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Zoledronic Acid for Prevention of Bone Loss in Patients Receiving Primary Therapy for Lymphomas: A Prospective, Randomized Controlled Phase III Trial

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Abstract

In patients with newly diagnosed lymphoma, low bone mineral density (BMD) is common at diagnosis and worsens with therapy. Our randomized phase III trial demonstrates that 2 doses of zoledronic acid (ZA) and supplementation with calcium and vitamin D effectively prevent further bone loss.

Background—Patients with lymphoma are at risk of development of bone mineral density (BMD) loss from therapy with high-dose corticosteroids and alkylating agents. Zoledronic acid (ZA), a bisphosphonate, may prevent this complication of therapy. We evaluated the effect of ZA on the change in BMD and surrogate biomarkers in patients with lymphoma receiving initial chemotherapy.

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Disclosure
The authors have stated that they have no conflicts of interest.

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Patients and Methods—Our phase III trial randomized 74 patients with newly diagnosed lymphoma and a baseline BMD of ≥ −2.0 to receive oral calcium and vitamin D daily with or without ZA at enrollment and at 6 months after enrollment. BMD was evaluated at baseline and 1 year after enrollment. Secondary biomarker endpoints were collected at baseline and at 3, 6, 9, and 12 months after enrollment.

Results—Forty-three percent of patients had baseline osteopenia. Fifty-three patients were evaluable for response: 24 received ZA and had stable BMD during the observation period, whereas 29 patients in the control group had decreased BMD ($P < .05$ at lumbar spine and bilateral femoral neck). Twenty-one randomized patients were not evaluable for response because of lymphoma progression or death, withdrawn consent/incomplete testing, or ineligibility. Bone biomarkers were higher in the control group at all intervals after treatment ($P < .001$). No fractures or intervention-related toxicities were observed during this trial.

Conclusions—Newly diagnosed patients with lymphoma are at risk of low BMD, which may worsen with therapy. Treatment with ZA effectively stabilizes BMD and prevents bone loss. Our data suggest that BMD testing and prophylaxis should be considered as an early intervention for a preventable problem.

Keywords

Bone density; Bone loss; Calcium; Lymphoma; Newly diagnosed; Osteopenia; Osteoporosis; Vitamin D; Zoledronic acid

Introduction

Over the past 50 years, investigators have made remarkable progress in the treatment of lymphoma, resulting in significant improvements in survival rates. With improving outcomes, complications of therapy have come into focus. Advances in supportive care have greatly improved short-term treatment-associated morbidity; however long-term sequelae, such as osteoporosis, remain problematic.[1]

Therapy of lymphoma with high-dose glucocorticoids and alkylating agents may result in premature bone loss, increasing the risk of vertebral and hip fractures. Exogenous glucocorticoids result in an increased risk of osteoporosis-related fractures by increasing bone resorption and decreasing bone formation, calcium retention, muscle mass, and endocrine gonadal function.[2–8] Brief high-dose exposure to corticosteroids results in a durable increased risk of fracture and potential for avascular necrosis.[4,9] In addition, alkylating agent–induced endocrine gonadal damage is a common complication and affects both men and women.[1,10–13]

Lost bone mass is difficult to restore. Daily use of the bisphosphonate alendronate in postmenopausal women yielded a > 3% increase in bone mineral density (BMD) in only 35% of the patients studied.[14]

Screening of BMD is not included in the current National Comprehensive Cancer Network (NCCN) lymphoma patient management guidelines but is recommended for patients receiving long-term corticosteroids and chemotherapy by several other groups.[15–19] We have previously reported that the majority of patients with newly diagnosed lymphomas have low BMD before the initiation of therapy, further emphasizing the potential importance of bone health as a survivorship issue.[20]

Bisphosphonates are effective inhibitors of osteoclastic bone resorption and have therapeutic efficacy in numerous malignancy-related bone conditions.[21–34] In patients with lymphoma

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receiving chemotherapy, treatment with the second-generation bisphosphonate pamidronate every 3 months for 1 year reduced both bone loss and the risk of new vertebral fractures.[35] Zoledronic acid (ZA), a third-generation bisphosphonate, has proved between 850 and 4000 times more potent than pamidronate in preclinical studies.[33,36] To date, the effect of ZA on bone health has not been evaluated in patients with previously untreated lymphomas. In this study, our objective was to determine the effect of ZA in prevention of bone loss for patients undergoing initial treatment for lymphomas.

