Effect of Alendronate on Bone Mineral Density and Biochemical Markers of Bone Turnover in Type 2 Diabetic Women

The Fracture Intervention Trial

THERESA H.M. KEEGAN, PHD[1]
ANN V. SCHWARTZ, PHD[2]
DOUGLAS C. BAUER, MD[2,3]
DEBORAH E. SELLMEYER, MD[4]
JENNIFER L. KELSEY, PHD[1]

OBJECTIVE — Alendronate sodium (ALN) increases bone mineral density (BMD) in heterogeneous populations of postmenopausal women, but its effect is unknown in women with type 2 diabetes. The objective of this project was to compare changes in BMD during 3 years of ALN treatment versus placebo in diabetic women.

RESEARCH DESIGN AND METHODS — We used data from the Fracture Intervention Trial, a randomized blinded placebo-controlled trial conducted at 11 centers in which 6,458 women aged 54–81 years with a femoral neck BMD of ≤0.68 g/cm^2 were randomly assigned to either placebo or 5 mg/day ALN for 2 years, followed by 10 mg/day for the remainder of the trial. BMD was measured by dual-energy X-ray absorptiometry. Type 2 diabetes (n = 297) was defined by self-report, use of insulin or other hypoglycemic agents, or a random nonfasting glucose value ≥200 mg/dl.

RESULTS — In diabetic women, 3 years of ALN treatment was associated with increased BMD at all sites studied, including 6.6% at the lumbar spine and 2.4% at the hip, whereas women in the placebo group experienced a decrease in BMD at all sites except the lumbar spine. The safety/tolerability of ALN was similar to placebo, except for abdominal pain, which was more likely in the ALN group.

CONCLUSIONS — ALN increased BMD relative to placebo in older women with type 2 diabetes and was generally well tolerated as a treatment for osteoporosis. Increases in BMD with ALN therapy compared with placebo were similar between women with and without diabetes.

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From the [1]Division of Epidemiology, Stanford University School of Medicine, Stanford, California; the [2]Department of Epidemiology and Biostatistics, University of California–San Francisco, San Francisco, California; the [3]Division of General Internal Medicine, University of California–San Francisco, San Francisco, California; and the [4]Division of Endocrinology, University of California–San Francisco, San Francisco, California.

Address correspondence and reprint requests to Dr. Theresa Keegan, Department of Health Research and Policy, Division of Epidemiology, HRP Redwood Building, T224, Stanford University School of Medicine, Stanford, CA 94305-5405. E-mail: tkeegan@nccc.org.

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Abbreviations: ALN, alendronate sodium; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; CTx, COOH-terminal telopeptide of type I collagen; FIT, Fracture Intervention Trial; NTx, NH_2-terminal propeptide of type I collagen.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Between 1990 and 1998, the prevalence of diabetes increased by 20% in the U.S. (1). Older women with type 2 diabetes have been reported to be at an increased risk for hip, proximal humerus, and foot fractures (2–5), possibly because of comorbidities that may increase the risk for falls, accelerate bone loss, or reduce bone quality (5,6). With this increased risk of fracture, preservation of bone mineral density (BMD) is particularly important, but little is known about how osteoporosis medications such as alendronate sodium (ALN) (Fosamax) affect women with type 2 diabetes.

The objective of this project was to determine the effects of ALN on BMD and biochemical markers of bone turnover compared with placebo in older women with low BMD and type 2 diabetes. A secondary objective was to compare changes in BMD and biochemical markers of bone turnover with ALN treatment in women with and without diabetes. Subsets of data from a randomized controlled trial designed to test the hypothesis that ALN reduces the rate of fractures in women aged 55–80 years with low femoral neck BMD are used to address these questions.

RESEARCH DESIGN AND METHODS

— The Fracture Intervention Trial (FIT) was conducted at 11 clinical centers in the U.S. and has been described previously (7,8). FIT had two study arms: the Vertebral Fracture Arm included women who had at least one vertebral deformity at baseline, whereas the Clinical Fracture Arm included women without vertebral deformities but with a femoral neck T score of −1.6 or less at baseline. Within each study arm, women were randomized to receive ALN or placebo. Diabetes status was not considered in the randomization assignment. Participants and study personnel were blinded to treatment assignment.

