0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(8):2882–2887

doi: 10.1210/jc.2006-0190

Effects of Teriparatide, Alendronate, or Both on Bone Turnover in Osteoporotic Men

Joel S. Finkelstein, Benjamin Z. Leder, Sherri-Ann M. Burnett, Jason J. Wyland, Hang Lee, Amanda Victoria de la Paz, Kate Gibson, and Robert M. Neer

Endocrine Unit, Department of Medicine (J.S.F., B.Z.L., S.-A.M.B., J.J.W., K.G., A.V.d.l.P., R.M.N.) and Biostatistics Center (H.L.), Massachusetts General Hospital, Boston, Massachusetts 02114

Context: We have previously demonstrated that alendronate reduces the ability of teriparatide to increase bone mineral density (BMD) in osteoporotic men. The underlying basis for this observation is poorly understood.

Objective: The primary aim of this study was to determine whether teriparatide increases osteoblast activity when the ability of teriparatide to increase osteoclast activity is suppressed by alendronate.

Design: This was a nonblinded, randomized, controlled trial.

Setting: The study was conducted at the General Clinical Research Center of a teaching hospital.

Patients: We studied 63 men, age 46–85, with low spine and/or hip BMD.

Interventions: Subjects received alendronate 10 mg daily (group 1), teriparatide 37 μg sc daily (group 2), or both (group 3) for 30 months. Teriparatide was begun at month 6.

Main Outcome Measures: The primary endpoint was the change in serum N-telopeptide, osteocalcin, and amino-terminal propeptide of type 1 procollagen.

Results: In men receiving teriparatide monotherapy (group 2), levels of all bone turnover markers increased markedly during the first 6 months of teriparatide administration and then declined toward baseline during the next 18 months. In men who received combination therapy (group 3), bone turnover marker levels declined in the first 6 months (while receiving alendronate alone) and then returned to baseline levels (N-telopeptide) or above (osteocalcin and amino-terminal propeptide of type 1 procollagen) after teriparatide was added. Changes in each marker were significantly different between groups 1 and 2 (all P values < 0.001), groups 1 and 3 (all P values < 0.001), and groups 2 and 3 (all P values < 0.03).

Conclusions: As with BMD, alendronate impairs the action of teriparatide to increase bone turnover in men. **(*J Clin Endocrinol Metab* 91: 2882–2887, 2006)**

OSTEOPOROSIS AFFECTS OVER 20 million Americans and leads to about 1.5 million fractures each year in the United States (1). Although more common in women, about 30% of all osteoporotic fractures occur in men (2).

Alendronate (3–8) and once-daily PTH fragment administration (9–13) both increase bone mineral density (BMD) in osteoporotic men and women but do so by different mechanisms. Alendronate, a potent nitrogen-containing bisphosphonate, inhibits osteoclastic bone resorption and reduces osteoblastic bone formation. In contrast, once-daily PTH administration increases both bone formation and bone resorption. Thus, it seemed likely that combining human PTH(1–34) (teriparatide) with alendronate might increase BMD more than either agent alone. Surprisingly, however, we and others recently demonstrated that combining alendronate and PTH either failed to increase BMD more than monotherapy with PTH or actually impaired the ability of PTH to increase BMD of the lumbar spine and femoral neck (14, 15). To explore the mechanism of this unexpected finding, we performed detailed measurements of multiple biochemical markers of bone turnover in these subjects and explored their relationships with each other and with longitudinal changes in BMD at multiple skeletal sites.

First Published Online May 9, 2006

Abbreviations: AUC, Area under the curve; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; NTX, N-telopeptide; OC, osteocalcin; P1NP, amino-terminal propeptide of type 1 procollagen; QCT, quantitative computed tomography.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Subjects and Methods

Study subjects

Recruitment of the cohort and eligibility criteria have been described previously (14). Briefly, all subjects were required to be 46–85 yr of age, have BMD of the lumbar spine in the posterior-anterior and/or lateral projection and/or the femoral neck at least 2 SD below the mean of young normal men, and have a serum calcium level less than 10.6 mg/dl, serum 25-hydroxyvitamin D of at least 15 ng/ml, and normal levels of serum intact PTH, TSH, and testosterone. Men with disorders or who were taking medications known to affect bone metabolism or other chronic diseases (14) were excluded. Because biochemical markers of bone turnover change rapidly once teriparatide treatment is stopped, men who failed to complete the study on their assigned treatment were excluded prospectively from all analyses as designated in the prestudy analysis plan.