Patients and Methods

Setting and Participants

Eligible patients were 18 years or older with newly diagnosed lymphomas, an Eastern Cooperative Oncology group performance status of 0 to 3, and an estimated creatinine clearance of 60 mL/min or greater. Exclusion criteria included radiologic evidence of vertebral or hip fractures, initial BMD T-scores worse than −2.0 at any location, and recent steroid or bisphosphonate use. Patients with hyperparathyroidism, vitamin D deficiency (<20 ng/mL), or testosterone deficiency (<240 ng/dL) were eligible if they were receiving appropriate therapy. A dental examination performed on each screened patient excluded those with abnormalities previously found to be associated with an increased risk of osteonecrosis of the jaw (ONJ).[37,38] The trial was a single-institution randomized phase III study and was conducted in accordance with the Declaration of Helsinki. All patients signed informed consent documents approved by the MD Anderson Cancer Center Institutional Review Board.

Randomization and Interventions

Patients were randomized 1:1 to receive oral calcium (1200 mg) and vitamin D (400 or 800 IU, control) daily with or without ZA 4 mg intravenously at enrollment and at 6 months. Randomization was stratified by sex and menopausal status. Lymphoma subtype–specific chemotherapy regimens were administered according to institutional guidelines. The primary endpoint was an evaluation of BMD changes at the lumbar spine and femoral neck from baseline to 12 months. Secondary endpoints included BMD change at the hip, treatment effect on development of fractures, and effects on the correlative markers urine N-telopeptide (NTx) and serum bone-specific alkaline phosphatase (BSAP) levels.

Outcomes and Follow-Up

BMD evaluation was performed at baseline and at 12 months after initiation of therapy at the lumbar spine, bilateral femoral neck, and bilateral hips. BMD was measured by dual-energy, x-ray absorptiometry scanners, which were calibrated and tested with a precision of 0.24% and an accuracy of 0.39%. Osteopenia and osteoporosis were defined according to the definition of the World Health Organization as a BMD T-score of −1.0 to −2.5 and less than −2.5, respectively.[39]

Urine NTx and serum BSAP levels were measured at baseline, and at 3, 6, and 12 months from initiation of therapy for lymphoma.[40,41] Urine NTx levels were assessed on a refrigerated second morning void using a competitive immunoassay (Quest Diagnostics, Houston, TX or Mayo Medical Laboratories, Rochester, MN). Serum BSAP levels were measured by an immunochemiluminescence assay (Quest Diagnostics, Houston, TX).

Statistical Analyses

The χ^2 test and the Fisher exact test were used to evaluate the association between 2 categorical variables (including treatment, stage, and histologic subtype). The Wilcoxon

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rank-sum test was used to compare the distributions of continuous variables among different groups. The Spearman correlation coefficient was used to estimate the correlation between 2 continuous variables. Repeated measures models were fit to assess the treatment effect and time effect on bone marker responses. To meet the underlying assumptions of the repeated measures analysis, the logarithmic transformation was performed on the original bone marker scores. Repeated measures models were also fit to assess the associations between changes in BMD T-scores at each location and bone marker scores for all patients and for patients grouped by treatment with ZA. General linear models were fit to examine the association between BMD changes and demographic factors. All tests were 2-sided. *P* values less than .05 were considered statistically significant. All analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC) and S-plus statistical software, version 8.0 (TIBCO, Palo Alto, CA).

Results

One hundred thirty-five patients seen at our lymphoma center from 2006 to 2009 were screened for eligibility to enter this trial. Of these patients, 61 (46.7%) were excluded for various reasons (Figure 1). Thirty-five patients were considered ineligible for therapy in this study because of dental abnormalities, including the need for dental extraction, active significant oral/dental infection, and significant tooth decay.[37,38] The ZA and control groups had similar demographics, baseline BMDs, and baseline biochemical markers of bone turnover (Tables 1 and 2). The chemotherapy treatments received by the ZA and control groups, including a steroid component, were also not significantly different, and no patient had previous exposure to chronic corticosteroid use.