Table 1—*Selected characteristics at baseline among women with and without type 2 diabetes by treatment group*

	Diabetic women		Nondiabetic women	
	ALN	Placebo	ALN	Placebo
n	148	149	3,087	3,074
Age at randomization (years)	69.3 ± 6.1	69.5 ± 5.9	68.5 ± 6.2	68.7 ± 6.1
White race	95.3	97.3	97.0	97.0
BMI (kg/m^2)	27.3 ± 5.1	26.9 ± 5.2	25.0 ± 3.9	25.1 ± 4.0
Years since menopause	23.2 ± 8.6	23.0 ± 8.0	21.1 ± 8.5	21.3 ± 8.5
Lumbar spine BMD (g/cm^2)	0.88 ± 0.15	0.86 ± 0.14	0.82 ± 0.13	0.82 ± 0.14
Total hip BMD (g/cm^2)	0.71 ± 0.09	0.70 ± 0.089	0.69 ± 0.09	0.69 ± 0.09
BSAP (units/l)	14.4 ± 5.1	13.5 ± 4.7	13.6 ± 4.3	13.8 ± 4.5
NTx (μg/l)	43.2 ± 17.6	44.9 ± 17.2	51.8 ± 20.6	52.0 ± 19.9
CTx (pmol/l)	3,096.7 ± 2,755.3	2,773.1 ± 1,287.5	3,337.3 ± 1,757.3	3,338.8 ± 1,646.1
Morphometric prevalent vertebral fracture	29.7	32.2	31.7	31.1
Health status excellent or very good	46.6	52.4	66.7	64.6
Participate in a regular activity program	42.6	38.3	46.5	47.8
Days stayed in bed because of an injury/illness 12 months before baseline				
1–3 days	25.0†	14.8	19.4	19.0
≥3 days*	4.1	6.7	3.5	2.4
Days cut down on usual activities because of injury/illness 12 months before baseline				
1–10 days	18.2†	9.4	11.9	12.5
≥10 days*	18.2	13.4	14.1	13.2
Ever use estrogen since menopause	47.3†	35.6	41.7	40.4
Type of hypoglycemic medication				
Insulin	8.1	6.7	—	—
Oral	22.3	19.5	—	—
Age of diabetes diagnosis (years)	57.5 ± 13.5	55.4 ± 14.5		
Duration of diabetes (years)	11.4 ± 12.3	14.9 ± 14.2	—	—

Data are means ± SD or percent. *Median value based on the distribution of entire cohort. †$P < 0.1$ for comparison of ALN and placebo groups in women with diabetes.

Women 54–81 years of age, in good health, who were postmenopausal for at least 2 years with a femoral neck BMD ≤0.68 g/cm^2 (Hologic QDR-2000) were included in the main study. At baseline, all women completed a questionnaire, had blood drawn, and had bone densitometry performed using QDR-2000 technology (Hologic, Waltham, MA). Women were excluded from the trial if they had major medical conditions or secondary osteoporosis, presence of significant upper gastrointestinal disease, therapy with drugs that affect bone metabolism, or factors making full compliance with the protocol unlikely. Women provided written informed consent, and the protocol was approved by the appropriate institutional review boards.

Treatment

The initial dose of ALN was 5 mg/day for 2 years but was increased to 10 mg/day at the second annual visit because of findings from other trials (9). Women in the Vertebral Fracture Arm were followed for 3 years, whereas women in the Clinical Fracture Arm were followed for 4 years. However, we report herein only data at 3 years. At baseline, 82% of women had dietary calcium intakes of <1,000 mg/day and were given a daily supplement of 500 mg elemental calcium (as the carbonate salt) and 250 IU cholecalciferol.

BMD and biochemical markers of bone turnover

BMD at the posterior-anterior lumbar spine, total hip, femoral neck, trochanter, and intertrochanter was measured yearly; 8% of women did not have baseline or year-3 BMD values.

