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The 25(OH)D Level Needed To Maintain A Favorable Bisphosphonate Response Is $\geq 33\text{ng/ml}$

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Abstract

Why only some osteoporotic patients maintain response to prolonged bisphosphonate therapy is unknown. We examined bisphosphonate response and its association with serum 25(OH)D level in a “real world” setting. Serum 25(OH)D level was strongly associated with maintaining bisphosphonate response arguing that vitamin D may be involved in optimizing prolonged bisphosphonate therapy.

Introduction: This study examined the maintenance of bisphosphonate response in the “real world” setting and the association between 25(OH)D and bisphosphonate response using an established composite definition of response.

Methods: Postmenopausal women with low bone mineral density (BMD) treated with bisphosphonates were identified from two New York City practices. Patients were excluded for a history of chronic steroid use, metabolic bone disease, or bisphosphonate non-adherence. Patients were categorized as bisphosphonate non-responders if they had a T-score < -3 that persisted between dual-energy X-ray absorptiometry (DEXA) scans, a $> 3\%$ decrease in BMD, or an incident fracture on bisphosphonate therapy, criteria based on the EUROFOR trial. Demographic and clinical data including mean 25(OH)D levels between DEXA scans were obtained. Mean 25(OH)D levels were compared between responders and nonresponders and multiple logistic regression analysis was performed to identify factors associated with non-response.

Results: A total of 210 patients were studied. A favorable response to bisphosphonate therapy was seen in 47% (N=99/210). Patients with a mean 25(OH)D $\geq 33\text{ ng/ml}$ had a ~ 4.5 -fold greater odds of a favorable response ($P < 0.0001$). 25(OH)D level was significantly associated with response—a 1 ng/ml decrease in 25(OH)D was associated with $\sim 5\%$ decrease in odds of responding (odds ratio=0.95; 95% confidence interval, 0.92–0.98; $P = 0.0006$).

Conclusions: Patients with a mean 25(OH)D $\geq 33\text{ ng/ml}$ had a substantially greater likelihood of maintaining bisphosphonate response. This threshold level of 25(OH)D is higher than that considered adequate by the Institute of Medicine, arguing that higher levels may be required for specific therapeutic outcomes.

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Conflicts of interest: None.

Keywords

Biphosphonates; Clinical response; Fracture; Osteoporosis; Vitamin D

Introduction

Osteoporosis is a major public health concern that affects millions of people. Hip fracture is associated with high morbidity, mortality, and cost [1]. Clinical trials have shown that bisphosphonates improve bone mineral density (BMD) and decrease fracture risk [2–5]. However, analyses of patients outside of the clinical trials, “real world” settings, have reported fewer patients respond to antiresorptive therapy [6,7]. Factors associated with optimal maintenance of response to bisphosphonate therapy have not been fully established.

Vitamin D deficiency can cause secondary hyperparathyroidism, muscle weakness, and osteomalacia [8–10]. A number of studies have illustrated a high prevalence of vitamin D insufficiency, especially in elderly populations including patients being treated for osteoporosis [8, 11, 12]. Elevated risk for fracture with low vitamin D levels has been reported, and risk of fracture can be reduced with appropriate vitamin D supplementation [13]. Several studies have evaluated the association between 25 hydroxy vitamin D levels (25(OH)D) and change in BMD or fracture incidence during bisphosphonate therapy [14–19]. We hypothesized that maintenance of response to bisphosphonate therapy in a real-world setting using established criteria would be associated with higher mean serum 25(OH)D levels during the study period and with a predicted cut point of 33 ng/ml [20–21].

Methods

Study population

The study was approved by the institutional review boards of Weill Cornell Medical College and the Hospital for Special Surgery (HSS). The subject population included 210 patients from two allied hospital-based practices: 160 patients from an osteoporosis specialty practice at HSS (site 1) and 50 patients from a primary care practice (site 2) Weill Cornell Internal Medicine Associates (WCIMA). Patients from both sites had undergone similar regular follow-up visits with history, physical exams, medications/supplement review along with laboratory studies (including 25(OH)D levels). The clinical care of patients at both sites was similar such that patients were recommended to take calcium and vitamin D supplementation and compliance with bisphosphonate therapy was monitored by complete medication reconciliation, treatment review and a panel of metabolic bone parameters (standard at site 1) during their regular follow-up visits. In both settings, treatment compliance was reviewed one on one, patient and physician.