In all, 74 patients were enrolled in this trial. However only 53 patients completed the required evaluations and remained compliant with ZA and calcium with vitamin D to be considered evaluable for response (Figure 1). Patients who are categorized as “withdrew consent” generally did not return to our referral center for their 1-year follow up visit because of financial or personal reasons. At baseline, 43% of patients had osteopenia at 1 or more evaluated sites (Table 3). In patients at least 50 years of age, 54% of men and 40% of women had baseline osteopenia. The screening failures and patients who were not evaluable had rates of baseline bone loss that were nearly identical to the evaluable group (Table 2). Neither disease stage nor bone or marrow involvement were significant factors for baseline osteopenia.

From baseline to 12 months, individuals in the control arm had more bone loss than did patients in the ZA arm at all locations except the left hip (Table 2; Figure 2), achieving statistical significance at our primary endpoint sites. No demographic feature was significantly associated with results on either univariate or multivariate analysis. No fractures were identified in either group during the observation period. Furthermore, ZA was well tolerated and resulted in no drug-related toxicities, including ONJ. To date, no difference in survival outcomes between the 2 groups has been observed.

The baseline values of urine NTx and serum BSAP levels were similar between the 2 groups (Table 3). Patients in the ZA group had significantly lower urine NTx levels at 3, 6, 9, and 12 months after starting therapy than did patients in the control group. In addition, patients in the ZA group had significantly lower BSAP levels at 3, 6, 9, and 12 months than did the patients in the control group (at all time points, $P < 0.05$). Using repeated measurement models, the logarithmic transformed urine NTx and serum BSAP levels were significantly associated with BMD changes in the control group but not in the ZA group.

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Discussion

Survivorship issues for patients with lymphomas, including bone health, are of increasing importance as long-term outcomes continue to improve. Our results demonstrate that 2 doses of ZA along with calcium and vitamin D supplementation effectively prevents further bone loss in patients with newly diagnosed lymphoma. The mechanisms for the low BMD seen at diagnosis, which may worsen after lymphoma therapy, are unclear but are in agreement with previous findings of others.[42,43] In comparison with community osteopenia rates, we found that men at least 50 years of age with newly diagnosed lymphomas had a higher rate of osteopenia (54% vs. 30%), whereas females at least 50 years of age with lymphomas had an equivalent rate (40% vs. 49%).[44] The reasons for this sex difference are unclear but may include the small sample size of our population or lymphoma-induced hormonal or cytokine-related bone changes.[1] Surprisingly, stage and bone or marrow involvement were not relevant factors in the rates of osteopenia or osteoporosis in this study. Regardless, these findings suggest that older male patients with lymphomas may be at higher risk of osteopenia than older men in the general population.

In our study, we monitored the compliance of our patients with the required calcium and vitamin D supplementation by frequent follow-up. It is possible that the effect of ZA may have been more impressive if our control arm consisted of observation alone because adherence to supplements is often poor in clinical practice.[45,46] Indeed, other bisphosphonates have demonstrated benefit in patients with lymphoma who did not receive supplemental vitamin D or calcium.[35]

Our study was limited to newly diagnosed patients with lymphoma who did not have osteoporosis. It is possible that patients with preexisting osteoporosis may have achieved different, and perhaps more pronounced, results. We chose our exclusion threshold of BMD of < -2 to avoid potentially randomizing patients with borderline osteoporosis to our control group. In the pivotal HORIZON trial, postmenopausal women with osteoporosis gained a significant increase in BMD from annual ZA treatment, as compared with our findings of BMD stabilization in our group without osteoporosis.[47] Based on these data, patients with osteoporosis undergoing chemotherapy for lymphoma are also likely to benefit from effective bone protective medication.

The bone-related biochemical markers, urine NTx and serum BSAP levels, provided evidence of bone loss as early as 3 months after enrollment in our trial. However the long-term utility of these biomarkers in our population is unclear. Other bisphosphonate clinical trials have reported that changes in bone biomarkers stabilized after the first year, although BMD continued to improve with prolonged bisphosphonate exposure, perhaps indicating a lack of long-term reliability as a bone health biomarker.[47] Although these biomarkers did correlate with BMD outcomes in our trial, additional trials will be necessary to determine if these markers can effectively risk stratify patients or alter treatment before the development of significant osteoporosis.