Each participant provided a serum specimen before randomization and at each annual visit. In 2001, paired baseline and follow-up specimens for the entire cohort were thawed and assayed for bone-specific alkaline phosphatase (BSAP), COOH-terminal telopeptide of type I collagen (CTx), and NH_2-terminal propeptide of type I collagen (NTx) and have been described previously (10); 14% of women did not have baseline or year-1 values, and only 20% of the cohort had fasting specimens.

Baseline visits

Diabetes was ascertained by self-report at baseline preliminary and secondary screening visits by asking, "Has a doctor ever told you that you had diabetes, sugar diabetes, or high blood glucose?" At the secondary visit, women were asked to describe the disease and the year of diagnosis. Women with only gestational diabetes were not classified as having diabetes. Women who reported diabetes at either visit, reported the use of insulin or oral hypoglycemic medication at baseline or follow-up, or had a random nonfasting plasma glucose value ≥200 mg/dl at baseline or follow-up were classified as having

Table 2—*Mean percent difference of BMD in grams per centimeter squared between ALN and placebo groups among women with and without type 2 diabetes at 3 years, by site of BMD measurement*

	Diabetic women		Nondiabetic women		*P* value, test for homogeneity*
	ALN	Placebo	ALN	Placebo	
Lumbar spine					
n	136	137	2,825	2,830	
Percent change from baseline	6.6 ± 0.5†‡	0.9 ± 0.4	7.5 ± 0.1†‡	1.3 ± 0.1‡	
Percent difference‖ (95% CI)		5.7 (4.4–7.0)		6.2 (5.9–6.4)	0.4
Hip					
n	137	139	2,842	2,847	
Total hip					
Percent change from baseline	2.4 ± 0.4†‡	−1.9 ± 0.4‡	3.1 ± 0.1†‡	−1.2 ± 0.1‡	
Percent difference‖		4.3 (3.2–5.3)		4.3 (4.1–4.5)	0.6
Femoral neck					
Percent change from baseline	2.6 ± 0.5†‡	−0.8 ± 0.6§	3.4 ± 0.1†‡	−0.5 ± 0.1‡	
Percent difference‖		3.4 (2.1–4.7)		3.8 (3.6–4.1)	0.6
Trochanter					
Percent change from baseline	4.1 ± 0.5†‡	−1.0 ± 0.4§	4.9 ± 0.1†‡	−0.5 ± 0.1‡	
Percent difference‖		5.1 (3.8–6.4)		5.4 (5.1–5.7)	1.0
Intertrochanter					
Percent change from baseline	1.8 ± 0.5†‡	−2.3 ± 0.4‡	2.4 ± 0.1†‡	−1.5 ± 0.1‡	
Percent difference‖		4.0 (2.9–5.2)		3.9 (3.7–4.1)	0.4

Data are *n*, means ± SE, or means (95% CI). *P value for interaction between treatment and history of diabetes among all women combined; †$P \leq 0.001$ vs. placebo; ‡$P < 0.001$ vs. baseline; §$P \leq 0.05$ vs. baseline; ‖mean percent difference between alendronate and placebo groups.

diabetes. Excluding women diagnosed solely from a high plasma glucose value ($n = 54$, 18%) did not alter our findings (data not shown). Women who did not use insulin at baseline ($n = 275$) or used insulin at baseline and had an age at diagnosis >30 years ($n = 22$) were classified as having type 2 diabetes. One woman with probable type 1 diabetes was excluded from these analyses.

At the baseline visit, information on demographic characteristics was collected, including height and weight (from which BMI [kg/m^2] was computed), age at last menstrual period (years since menopause was calculated by subtracting age at randomization from age at last menstrual period), self-reported health status (very good or excellent versus poor, fair, or good), use of diuretics or water pill every day or almost every day, use of estrogen since menopause, and smoking status.