Patients were included if they (1) were postmenopausal; (2) had been on a bisphosphonate (alendronate, risedronate, ibandronate, or zoledronic acid) for 18 months; (3) had data available from two dual-energy X-ray absorptiometry (DEXA) scans conducted on the same machine separated by 18 months. Patients were excluded if they (1) had a history of chronic steroid use (equivalent of 5 mg of daily prednisone for 2 months); (2) had a prior diagnosis of metabolic bone disease; (3) were non-compliant with bisphosphonate therapy.

Subject identification

For the site 1 patients, charts from all initial visits from 2006 to 2009 were screened to identify patients who met the study criteria. For site 2, patients who were being treated with bisphosphonates between January 2009 and October 2010 and who had a DEXA scan ordered were identified through their electronic medical record. Patients who met the

eligibility criteria and agreed to participate were invited for a study visit conducted within 2 months of their follow-up DEXA scan. Informed consent was obtained for each participant.

Data collection

For each patient, the following chart data were collected: age, race, body mass index (BMI), medication use, supplemental calcium and vitamin D use, duration of bisphosphonate therapy, evidence of incident fracture (obtained through chart review, radiological data, patient report, and reviewed by the attending physician), baseline and follow-up BMD at the lumbar spine, femoral neck, trochanter, and total hip, all available serum 25(OH)D (ng/ml) levels measured using the same liquid chromatography-mass spectrometry (LC/MS) methodology between the baseline and follow-up DEXA scans, and urine N-telopeptide (NTX) levels at the time of the follow-up visits. For the site 1 patients, information on laboratory values and on bisphosphonate/supplement use and compliance were obtained through chart review of their prior routine visits and laboratory studies. For the site 2 patients, 25(OH)D and NTX levels were specifically obtained at their one study visit which occurred at the time of the follow-up DEXA scan, and prior laboratory levels during the study period were obtained through chart review. The Morisky medication adherence questionnaire including four standard adherence questions was administered to the site 2 cohort at the time of the study visit [22].

A Charlson Co-morbidity Index was generated through review of each patient's medical record [23].

Outcomes definitions

The definition of non-response to bisphosphonate therapy was based on the EUROFORS study, which identified patients for teriparatide therapy after “failing” antiresorptive agents (median duration of bisphosphonate treatment was 36 months) [6]. Non-response included any of the following: (1) T-score of <-3.0 at the lumbar spine, femoral neck, total hip, or trochanter despite >24 months of bisphosphonate therapy (2) Decrease of $>3.0\%$ in BMD at the lumbar spine, bilateral femoral neck, total hip, or trochanter between the baseline and follow-up DEXA scans (3) Incident low-trauma fracture despite >12 months of bisphosphonate therapy.

No change (-3.0% to 3.0% based on the measurement error of DEXA scans) or an increase in BMD at all of the above sites was considered an adequate response [24]. For patients with multiple DEXA scans, the baseline and follow-up were chosen to coincide chronologically with vitamin D levels.

A 25(OH)D level of 33 ng/ml was hypothesized prior to initiating the study as the critical cutoff level based on findings of four large clinical trials that levels exceeding 32 ng/ml (75 nmol/l) were associated with lower fracture incidence [20, 21]. The mean of all available 25(OH)D levels for an individual subject obtained in the time period between the baseline and follow-up DEXA scans was used.

Statistics

Patient characteristics were compared for study site as well as response status. Continuous data were summarized by mean and standard deviation and categorical data by percentage. Differences between groups in the continuous data were assessed by the Wilcoxon test and categorical data by the Fisher exact test.