Although our BMD monitoring period was 1 year, we plan to follow these patients in the future to detect any episodes of fracture or ONJ. The incidence of ONJ after bisphosphonate use correlates with duration of bisphosphonate exposure (median exposure in patients with multiple myeloma and ONJ was 39 months).[48] In addition, long-term bisphosphonate use has been associated with femoral insufficiency fractures.[49] Because the bisphosphonate exposure in our trial was brief and prospective dental screening was performed, we do not expect to diagnose late ONJ or femoral insufficiency fractures. We also did not find a difference in survival rates between our treatment groups, although our study was not powered to evaluate this as an endpoint.

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In conclusion, as outcomes for patients with lymphoma continue to improve, an increasing number of patients are becoming long-term survivors. This welcome development will require an increased focus on survivorship issues, including bone health. Our study supports the Center for Disease Control's National Action Plan, which aims to identify factors associated with ongoing health concerns of cancer survivors to best address their long-term needs.[50] Finally, screening for low BMD is not included in the current NCCN lymphoma treatment guidelines; however our data suggest that it should be considered. BMD screening at diagnosis may identify a common and preventable problem and allow a simple intervention to potentially modify outcomes.

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Clinical Practice Points

- A significant portion of patients with newly diagnosed lymphoma have evidence of low bone density, which is more pronounced after lymphoma therapy.
- Two doses of ZA with calcium and vitamin D supplementation stabilize BMD in lymphoma patients undergoing chemotherapy.
- Screening for bone loss in newly diagnosed lymphoma patients should be considered.

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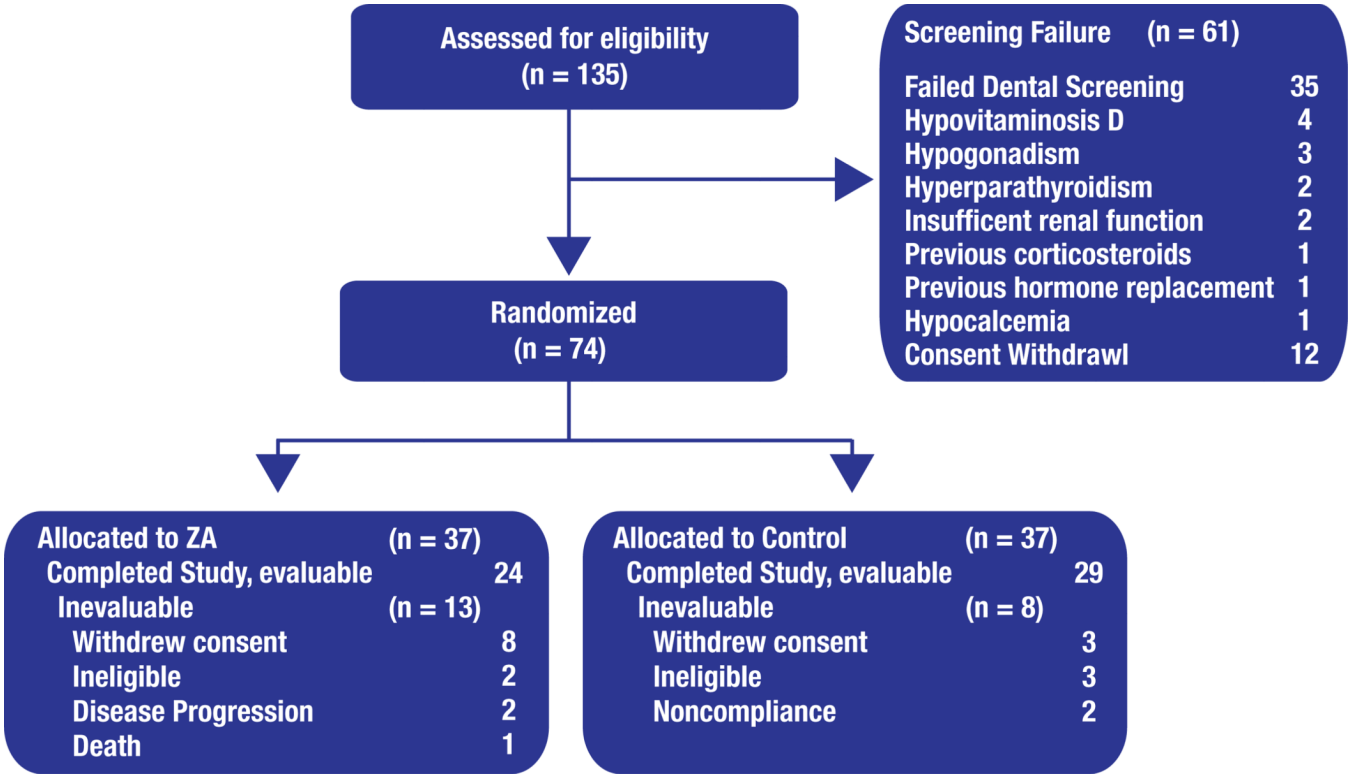

Figure 1.
CONSORT Diagram Detailing Patients Screened, Randomized, and Evaluable for the Trial
Abbreviation: ZA = zoledronic acid.