Health status in the 12 months before the baseline interview was further assessed by asking women the number of days they stayed in bed because of an injury or illness and the number of days they cut down on their usual activities such as going to work or working around the house because of illness or injury. For each of these two health status indicators, women were placed into three categories: *1*) none, *2*) at least 1 day but less than the median, and *3*) greater than or equal to the median, based on the distribution of the entire cohort who had a value greater than zero. Physical activity was measured by asking whether the woman currently participated in any regular activity or program (either on their own or in a formal class) designed to improve or maintain physical fitness.

At baseline and follow-up visits, plasma glucose levels and renal function (as measured by serum creatinine) were measured. Adverse experiences, defined as any untoward condition, were assessed as part of the safety protocol.

Statistical analysis

Women with baseline and year-3 values of BMD and baseline and year-1 values of biochemical markers of bone turnover were analyzed using SAS version 8 software (SAS Institute, Cary, NC) according to their randomized assignment, regardless of whether they continued to take the study medication. ANOVA was used to assess the difference in annualized mean percent change from baseline of *1*) lumbar spine, total hip, femoral neck, trochanter, and intertrochanter BMD (g/cm^2) to 3 years and *2*) the difference in mean percent change from baseline of BSAP, NTx, and CTx to 1 year between ALN and placebo groups. Adjusted models were also considered using ANCOVA to control for covariates associated with treatment group among women with diabetes ($P < 0.1$). A history of diabetes as a possible effect modifier was examined in the entire cohort by including an interaction term (treatment by diabetes) in ANOVA.

To test the appropriateness of combining women in the Vertebral and Clinical Fracture Arms, effect modification was assessed visually and by including an interaction term (treatment by Fracture Arm) in ANOVA. For the analyses presented, the results were consistent for the two Fracture Arms, and the data were combined.

RESULTS — Among diabetic women, there were minimal differences between the treatment and placebo group for most variables presented (Table 1). However, there was a suggestion ($P < 0.1$) that more diabetic women in the ALN group versus the placebo group cut down on usual activities, stayed in bed because of injury/illness, and used estrogen since menopause. Compliance, adherence to study medication for at least 75% of the days of therapy, and use of 70% of the

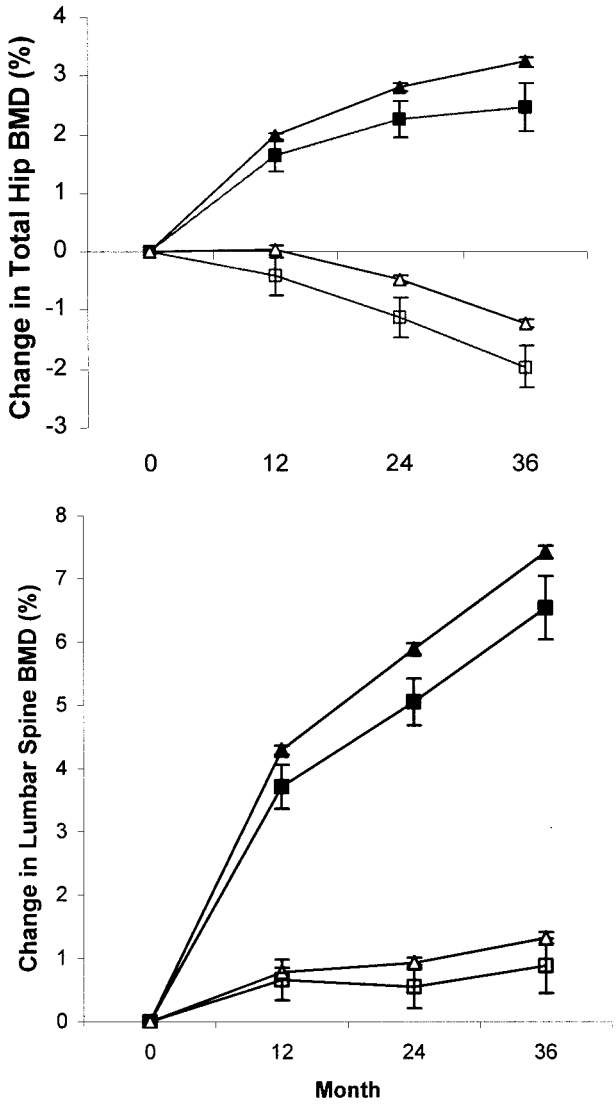

Figure 1—*Mean percent change (SE) in total hip BMD and lumbar spine BMD in diabetic and nondiabetic women, by treatment group.* ▲*, ALN, nondiabetic women;* ■*, ALN, diabetic women;* △*, placebo, nondiabetic women;* □*, placebo, diabetic women.*