To identify patient characteristics associated with response status, we used multiple logistic regression. In order to evaluate the performance of our hypothesized cut point of 33 ng/ml as

well as different 25(OH)D cut points in the prediction of the endpoint (i.e., non-response), we also adopted various statistical measures such as the area under the receiver operating characteristics curve (AUC), and two information criteria, Akaike information criteria (AIC) and Bayesian information criteria (BIC). These were computed from logistic regression models with 25(OH)D as a single covariate as well as further adjusting for other of a risk factor and information criteria (AIC and BIC) assess the model fit so these statistics may guide model and cut variables in the model. AUC assesses the discrimination capability point selection [25, 26].

Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). For statistical estimation and inference, two-sided tests were used.

Results

Subject enrollment is summarized in Fig. 1. A total of 210 subjects were included. Patient characteristics based on study site are summarized in Table 1. The two study populations differed slightly with regard to BMI and Charlson index score, though each site had a mean Charlson score of <1 (i.e., low comorbidity scores). The site 2 patients had higher baseline BMD at the lumbar spine, femoral neck, and total hip (data not shown). The mean 25(OH)D levels were higher in site 1 patients, while the bone resorption marker (mean urine N-telopeptide [NTX]) was lower in site 1 patients. There was a similar distribution of oral bisphosphonate compounds used; however, no patients in the site 2 group received intravenous bisphosphonate. The mean duration between DEXA scans was 26 months (SD 9) and the mean duration of treatment prior to the baseline scan was 38 months (SD 36), which was not different between sites and was similar to that of the EUROFORs study [6]. While there were some differences between site 1 and site 2 patients, the differences were not considered to be clinically significant. Furthermore, as discussed below, characteristics for responders and non-responders were similar, and the clinical site was not shown to be significantly associated with maintenance of bisphosphonate response by multiple logistic regression analysis. Thus, the full cohort of patients were analyzed and presented together as initially intended.

The demographic and study data for the responder and non-responder populations is presented in Table 2. There were significant differences between the responders and nonresponders with regard to age, duration of bisphosphonate therapy, duration between the baseline and follow-up DEXA scans, and duration of treatment prior to the study period. There were no differences in the baseline BMI, or T score at any site. There was no difference in response rates amongst the oral bisphosphonates; however, 63.2% of patients taking IV zoledronate had a favorable response compared to 43.6% of patients taking oral bisphosphonates ($P=0.03$). Importantly, the difference in response rates for oral and intravenous treatments was not significant when adjusted for 25(OH)D level ($P=0.27$). The overall response rate was 47% ($N=99$). The most common cause of non-response was a >3% decline in BMD (77%, $N=86$), followed by incident fracture (23%, $N=26$), and persistent T score <-3.0 (16%, $N=18$). The following fractures were documented: leg ($N=7$), wrist ($N=5$), hip ($N=3$), ankle ($N=3$), foot ($N=2$), spine ($N=2$), rib ($N=2$), arm ($N=1$), hand ($N=2$).

For the total study population, 40% ($N=85$) of patients were below the predetermined cutoff, as defined by a mean 25(OH)D <33 ng/ml. All patients had a “follow-up” 25(OH)D value obtained within 2 months of the final DEXA scan. The mean 25(OH)D level (obtained by averaging the levels over the study period) and the single follow-up value for 25(OH)D were highly correlated with a correlation coefficient of 0.95. When the regression model was refitted using only the follow-up 25(OH)D values, the same outcome was obtained (data not shown).

The incidence of 25(OH)D <33 ng/ml was 58% (N=64/111) among non-responders and 21% (N=21/99) among responders (P<0.0001). In order to look beyond the single predetermined cutoff of 33 ng/ml, patients were stratified by 25(OH)D level into three common clinical categories: (1) 25(OH)D <30 ng/ml (N=66), (2) 25(OH)D 30 and <40 ng/ml (N=68), and (3) 25(OH)D ≥40 ng/ml (N=76) (Fig. 2). As demonstrated in Fig. 2, the incidence of non-response to bisphosphonate therapy decreased as mean 25(OH)D levels increased.