Study protocol

The study protocol has been described previously (14). Briefly, participants were randomly assigned by a computerized program to receive alendronate alone (10 mg orally once daily, group 1; n = 28), teriparatide alone (40 μg sc once daily, group 2; n = 27), or both (group 3; n = 28). Twenty men (three in group 1, 10 in group 2, and seven in group 3) discontinued study medication before completing the protocol. Thus, the final cohort consisted of 63 men who completed the protocol on assigned treatment.

Alendronate was begun at the baseline visit and continued for 30 months in groups 1 and 3. Teriparatide was begun at the 6-month visit and continued for 24 months in groups 2 and 3. Teriparatide was started after 6 months of alendronate to determine whether teriparatide's ability to increase osteoblast activity is attenuated when its ability to increase osteoclast activity is suppressed. Calcium intake was estimated by a research dietitian and maintained at 1000–1200 mg daily through diet and/or supplements. All subjects received 400 U vitamin D daily. If the 25-hydroxyvitamin D level (measured every 6 months) fell to less than 15 ng/ml, additional vitamin D supplementation was given.

Blood was collected at baseline and at 1, 2, 3, 6, 7, 8, 9, 12, 18, 24, and 30 months to assess routine chemistries and biochemical markers of bone turnover including serum N-telopeptide (NTX), osteocalcin (OC), and amino-terminal propeptide of type 1 procollagen (P1NP). Serum calcium was measured before and 4–6 h after teriparatide injection. Twenty-four-hour urinary calcium excretion was measured before and 1 month after starting teriparatide (month 7) and then every 6 months. BMD was measured by dual-energy x-ray absorptiometry (DXA) at baseline and every 6 months and by quantitative computed tomography (QCT) at baseline and month 30. Compliance with study medications was assessed by medication diaries and by counting residual medication supplies. The study was approved by the Institutional Review Board of Partners HealthCare System, and all subjects provided written informed consent.

PTH preparation and dose adjustments

Good-manufacturing-practices-grade synthetic human PTH(1–34) (Bachem, Inc., Torrence, CA) was placed into vials as a sterile lyophilized powder (with mannitol, U.S.P.) under good-manufacturing-practices conditions by Ben-Venue Laboratories (Bedford, OH). Amino acid and HPLC analysis of the teriparatide preparation revealed that each vial contained 37 μg rather than the intended 40 μg.

The teriparatide dose was reduced by 25% if any serum calcium value was above 10.5 mg/dl or if the investigators felt that the subject was experiencing a side effect of therapy. If hypercalcemia or symptoms persisted, the teriparatide dose was reduced by another 25%. If hypercalcemia or symptoms persisted after two dose reductions, teriparatide was discontinued. If the 24-h urinary calcium excretion was above 400 mg/d, dietary calcium and/or sodium was reduced by 25–50%. If hypercalciuria persisted, the teriparatide dose was reduced by 25–50% as described above. If hypercalciuria persisted after a 50% dose reduction, teriparatide was discontinued.

Measurements of bone turnover

Serum NTX was measured using an enzyme-linked immunoassay (Wampole Laboratories, Princeton, NJ). Serum OC was measured using an enzyme-linked immunoassay (ALPCO Diagnostics, Windham, NH). Serum P1NP was measured using a RIA (Orion Diagnostica, Espoo, Finland). All samples for each subject were run in the same assay unless an individual value needed to be repeated.

Measurements of BMD

BMD of the lumbar spine in the posterior-anterior and lateral projections, the proximal femur, the distal one-third radius shaft, and total body was measured by DXA using a Hologic QDR 4500A densitometer (Hologic, Waltham, MA). Our short-term *in vivo* measurement SD values (with repositioning) are 0.005, 0.014, 0.007, and 0.006 g/cm^2 for posterior-anterior spine, lateral spine, femoral neck, and total hip, respectively. For men with T scores of 0, these values correspond to reproducibility errors of 0.5, 0.8, and 0.6% for the posterior-anterior spine, femoral neck, and total hip.