tablets were similar in the ALN and placebo groups among women with (80.5% in the ALN group vs. 79.1% in the placebo group) and without (83.9% in the ALN group vs. 83.1% in the placebo group) diabetes.

Diabetic women in the ALN group experienced gains in BMD at all sites, including 2.4% at the total hip and 6.6% at the lumbar spine, whereas in the placebo group, BMD increased 0.5% at the lumbar spine and decreased at all the other sites (Table 2 and Fig. 1). The mean percent change of BMD in the ALN and placebo groups did not differ appreciably from the values in Table 2 when adjusted for the effects of study arm, number of days cut down on usual activities because of injury/illness, number of days in bed because of injury/illness, and use of estrogen at any time since menopause (data not shown). A history of diabetes did not modify the effect of ALN treatment on BMD. However, in the placebo group, diabetic women lost more bone than nondiabetic women ($P = 0.04$) at the total hip and intertrochanter.

Diabetic women on ALN had mean decreases of 30.2% for BSAP, 41.9% for NTx, and 52.4% for CTx from baseline—values much larger than in the placebo group (Table 3). Diabetic and nondiabetic women in the placebo group experienced similar decreases in markers of bone turnover.

Clinical adverse experiences were generally not related to the study drug and were relatively uncommon (Table 4). There were small nonsignificant differences in most adverse upper gastrointestinal events in diabetic women, except for abdominal pain, which was more frequent in the ALN group. Four women with diabetes (three in the ALN group [2.04%] and one in the placebo group [0.67%]) had abdominal pain that resulted in hospitalization, but the number of women with abdominal pain who discontinued study medication was similar in the ALN and placebo groups. Among nondiabetic women, adverse experiences were similar in the ALN and placebo groups (two in the ALN group [0.06%] and six in the placebo group [0.20%] had abdominal pain that resulted in hospitalization).

CONCLUSIONS — We found that ALN increases BMD in older women with low BMD and type 2 diabetes. On average, ALN treatment was associated with BMD increases of 6.6% at the lumbar spine and 2.4% at the total hip over 3 years in women with diabetes. The increase in BMD in the ALN group relative to placebo was similar for women with and without diabetes. However, diabetic women in the placebo group lost more BMD than nondiabetic women over the study period at the total hip—a finding consistent with previous reports (11,12).

ALN was generally well tolerated in participants with and without diabetes, except for abdominal pain, which was more frequent in diabetic women taking ALN than in diabetic women taking placebo. This finding could have been due to chance, because it was not hypothesized a priori. In other clinical trials (9,13,14), the overall safety profile of ALN was similar to that of placebo, although abdominal pain was the adverse event most commonly associated with ALN use (13). As in our study, abdominal pain was generally mild and did not lead to excess discontinuation rates relative to placebo (13). In general, the overall safety/tolerability profile of ALN was comparable in diabetic and nondiabetic women.

In our study, treatment with ALN in diabetic women decreased concentrations of two markers of bone formation and one marker of bone resorption over 1 year, consistent with previous findings that ALN inhibits osteoclast-mediated bone resorption, increases calcium bal-

Table 3—*Mean percent difference of biochemical markers of bone turnover between ALN and placebo groups among women with and without type 2 diabetes at 1 year*