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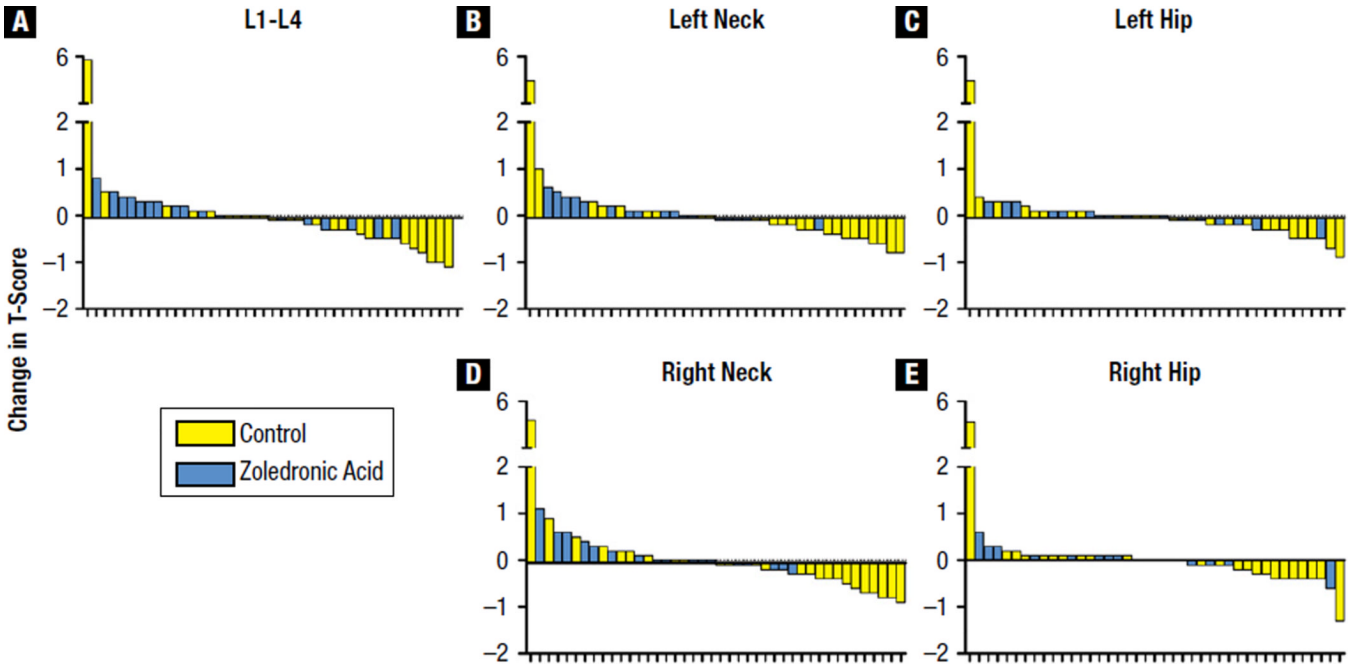

Figure 2.
Waterfall Plot of Change in the T-Score of Each Patient at Each Location Assessed. (A) Lumbar Spine, L1–L4; (B) Left Femoral Neck; (C), Left Hip; (D) Right Femoral Neck; (E) Right Hip