The ability of the mean 25(OH)D level to predict response outcome is presented in Table 3 where the OR, confidence intervals (CI), and significance of the OR are presented for different 25(OH)D cut points (<20, 20–30, 30–33 and ≥40 ng/ml). The 25(OH)D levels were selected based on their frequent use as clinically relevant cut points. Comparisons were made as follows: <20 vs. 20–30; <30 vs. 30–33; and <40 vs. ≥40. Thus each level of 25(OH)D compares subjects with lower values below the cut point (reference) vs. those at and above the cutoff value (experimental). The adjusted odds ratio (OR) of the preselected 33 ng/ml cut point was 4.53 (95% CI, 2.17–9.48; P<0.0001). The cut point of 33 ng/ml also had the largest AUC and smallest AIC and BIC in both unadjusted and adjusted models (AUC=0.814, AIC=231, BIC=276, OR=0.22, P<0.0001).

To identify other risk factors that were potentially associated with non-response, multiple logistic regression analysis was utilized. A total of 193 subjects were included in the regression model; 17 subjects were excluded from this analysis due to missing data in at least one variable. Factors analyzed included age, BMI, race, baseline T-score at the lumbar spine, oral bisphosphonate vs. IV zoledronate, concurrent calcium supplementation, history of SERM use, history of HRT use, study site, Charlson index, total duration of bisphosphonate therapy, duration between DEXA scans, and 25(OH)D level. Of the factors above, only duration of bisphosphonate treatment, time between scans, and 25(OH)D levels were significantly associated with response or non-response to bisphosphonate therapy, with 25(OH)D level having the strongest association. 25(OH)D level (as a continuous variable) was significantly associated with nonresponse to bisphosphonates, such that a 1 ng/ml decrease in 25(OH)D level was associated with approximately a 5% decrease in odds of being a responder (OR=0.95; 95% CI, 0.92–0.98; P=0.0006). Duration of bisphosphonate treatment was also significantly associated with non-response (OR=1.02; 95% CI, 1.01–1.03; P=0.005). Specifically, a 1-month increase in duration of treatment was associated with 2% increase in the odds of being a non-responder, i.e., longer duration was associated with increased likelihood of being a non-responder.

For the academic practice (WCIMA, site 2) in which several physicians were involved in patient care, drug compliance for the 50 patients was monitored by a Morisky drug compliance questionnaire and showed high compliance with a mean score of 2.72, SD 1.2 with the score range of 0 to 4. There was a significant positive correlation of Morisky score with 25(OH)D level (M score, 25(OH)D=0.42 with P=0.002). The mean Morisky score at site 2 was not different between responders and non-responders (2.93±1.16 vs. 2.93±1.26; P=0.43). For the 160 patients in the specialist practice (HSS, site 1) where the Morisky score was not obtained, bone turnover markers were quite low and no significant differences were noted between the responders and non-responders (22.3±10.7 vs. 25.7±11.6 nMBCE/mMCR, P=0.89) demonstrating persistence of bisphosphonate effect and providing indirect evidence of drug compliance for bisphosphonate [27].

In the subgroup of patients who received intravenous zoledronate (N=37), there was a clear association between response and mean 25(OH)D level. More specifically, 33.3% of non-responders (N=12) had 25(OH)D levels <33 ng/ml compared to 8.0% among responders (N=25) (P=0.07).

Discussion

In a cohort of closely followed, highly compliant patients who were maintained on bisphosphonate therapy, a significant fall in BMD, a new fracture, or persistently low BMD (the Eurofors criteria [6]) occurred in nearly half of the subjects. Of the many variables/parameters followed during the observation period, a nearly 5-fold (by far the strongest signal) difference in mean circulating 25(OH)D levels, with a cutoff of 33 ng/ml was observed between responders and non-responders. Notably, the specific bisphosphonate used, the treatment setting, age, weight, starting BMD were not correlated with treatment response.