	Diabetic women		Nondiabetic women		*P* value, test for homogeneity*
	ALN	Placebo	ALN	Placebo	
BSAP (units/l)					
n	143	139	2,927	2,918	
Percent change from baseline	−29.7 ± 1.9†‡	−7.6 ± 2.3§	−31.2 ± 0.4†‡	−8.5 ± 0.4§	
Percent difference‖		−22.1 (−27.5 to −16.7)		−22.7 (−23.9 to −21.5)	0.9
NTx (μg/l)					
n	136	126	2,638	2,659	
Percent change from baseline	−42.8 ± 2.6†‡	−10.9 ± 3.2§	−51.3 ± 0.7†‡	−9.5 ± 0.7§	
Percent difference‖		−31.9 (−40.9 to −23.0)		−41.8 (−43.6 to −39.9)	0.1
CTx (pmol/l)					
n	141	138	2,918	2,907	
Percent change from baseline	−52.4 ± 2.6†‡	−22.9 ± 4.0§	−59.6 ± 0.6†‡	−31.0 ± 0.7§	
Percent difference‖		−29.6 (−38.9 to −20.2)		−28.6 (−30.4 to −26.8)	0.2

Data are *n*, means ± SE, or means (95% CI). **P* value for interaction between treatment and history of diabetes among all women combined; †$P \leq 0.001$ vs. placebo; ‡$P \leq 0.001$ vs. baseline; §$P \leq 0.05$ vs. baseline; ‖mean percent difference between alendronate and placebo groups.

ance, and secondarily suppresses bone formation (15). ALN had a similar effect on bone turnover markers compared with placebo in women with and without diabetes. Our findings are supported by a 6-month study of periodontal disease among type 2 diabetic men and women 50–60 years of age, where 10 mg/day ALN treatment decreased type I collagen cross-links of N-telopeptide, a biochemical marker of bone resorption (16). Diabetic women in the placebo group also experienced modest decreases in concentrations of markers of bone turnover, which likely resulted from the antiresorptive effects of calcium supplements given to women with low dietary calcium intake (17).

Although this study found that ALN increases BMD in older women with diabetes and low BMD, other studies would be needed to determine whether ALN reduces the risk for fractures in these women as well. (In this study, the relative risk of all nonspine fractures with ALN treatment in diabetic women was 0.74 [95% CI 0.40–1.37].) FIT and other studies (8,9,18,19) have demonstrated that ALN reduces the incidence of fractures by ~50% in older women with low BMD, but the specific effect of ALN on fracture risk in women with type 2 diabetes and low BMD is not known. Because type 2 diabetes is associated with an increased risk for fracture in women without low BMD (5), it is important to determine the efficacy of ALN on BMD and fractures in these women as well. It is possible that other factors unlikely to be affected by ALN therapy (such as altered proprioception, balance and gait problems from neuropathy, and visual impairment from diabetic retinopathy and cataracts) may influence the risk for falls and fractures. A recent study found that older women with diabetes were at an increased risk for falling, partly because of an increased frequency of known fall risk factors in diabetic subjects (20).

This is the first analysis to evaluate the effectiveness of ALN specifically in older women with type 2 diabetes. Strengths of this analysis are that self-reported history of diabetes was supplemented with information on medications, the trial had balanced numbers of diabetic subjects in treatment arms and treatment groups, and there was good power to assess changes in BMD. Although there was no way to exclude women who reported diabetes but did not actually have the disease, published studies indicate that the misclassification of diagnosed diabetes in-

Table 4—*Adverse experiences among women with and without type 2 diabetes, by treatment group*

	Diabetic women		Nondiabetic women	
	ALN	Placebo	ALN	Placebo
Experience leading to permanent discontinuation	15.5 (23)	12.8 (23)	8.9 (276)	10.1 (310)
Experience resulting in hospitalization	10.8 (16)	8.7 (13)	4.9 (151)	4.8 (147)
Upper gastrointestinal events				
Any	53.4 (79)	45.6 (68)	43.2 (1,334)	43.2 (1,327)
Abdominal pain	27.0 (40)*	14.8 (22)	13.1 (403)	13.0 (400)
Esophagitis	2.7 (4)	0.7 (1)	0.7 (22)	0.4 (13)
Esophageal ulcer	0.7 (1)	0 (0)	0.2 (6)	0.2 (6)
Other esophageal	2.0 (3)	2.0 (3)	1.9 (57)	1.6 (49)
Acid regurgitation/reflux	8.8 (13)	6.7 (10)	8.5 (262)	8.3 (255)

