight, annualized weight change, and number of medications each improved a hip D-BMD model based on adherence.

Discussion

Little is known about men's BMD response to alendronate in clinical practice. In one study of 41 men receiving alendronate in a clinical practice setting, any decrease in spine or hip BMD occurred in 10% and 24%, respectively [18], in comparison to 20% and 38% in our study. Veterans' mean spine D-BMD was 4.2%, similar to a reported one-year increase of 4.2% [19]. With a mean baseline spine BMD of 1.072g/cm^2 , two-thirds of veterans had 3% (0.032g/cm^2) improvement between DXAs (mean 1.6 year interval) compared to 87% with 3% gain over two years [5]. In veterans, mean hip D-BMD was 0.8% compared to a reported one year increase of 1.6% [18]. With a mean baseline hip BMD of 0.836g/cm^2 , 35% of veterans had 3% (0.025g/cm^2) improvement between DXAs compared to 63% of men with 3% increase in hip BMD over three years [6].

To our knowledge, ours is the first report linking men's characteristics with BMD response to alendronate. Adherence associated positively with hip and spine D-BMD, weight gain associated positively with hip D-BMD, and multivitamin use associated positively with spine D-BMD. Baseline body weight inversely associated with spine D-BMD, whereas age and number of medications associated inversely with hip D-BMD. Age, baseline body weight, annualized weight change, number of medications, and multivitamin use each significantly improved models based on adherence for spine D-BMD, hip D-BMD, or both.

Although women's BMD response to therapy was positively linked to adherence [9], ours is the first such report in men. This linkage underscores the importance of assessing and improving adherence in men, although it is unknown whether strategies recommended for women (communication with the patient, monitoring by BMD, and consultation with a nurse) [21] could be helpful in men.

Veterans' baseline body weight associated positively with initial hip and spine bone mineral density. Unexpectedly, veterans' baseline body weight inversely associated with spine D-BMD. In untreated older men [22,23] and women [24], baseline body weight positively correlated with BMD change, with thinner persons losing more BMD. However, BMD loss in thinner patients appears to be mitigated by alendronate treatment. Hip and spine BMD

responses in women randomized to alendronate (n=403) did not vary by baseline body weight, although in placebo subjects (n=417) BMD loss was associated with low body weight [24]. In the veterans, it is uncertain why BMD response to alendronate was negatively associated with baseline weight.

For the first time, we report that weight change in men receiving alendronate was positively associated with hip D-BMD. Decreased BMD accompanying weight loss has been seen in untreated men and women [22,25,26]. Consideration of weight loss is essential in assessment of the osteoporotic patient, and our work emphasizes the importance of maintaining a healthy weight during therapy. Contributors to weight loss in elderly patients include cancer chemotherapy, comorbidities, cognitive deficits, low income, poor nutrition, dysphagia, and edentulous status. Interventions to maintain weight in such patients might improve their response to antiresorptive therapy.

Age was negatively associated with change in hip BMD in the veterans ($p=0.027$), but was not associated with BMD response to alendronate in clinical trials of men [5] or women [28,29]. Age may be a surrogate for greater comorbidities, increased medication use or lower adherence, characteristics more common in clinical practice than in clinical trials. Regardless of the reason for the association, the clinician may be wise to provide close monitoring for the very elderly patient with osteoporosis.

Multivitamin use was associated with improved spine BMD. This association might relate to vitamin D content of VA multivitamins (400 International Units per tablet). Vitamin D status was positively linked to BMD response to bisphosphonates in some [30,31] but not all [32] studies. Multivitamin use could indicate a healthier lifestyle, as improved diet and physical activity have been associated with supplement intake [33]. The multivitamin link noted here could also be associated with vitamins B6, B12, or C, as these were associated with improved BMD in untreated persons [34–36].

Association between the number of medications and BMD response to therapy in men has not been reported. Number of medications may be a surrogate marker for worse health status, which could in turn contribute to bone loss.