Several large randomized controlled trials (RCTs) have shown that bisphosphonates improve BMD and decrease fracture risk [2–5]. Reasons for non-response to bisphosphonates have not been clearly established but prior studies have suggested that clinical response to bisphosphonates could in part be dependent on circulating vitamin D [15–18]. Overall, the role and importance of vitamin D in osteoporosis outcomes may be considered controversial. Furthermore, optimal 25(OH)D levels and supplement dosage have been called into question based on a recent review by the Institute of Medicine [28]. Nevertheless, prior clinical trials have reported that adequate vitamin D supplementation, i.e., 25(OH)D levels >32 ng/ml were associated with decreased fracture risk [20]. In all the pivotal RCTs to evaluate treatments for osteoporosis, vitamin D and calcium supplementation were provided to both the treatment and placebo arms [2, 4, 5, 29]. In the latter studies, 25(OH)D levels were not consistently measured though it was likely that adequate calcium and vitamin D supplementation was a critical component of optimized antiresorptive therapy in these trials which examined the early effects of bisphosphonate therapy.

Other studies have also suggested that vitamin D may play a role in the lower response rates with persistent bisphosphonate treatment seen in real world settings as compared with the pivotal clinical trials. For example, Adami et al. [19] found that among patients who took calcium and vitamin D supplements correctly, the rate of incident fracture during treatment with alendronate, risedronate, or raloxifene was significantly lower compared with those who did not take supplements. In a related study, odds of incident fracture were significantly higher in vitamin D deficient women as compared to those who were vitamin D replete [18]. However, this latter study was limited in that 25(OH)D measurements were not available for the majority of patients so vitamin D sufficiency was estimated through indirect measures.

Multiple studies have addressed treatment with antiresorptive therapies in patients with 25(OH)D levels below 30 ng/ml [14–17, 30, 31]. Several of these showed an association between baseline 25(OH)D level or secondary hyperparathyroidism, a probable indicator of vitamin D insufficiency, and reduced BMD response to treatment [15–17]. In addition, Barone et al. [15] showed that lumbar spine BMD increased more in patients treated with alendronate plus calcitriol (1,25-D3) compared to alendronate alone. However, Antoniucci et al. [14] found that 25(OH)D status at baseline did not affect early BMD response to alendronate when it was administered with cholecalciferol and calcium. Finally, Koster et al. [17] showed that in patients treated with etidronate, for those with a mean 25(OH)D value of ~24 ng/ml, bone mass in the lumbar spine and femoral neck was significantly increased compared to those with a mean 25(OH)D value of ~9 ng/ml. This suggests that vitamin D status may affect the initial BMD response to bisphosphonate therapy. The current study takes a further step by testing whether vitamin D status affects long-term bisphosphonate efficacy rather than the response in the early phase of bisphosphonate treatment.

This study demonstrates a statistically significant association between mean serum 25(OH)D levels and maintenance of bisphosphonate response using only quantitative measurements of

vitamin D as opposed to surrogate estimates of vitamin D status. Our study adds to the current literature in that it associates 25(OH)D level with predefined clinically meaningful criteria for maintaining bisphosphonate response. It also suggests a threshold level of 25(OH)D (33 ng/ml) that defines improved outcome to bisphosphonate therapy. These findings suggest that the currently accepted population standards for vitamin D repletion may not be sufficient for optimal therapeutic outcomes in patients taking bisphosphonates for low BMD and osteoporosis [28].

Serum 25(OH)D level best reflects the total body vitamin D status from all sources including dietary intake and sun exposure with endogenous synthesis [32]. At this time, it is not known how 25(OH)D or 1,25 dihydroxy vitamin D might function to enable bisphosphonates' beneficial effects on bone. A specific facilitative role for vitamin D hormones on biochemical targets for bisphosphonates such as the mevalonate pathway or on osteoblast, osteocyte or osteoclast function is unknown.

In addition to vitamin D status, we also found prolonged duration of bisphosphonate therapy was associated with significantly increased odds of non-response. Less than half of the patients in this study showed a durable response to bisphosphonate therapy such that most did not maintain BMD. In comparison, the majority of subjects in the FLEX trial maintained BMD over 10 years of bisphosphonate treatment [33]. This shows significant contrast between prolonged real-world treatment versus that of a clinical trial.