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Table 1

Baseline Characteristics of Randomized Patients

	Median (range)				*P* Value
	Zoledronic Acid		Control		
Age (y)	57.6 (24–80)		53.4 (19 – 75)		.23
Vitamin D, Serum	27 (6–69)		24 (4 – 46)		.66
Calcium, Serum	9.1 (8.2–10)		9 (7.8 – 9.9)		.63
BMI	29 (19–42)		29.5 (19 – 44)		.73
	n = 37	**%**	**n = 37**	**%**	***P* Value**
Sex					.81
Male	23	62	24	65	
Female	14	38	13	35	
Postmenopausal	9	64	8	62	
Diagnosis Category[a]					.24
Aggressive	20	54	15	41	
Indolent	17	46	22	59	
Stage					.39
I–II	9	24	6	16	
III–IV	28	76	31	84	
Chemotherapy Regimen					.32
R-CHOP	25	68	17	46	
R-HyperCVAD	3	8	6	16	
R-FND	5	14	5	14	
PACE	2	5	1	3	
ABVD	2	5	6	16	
FCR	0	0	1	3	
Velcade	0	0	1	3	
Corticosteroids With Chemotherapy					.09
No	2	5	8	22	
Yes	35	95	29	78	

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New Fractures					1.00
No	37	100	37	100	
History of Smoking					.34
No	20	54	24	65	
Yes	17	46	13	35	

Data from evaluable patients were not statistically different from all randomized patients.

Vitamin D units, ng/mL; reference range, 20–100.

Calcium units, mg/dL; reference range, 8.2–10.2.

[a]Diagnosis category of aggressive includes diffuse large B-cell, mantle cell, and primary mediastinal B-cell lymphoma. Indolent includes follicular, Hodgkin, small lymphocytic lymphoma and Waldenström macroglobulinemia. Of 53 total patients, 50 had non-Hodgkin lymphoma. *P* value was based on the Chi-square test or Fisher's exact test.

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Table 2

Bone Mineral Density Assessment

Location	Baseline Bone Mineral Density		
	Baseline T-Score Mean ± SD	**Osteopenia n**	**n = 53 % of total**
Lumbar	0.4 ± 1.54	12	23
Left Neck	−0.41 ± 0.95	15	28
Left Hip	0.13 ± 0.81	2	4
Right Neck	−0.35 ± 1.03	15	28
Right Hip	0.12 ± 0.85	5	9
Patients With Baseline T-Score ≤ −1.0 at ≥ 1 location		**n = 53**	**%**
Baseline Osteopenia in All Evaluable Patients			
No		30	57
Yes		23	43
Osteopenia in Evaluable Patients Aged ≥ 50 Years			
Male, n = 26		14	54
Female, n = 15		6	40
Osteopenia in All Patients (Screening Failures + Evaluable + Not Evaluable)		n = 133[a]	%
No		73	55
Yes		60	45
Baseline Osteopenia in All Patients Aged ≥ 50 Years			
Male, n = 60		34	57
Female, n = 37		18	49

Change In Bone Mineral Density T-Score from Baseline to 12 mo

Location	Zoledronic Acid	Controls	*P* Value
	n = 24	**n = 29**	
	Mean ± SD		
Lumbar	0.08 ± 0.34	−0.09 ± 1.23	.015
Left Femoral Neck	0.04 ± 0.27	−0.04 ± 0.93	.031
Left Hip	−0.04 ± 0.24	−0.03 ± 0.86	.342
Right Femoral Neck	0.09 ± 0.38	−0.16 ± 1.04	.016
Right Hip	0.004 ± 0.25	−0.08 ± 0.92	.089

P value is based on the Wilcoxon rank-sum test.

Abbreviation: SD = standard deviation.

[a]Baseline bone mineral density data available on 133 patients.

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Table 3

Biochemical Bone Markers

Urine NTx Level	Log Transformed Mean ± SD				*P* Value
	Zoledronic Acid	n	Controls	n	
Mo					
0	3.31 ± 0.42	22	3.43 ± 0.56	27	.39
3	2.76 ± 0.74	21	3.60 ± 0.37	24	< .001
6	2.95 ± 0.31	21	3.68 ± 0.53	24	< .001
9	2.96 ± 0.35	23	3.58 ± 0.53	23	< .001
12	2.85 ± 0.39	21	3.76 ± 0.63	26	< .001
Serum BSAP Level					
0	2.4 ± 0.39	22	2.53 ± 0.53	26	.357
3	2.22 ± 0.25	24	2.56 ± 0.31	27	< .001
6	2.24 ± 0.27	23	2.7 ± 0.36	28	< .001
9	2.14 ± 0.38	23	2.93 ± 0.79	27	< .001
12	2.19 ± 0.28	24	2.87 ± 0.82	27	< .001

Abbreviations: Urine NTx = N-telopeptide levels in nmol bone collagen equivalents/mmol creatinine; BSAP = bone-specific alkaline phosphatase levels in ug/L.