This small study in veterans indicates that in men treated with alendronate for osteoporosis, that low adherence, advanced age, use of many medications, and weight loss may be associated with a poor BMD response to therapy. Identifying patients with these characteristics may help improve response through optimizing adherence and remedying secondary causes. Measurement of BMD after one year of therapy, rather than every two years as covered by Medicare, may be prudent for selected patients. Nine of the 19 veterans with significant loss in BMD in fact showed significant loss over one year.

Our study has limitations. An important limitation is the lack of a control group of veterans with serial bone density tests without concomitant bisphosphonate treatment. Thus we cannot rule out the influences of age, baseline weight, weight change, medications, or other factors separately from alendronate's effect. Such a control was not possible, as serial DXA measurements are rarely performed for untreated veterans. Adherence was based on the medication possession ratio rather than pill counts. Our small sample size limited the power

to examine relationships between patient characteristics and bone density responses. Intervals between DXAs were not standardized, as they were ordered by individual clinicians. Our study of veterans at one institution and exclusion of those with glucocorticoid-induced osteoporosis limits its generalizability. Tobacco use was reported as dichotomous rather than a continuous (quantified) variable, and insufficient data on alcohol use precluded its analysis. Finally, we did not include laboratory tests for creatinine, 25-hydroxyvitamin D, or testosterone, although hypogonadism did not alter response to alendronate therapy in men in a two year clinical trial [13].

Despite these limitations, our study has strengths. Reviewer bias was limited, as two reviewers extracted data for each subject. We included patient data that is often unavailable in insurance claims or pharmacy databases (e.g. body weight). All BMD measurements were conducted using the same instrument, technician and physician interpreter [37]. Finally, we annualized changes in bone density to control for variation in clinician decisions about intervals between BMD tests.

An important strength of our study is its sole focus on men, whose response to osteoporosis therapy is rarely investigated, although men comprise 20% of the osteoporotic population [38]. Our study is the first to report characteristics associated with men's bone density responses to alendronate therapy in a clinical practice setting, where patients are quite different from those in clinical trials including their comorbidities, medications, age, and lifestyle [39].

In summary, 17% of veterans treated with alendronate experienced clinically significant loss of BMD at the lumbar spine, total hip, or both sites. Adherence to alendronate, weight change during therapy, and multivitamin use were each significantly and positively associated with bone density response to alendronate, whereas age, baseline body weight and number of concomitant medications were negatively associated with response.

In conclusion, a significant fraction of men in a "real-world" clinical practice setting experienced a decline in BMD during oral bisphosphonate therapy, underscoring the importance of BMD testing to identify and re-evaluate such patients and their treatment. Identifying patients who do not respond to bisphosphonate therapy is essential, given their increased fracture risk compared to responders [9,10]. Patients' BMD responses may be improved by treating secondary causes, improving adherence, or switching to anabolic therapy [15,40]. Our study suggests that age, adherence to therapy, weight, number of concomitant medications and multivitamin use are potential characteristics associated with response to therapy. If confirmed in other studies, identification of such characteristics could be helpful, especially at the onset of bisphosphonate therapy. Closer monitoring of men with risk factors for a poor response could optimize response to alendronate and thus help such patients avoid fractures.

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Figure 1. Identification of Subjects

The figure depicts the selection of study subjects from an initial pool of 1283 veterans identified by the VA Pharmacy Service. We sequentially excluded potential subjects from the study based on the characteristics as noted, yielding a final pool of 115 male veterans to include in the study.

Figure 2. Number of Subjects with Site-Specific Changes in Bone Mineral Density

The figure illustrates the number of men who had stable or increased BMD at the spine and hip during alendronate treatment, with no fractures during therapy (responders). Men who experienced a clinically significant decrease (greater than the least significant change detectable) at the lumbar spine or hip, or a fracture during therapy are shown as nonresponders.

Figure 3. Relationship between Alendronate Adherence and Site-Specific Changes in Bone Mineral Density

Student's two-sided t-test was used to test for significant difference between nonadherent and adherent subjects for D-BMD at the hip and spine. Data was unavailable for some sites. The number of nonadherent subjects and adherent subjects respectively were 42 and 72 for spine, and 42 and 71 for hip.