Data are percent (*n*). **P* < 0.05 for diabetic women in the ALN vs. placebo treatment arm.

troduced by self-report is relatively small (21,22). In addition, some women with late-onset type 1 diabetes may have been included in our group of type 2 diabetic subjects. Alternatively, individuals classified without diabetes may have included women with diabetes. However, this would most likely cause our reported differences between individuals with and without diabetes to be underestimated. In addition, only community-dwelling older postmenopausal women with low BMD and/or existing vertebral fractures were included, of which 97% were white. Therefore, these findings may not be generalizable to men, other race/ethnicities, institutionalized women, or women with higher BMD. Finally, because this trial lasted for 3 years, important questions on the effect of longer treatment could not be assessed.

In summary, 5 mg/day oral ALN for 2 years followed by 10 mg/day oral ALN for 1 year among women with type 2 diabetes increased BMD at all skeletal sites studied and reduced concentrations of biochemical markers of bone turnover. Women with diabetes in the placebo group experienced decreases in BMD at all sites except the lumbar spine. In general, the magnitude of change in BMD with ALN treatment compared with placebo was similar in women with and without diabetes. Because numbers of diabetic subjects were too small to consider fracture as an end point, further studies may be needed to evaluate the antifracture effectiveness of ALN in diabetic women with and without low BMD.

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APPENDIX

Coordinating center and radiology group

University of California, San Francisco, California: S.R. Cummings, D.M. Black, M.C. Nevitt, H.K. Genant, D. Bauer, S. Rubin, T. Fuerst, M. Jergas, C. Fox, L. Palermo, P. Ramsay, L. Christianson, M. Dockrell, B. Forsyth, F. Harris, L. Laidlaw, R. san Valentin, H. Tabor, and L. Vallee.

Clinical centers

Group Health Cooperative of Puget Sound, Seattle, Washington: A.Z. LaCroix, S. Ott, D. Scholes, and D. Edgerton. Kaiser Permanente Center for Health Research, Portland, Oregon: T.M. Vogt, W. Vollmer, E. Orwoll, J. Blank, D. Towery, H. Houston, C. Romero, and J. Downing. Stanford Medical Center, Palo Alto, California: W.L. Haskell, R. Marcus, M.L. Villa, J. Fair, J. Myll, A. Mylod, J. Shelby, and L. Cadelgo. University of California, San Diego, California: E. Barrett-Connor, M. Schulman, M.L. Carrion-Petersen, M. Wong, D. Price, K. Kadlec, N. Kamantigue, and C. Kotewa. University of Iowa, Iowa City, Iowa: J.C. Torner, R.B. Wallace, K.A. Brake, C. van Hofwegen, R. Hartung, T. Peters, K. Brasch, and K. Canady. University of Maryland, Baltimore, Maryland: R. Sherwin, J.C. Scott, M.C. Hochberg, J.C. Lewis, and B. Ballard. University of Miami Medical School, Miami, Florida: R.J. Prineas, A. Sampson, C. Crutchfield, T.I. Blake, E. Eismont, C. Casanova, and C.H. Lee. University of Minnesota, Minneapolis, Minnesota: K. Ensrud, C. Bell, L. Stocke, J. Griffith, F. Galle, C. Quinton, R. Hansen, and K. Pladsen. University of Pittsburgh, Pittsburgh, Pennsylvania: J. Cauley, R. McDonald, M. Vogt, J. Bonk, L. Harper, and K. Lucas. University of Tennessee, Memphis, Tennessee: W. Applegate, N. Miles, J. Elam, L. Lichtermann, K. Phillips, and S. Satterfiel. Wake Forest University, Winston-Salem, North Carolina: S.A. Quandt, C. Furberg, G. Tell, T. Pope, E.M. Cody, S. Marion, and J. Stough.

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