A secondary analysis of the patients treated with parenteral bisphosphonate (zoledronate) in this study did suggest better response rates compared to the patients on oral agents; however this finding is confounded by the comparison of few (38) patients treated with a parenteral agent versus many (172) treated with oral agents. Furthermore, a significantly greater percentage of the patients taking IV zoledronate had 25(OH)D levels at or above 33 ng/ml (79%) compared to those on oral bisphosphonates (54%). Since 25(OH)D level was associated with such a profound improvement in outcome, the results seen may merely be a reflection of the vitamin D status of that subgroup. In fact, when this analysis is adjusted for 25(OH)D level, the difference between response rates among oral bisphosphonate versus zoledronate treated patients was no longer significant ($P=0.27$). Importantly, the percent of zoledronate responders with 25(OH)D levels ≥ 33 ng was four times that of the non-responders. Thus in a subgroup with 100% bisphosphonate-treatment compliance, a similar association of treatment response with 25(OH)D was seen.

Several limitations should be noted in this study. The main limitation was the retrospective design. While 25(OH)D level appeared to be associated with response status, there may have been confounding factors that were not explicitly measured and would likely be eliminated in a prospective trial. Future prospective cohort studies and/or RCTs are needed to evaluate the role of vitamin D and other factors that could be more accurately and systematically measured.

A potential limitation in this study could be a confounding of the association between bisphosphonate response and mean 25(OH)D level by poor compliance with bisphosphonate, vitamin D or both. The general practices of the treating physicians to conduct thorough drug reconciliation and their emphasis on proper treatment during the regular office visits we believe strongly fostered drug and supplement compliance. In addition, the mean Morisky compliance score was relatively high among the 50 site 2 patients. There was a positive correlation between Morisky score and 25(OH)D levels in the small subset of patients in whom this data is available and the score was not different comparing responders to non-responders. Unfortunately, the subset of patients for whom we have the Morisky score was too small to adjust for this score in our regression model or to

conduct rigorous analyses using the Morisky score to statistically address the issue of compliance as a confounding factor. Low bone turnover marker values in responders and nonresponders argued for persistence of bisphosphonate effect, hence compliance. The same strong association of 25(OH)D levels with response rates was seen in the IV zoledronate treated patients, in whom compliance with bisphosphonate was not a factor, which supports the association of vitamin D with response. Lastly, stable 25(OH)D levels throughout the study period where mean values and final 25(OH)D levels were not significantly different argued for consistent compliance with vitamin D supplements. Compliance with vitamin D supplementation is not the sole reason for variation in circulating 25(OH)D levels. Variations in 25(OH)D levels are dependent on GI absorption, liver conversion (hydroxylation) and tissue metabolism to inactive metabolites. These processes are hardly static and are rapidly altered with changes in medical treatments or dietary and physiologic changes accounting for differences in measured 25(OH)D levels between or within patients over time.

Finally, this study utilized a composite definition of nonresponse, which included BMD levels and changes as well as incident fracture. The response rates reported here thus cannot be directly compared with studies that looked at only incident fracture and/or decline in BMD. Since only 5% (N=11) of the patients in the current study were characterized as non-responders based on the criteria of persistent low BMD levels alone this criteria did not have a major influence in this study.

Conclusions

These data from real-world practices showed lower longterm response rates to bisphosphonate therapy than would be anticipated based on prior trials. Importantly, this study provides evidence that circulating 25(OH) vitamin D level was strongly associated with persistent response to bisphosphonate therapy. This finding has importance for clinical practice as many patients receiving bisphosphonate therapy have vitamin D levels well below 33 ng/ml [11]. Vitamin D supplementation to provide adequate 25(OH)D levels as described in this study would be considered safe based on a recent survey by the IOM [28]. Such supplementation is inexpensive and represents an easily modifiable factor that could enhance bisphosphonate therapy. While an optimal 25(OH)D level for bisphosphonate response cannot be precisely determined from this study, the findings presented here suggest that levels higher than the range of 20–30 ng/ml recently recommended by the IOM for the general population may be required to maximize the benefit of bisphosphonate therapy for patients with low bone density and osteoporosis.

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Figure 1.
Subject screening and enrollment

Figure 2.

Association between 25OHD level and bisphosphonate response. When patients are stratified by 25OHD level, the rate of non-response decreases as vitamin D level increases.