Trabecular BMD of the first four lumbar vertebrae was determined by QCT with General Electric model QXI or Lightspeed Plus scanners. Our short-term *in vivo* measurement SD (with repositioning) is 5 mg/cc (16). All DXA and QCT bone density scans were analyzed by individuals who were blinded to study treatment.

Statistical analysis

The predetermined primary endpoints were the differences in area under the curve (AUC) of serum OC, P1NP, and NTX across the three treatment groups. As per the prespecified analysis plan, we performed a per-protocol analysis. AUC was calculated using the trapezoidal rule. For group 1, AUC was determined from months 0–30. Because teriparatide was started at month 6, AUC was determined from months 6–30 for groups 2 and 3. The AUCs were then compared using a one-way ANOVA. If significant differences were found, pairwise comparisons were performed and the type-1 error rate was adjusted for the multiple comparisons using Bonferroni's method. If the normality assumption was not held, Kruskal-Wallis test and Mann-Whitney *U* test were used. Pearson correlation coefficients were determined to assess associations among the three markers of bone turnover. To assess the relationships between changes in bone turnover and changes in BMD, Pearson correlation coefficients were also determined between changes in AUC of OC, P1NP, and NTX and the percent change in BMD at each skeletal site. To determine whether early changes in bone turnover could predict changes in BMD, Pearson correlations were determined between the percent change in each marker during the first 6 months of active therapy in each group (months 0–6 for group 1 and months 6–12 for groups 2 and 3) and the percent change in BMD at each site. Baseline values of the three treatment groups were compared by ANOVA. All *P* values are two sided and values <0.05 are considered statistically significant. Unless otherwise noted, data are presented as the mean ± SD.

Results

Characteristics of the subjects

The baseline characteristics of the 63 subjects (group 1, n = 25; group 2, n = 21; group 3, n = 17) are shown in Table 1. Two men were Asian, one was Indian, one was African-American, one was a Pacific Islander, and the remaining 58 were non-Hispanic Caucasians. There were no significant differences in baseline characteristics among groups.

Adherence to protocol medication

All but three men took at least 95% of their alendronate doses, and all but nine men took at least 90% of their teriparatide doses. Five (24%) men in group 2 had their teriparatide dose reduced by 25% and five (24%) by 50%. Four (24%) men in group 3 had their teriparatide dose reduced by 25% and five (29%) by 50%. Two men in group 2 had their teriparatide dose reduced because of hypercalcemia and four because of hypercalciuria. Four men in group 3 had their teriparatide dose reduced because of hypercalcemia and two because of hypercalciuria. The remaining dose reductions were because of possible side effects.

Changes in bone turnover markers

Mean (± SE) percent change in serum OC, P1NP, and NTX levels during the 30-month study period are shown in Fig. 1. In men treated with alendronate alone, mean serum OC and P1NP declined from baseline to month 6 and then remained stable, whereas mean serum NTX reached its nadir within 1–2 months. In men treated with teriparatide alone, mean serum OC, P1NP, and NTX reached peak values by month 12 (*i.e.* 6 months after starting teriparatide) and then declined gradually. Serum NTX increased less rapidly than did OC or P1NP in response to teriparatide alone. In men treated with teriparatide plus alendronate, changes in all three markers mirrored those observed in men treated with alendronate alone from month 0–6, the time when both groups received only alendronate. During the first 2 months of combined therapy, mean serum OC and P1NP levels rose steeply and continued to increase throughout the study period, eventu-

TABLE 1. Baseline characteristics of men with osteoporosis treated with alendronate alone (ALN, group 1), PTH alone (group 2), or both (group 3)