Figure 4. Relationship between Age and Annualized Change in Hip Bone Mineral Density
One-way analysis of variance and Student's two-sided t-test were used to determine the significance of association between age and annualized changes in hip bone density

Table 1

Demographic Characteristics of 115 Male Veterans

Characteristic ¹	N (%) or mean (SD)	
Age, years	69 (9)	
Race		
Caucasian	103 (90%)	
Other	3 (2%)	
Unknown	9 (8%)	
Baseline weight, kg	80.0 (15.7)	
Baseline height, cm	172 (8)	
Baseline body mass Index, kg/m ²²	26.4 (4.5)	
Current tobacco use	42 (37%)	
Subjects with required co-pay	59 (51%)	
Number of concomitant medications	9 (5)	
Prescription of		
Calcium	96 (83%)	
Vitamin D	27 (23%)	
Multivitamin	85 (74%)	
Clinical fracture		
Prior to alendronate	68 (59%)	
During alendronate	11 (10%)	
Baseline T scores	Mean (SD)	n (%) with T score $\leq$ -2.5
Lumbar spine	-1.2 (1.6)	27 (24)
Total hip	-2.0 (0.9)	32 (28)
Either site	N/A	47 (41)

¹ Alcohol consumption data was only available for 37 subjects (32%) and was not further analyzed

² Four subjects were underweight (BMI < 18.5 kg/m²), 38 were normal (BMI 18.5 to 24.9 kg/m²), 55 were overweight (BMI 25.0 to 29.9 kg/m²), and 18 were obese (BMI $\geq$ 30 kg/m²).

Table 2Univariate Analysis of Characteristics Associated with Bone Mineral Density Response to Alendronate¹

Skeletal site	Spine		Hip	
Characteristic	Correlation Coefficient (95% CI)	p value	Correlation Coefficient (95% CI)	p value
Adherence	0.23 (0.04 to 0.39)	0.02	0.17 (-0.01 to 0.35)	0.07
Age	0.03 (-0.16 to 0.21)	0.76	-0.21 (-0.38 to -0.024)	0.03
Baseline body weight ²	-0.21 (-0.38 to -0.02)	0.03	-0.18 (-0.35 to 0.01)	0.06
Annualized weight change	0.06 (-0.13 to 0.24)	0.54	0.19 (0.0003 to 0.36)	0.0498
Number of medications	-0.05 (-0.23 to 0.14)	0.62	-0.20 (-0.37 to -0.02)	0.03

¹ In this analysis, race, annualized body mass index change, current tobacco use, co-pay requirement, use of supplemental calcium, vitamin D or multivitamin and prior fracture were not significantly related to change in BMD at hip or spine and are not shown. Adherence was defined using the medication possession ratio.

² The association of body mass index with change in spine BMD provided the same correlation coefficient (-0.021) and p value (0.03) as that of baseline body weight and change in spine BMD

Table 3

Linear Modeling of Characteristics Associated with Bone Mineral Density Response to Alendronate

Skeletal Site	Spine		Hip	
Characteristic	Beta Coefficient (standard error)	p value	Beta Coefficient (standard error)	p value
Total Adherence	0.036 (0.015)	0.02	0.013 (0.007)	0.07
Age¹	-0.00002 (0.001)	0.97	-0.00058 (0.00023)	0.01
Baseline Body Weight^{1,2}	-0.00027 (0.00013)	0.046	-0.00011 (0.00006)	0.09
Annualized weight change¹	0.0001 (0.001)	0.82	0.00041 (0.00024)	0.09
Number of medications¹	0.00003 (0.001)	0.97	-0.00078 (0.00044)	0.07
Use of Multivitamin²	0.021 (0.010)	0.04	-0.005 (0.005)	0.32

¹ Addition of variable to adherence improves the model for change in hip BMD² Addition of variable to adherence improves the model for change in spine BMD.³ In this analysis, race, co-pay requirement, use of supplemental calcium or vitamin D, or prior fracture were not significantly related to change in BMD at hip or spine and are not shown.