Table 1
Patient characteristics based on study site

	Site 1 N=160 Mean (SD), N, or %	Site 2 N=50 Mean (SD), N, or %	p-value
Age (years)	65.4 (8.8)	66.7 (8.5)	0.26
BMI (kg/m ²)	22.4 (4.6)	25.0 (6.0)	0.003
Caucasian (%)	96.9	68.0	<0.0001
Charlson index	0.17 (0.38)	0.46 (0.68)	0.001
Baseline T-score			
Lumbar spine	-2.15(0.90)	-1.81 (1.21)	0.16
Femoral neck	-2.19 (0.61)	1.51 (0.77)	<0.0001
Bisphosphonate type			
Alendronate (N)	75	32	<0.0001 *
Ibandronate (N)	2	7	
Risedronate (N)	45	11	
Zoledronate (N)	38	0	
Treatment duration before study (months)	36.5 (35.1)	42.2 (36.9)	0.36
Total duration of therapy (months)	61.7 (35.8)	70.6 (36.3)	0.10
Mean 25OHD level (ng/ml)	39.7 (15.1)	28.0 (10.6)	<0.0001
Follow-up urinary NTx	23.7 (11.2)	33.5 (19.0)	<0.0001

* Overall test was used.

SD denotes standard deviation.

Table 2
Patient characteristics based on response status (N=210)

	Responders N=99 Mean (SD), N, or %	Non-Responders N=111 Mean (SD), N, or %	p-value
Age (years)	64.3 (8.0)	66.9 (9.2)	0.03
BMI (kg/m ²)	22.5 (4.1)	23.5 (5.8)	0.44
Caucasian (%)	90.9	91.0	1
Charlson index	0.24 (0.50)	0.23 (0.47)	0.94
Baseline T-score			
Lumbar spine	-2.06 (0.93)	-2.06 (1.05)	0.71
Femoral neck	1.98 (0.69)	2.01 (0.76)	0.72
Total hip	-1.54(0.78)	-1.60(0.91)	0.68
Bisphosphonate type			
Alendronate (N)	45	56	0.16*
Ibandronate (N)	4	5	
Risedronate (N)	26	27	
Zoledronate (N)	24	13	
Treatment duration before study (months)	30.3 (33.6)	44.7 (36.1)	0.0015
Total duration of therapy (months)	54.4 (34.3)	72.2 (35.6)	0.0001
Duration between DEXA scans (months)	24.5 (8.7)	28.3 (9.1)	<0.0001

Sample size was reduced for some variables due to missing data.

P-values for categorical data were computed by the Fisher exact test.

P-values for continuous data were computed by the Wilcoxon test.

P-values were unadjusted for multiple testing.

SD denotes standard deviation.

* Overall test was used.

Table 3

Predictive performance for response of various vitamin D cut points.

	N (Ref/Exp) ¹	Odds Ratio	95% CI	P-Value
Unadjusted models				
25(OH)D (ng/ml)				
20	26/184	1.81	0.77-4.27	0.18
30	66/144	5.35	2.72-10.53	<0.0001
33	85/125	5.06	2.74-9.32	<0.0001
40	134/76	3.65	2.02-6.62	<0.0001
Adjusted models ²				
25(OH)D (ng/ml)				
20	26/184	1.001	0.35-2.83	0.999
30	66/144	4.45	1.98-9.99	0.0003
33	85/125	4.53	2.17-9.48	<0.0001
40	134/76	4.32	1.96-9.52	0.003

p-values in reference to OR=1.

CI denotes confidence interval

¹The 25 (OH)D levels were selected based on their frequent use as clinically relevant cut points.

Comparisons were made as follows <20 vs. 20; <30 vs. 30; <33 vs. 33; and <40 vs. 40. Thus each level of 25(OH)D uses all the subjects with lower values (reference [ref]) vs. those at and above the cutoff value (experimental [exp]).

²Adjusted for age, BMI, race, baseline T-score at the lumbar spine, oral bisphosphonate vs. iv zoledronate, concurrent calcium supplementation, history of SERM use, history of HRT use, study site, Charlson index, total duration of bisphosphonate therapy, duration between DEXA scans, and 25(OH)D level