Characteristic	Group 1 (n = 25), ALN	Group 2 (n = 17), PTH	Group 3 (n = 21), both	*P* value
Age (yr)	57 ± 7	57 ± 9	58 ± 8	0.84
Height (cm)	174.2 ± 5.4	175.6 ± 5.0	174.8 ± 5.5	0.78
Weight (kg)	76.5 ± 9.7	77.6 ± 13.1	77.8 ± 6.6	0.74
Body mass index (kg/m^2)	25.2 ± 2.7	25.2 ± 4.4	25.5 ± 2.4	0.87
Calcium intake (mg/d)	1162 ± 700	1023 ± 554	1282 ± 602	0.55
Testosterone (ng/dl)[a]	485 ± 137	456 ± 85	546 ± 146	0.06
25-Hydroxyvitamin D (ng/ml)[b]	24 ± 11	22 ± 7	28 ± 11	0.33
Alkaline phosphatase (U/liter)	72 ± 16	78 ± 28	75 ± 14	0.56
DXA BMD (g/cm^2)				
Posterior-anterior spine	0.839 ± 0.115	0.876 ± 0.124	0.860 ± 0.102	0.49
Lateral spine	0.647 ± 0.087	0.680 ± 0.077	0.667 ± 0.061	0.39
Femoral neck	0.669 ± 0.112	0.696 ± 0.089	0.694 ± 0.059	0.43
Total hip	0.828 ± 0.118	0.884 ± 0.101	0.884 ± 0.068	0.15
One third radius	0.744 ± 0.075	0.749 ± 0.046	0.764 ± 0.054	0.45
Total body	0.981 ± 0.114	1.008 ± 0.096	1.008 ± 0.105	0.51
QCT spinal bone density (g/cm^3)	93 ± 22	97 ± 23	97 ± 25	0.70
OC (ng/ml)	25 ± 8	27 ± 6	22 ± 8	0.10
P1NP (ng/ml)	44 ± 13	46 ± 12	41 ± 16	0.21
NTX (nM BCE)	14 ± 3	14 ± 3	13 ± 3	0.54

Values are the mean ± SD. The *last column* shows the *P* values determined by ANOVA across all three groups. BCE, Bone collagen equivalents.
[a] To convert to nanomoles per liter, multiply by 0.0347.
[b] To convert to nanomoles per liter, multiply by 2.496.

ally reaching levels that were approximately twice baseline. Mean serum NTX levels also rose once teriparatide was added to alendronate therapy, but the increases were more gradual and much more modest than for OC or P1NP such that mean NTX levels never exceeded baseline. As a result, mean levels of all three markers converged in men receiving teriparatide alone and in men receiving teriparatide plus alendronate as teriparatide was continued for 2 yr. For each marker, the mean AUC was highest in men treated with teriparatide alone, next highest in men treated with teriparatide plus alendronate, and lowest in men treated with alendronate alone, and all groups differed from one another ($P < 0.001$ for all comparisons between groups 1 and 2 and groups 1 and 3 and $P < 0.03$ for all comparisons between groups 2 and 3).

Associations among bone turnover markers and BMD

There were significant associations among serum OC, P1NP, and NTX in all three groups during treatment (Table 2). In group 1, these associations ranged from 0.52–0.78. Associations among markers were slightly stronger in the two PTH-treated groups than in the group treated with alendronate alone. In men treated with PTH alone or alendronate alone, the association between OC and P1NP was somewhat stronger than the association between NTX and OC or NTX and P1NP.

Associations between the percent change in AUC for bone turnover markers and percent change in BMD of the spine, hip, total body, and radius shaft are shown in Table 3. In group 1, associations were consistently negative and significant only

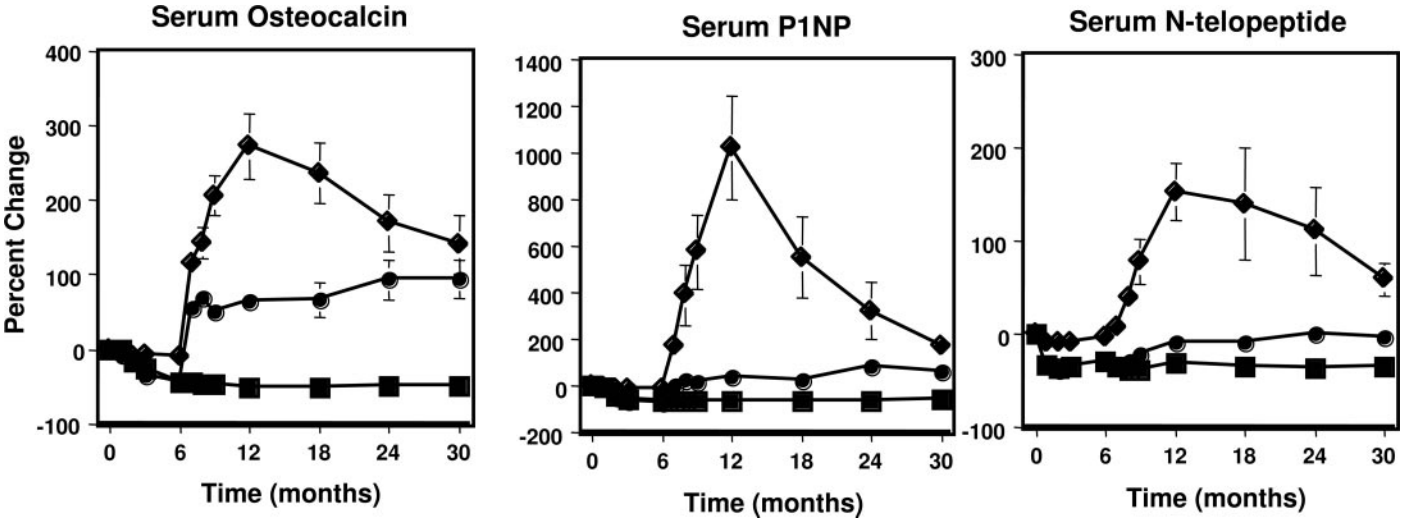

FIG. 1. Mean percent change from baseline for serum OC, P1NP, and NTX in men receiving alendronate alone (■), human PTH(1–34) alone (♦), or both (●). PTH was begun at month 6. Data are plotted as the mean (±SE). *Error bars* that are not seen are contained within the *symbols*.

TABLE 2. Associations among changes in AUC of bone turnover markers in men with osteoporosis during treatment with alendronate alone (group 1), PTH alone (group 2), or both (group 3)

Group	P1NP *vs.* OC	P1NP *vs.* NTX	OC *vs.* NTX
1	0.78[a]	0.62[a]	0.52[b]
2	0.86[a]	0.68[b]	0.67[b]
3	0.88[a]	0.85[a]	0.91[a]

[a] $P < 0.001$.
[b] $P < 0.01$.

when comparing changes in OC AUC with changes in lateral spine (r = −0.64) or total body (r = −0.49) BMD, NTX AUC with changes in femoral neck BMD (r = −0.46), or P1NP AUC with changes in lateral spine BMD (r = −0.64). In group 2, there were moderately strong positive associations between the percent change in femoral neck BMD and the change in AUC for P1NP (r = 0.74), OC (r = 0.67), and NTX (r = 0.64) and moderate associations between changes in bone markers and the percent change in radius shaft BMD (r = −0.45 to −0.48) and total hip BMD (r = 0.31 to 0.48). In group 3, there were moderately strong associations between the percent change in radius shaft and lateral spine BMD and the percent change in AUC for each marker (r = −0.58 to −0.65 for radius shaft, and r = 0.53 to 0.69 for lateral spine) and moderate associations between changes in bone markers and the percent change in total hip BMD (r = −0.27 to −0.61). In general, associations between changes in bone turnover and changes in BMD at a given skeletal site were of similar magnitude for each marker.

TABLE 3. Associations between changes in AUC of bone turnover markers and percent change in BMD from months 0–30 in men with osteoporosis during treatment with alendronate alone (group 1), PTH alone (group 2), or both (group 3)

	P1NP	OC	NTX
Posterior-anterior spine			
Group 1	−0.18	−0.45	0.01
Group 2	0.32	0.38	0.08
Group 3	0.08	0.51[a]	0.38
Lateral spine			
Group 1	−0.37	−0.64[b]	−0.42
Group 2	0.26	0.06	−0.12
Group 3	0.53[a]	0.65[b]	0.69[b]
Total hip			
Group 1	−0.08	−0.18	−0.28
Group 2	0.48[a]	0.43	0.31
Group 3	−0.61[b]	−0.27	−0.33
Femoral neck			
Group 1	−0.05	−0.12	−0.46[a]
Group 2	0.74[b]	0.67[b]	0.64[b]
Group 3	0.00	0.14	0.18
Total body			
Group 1	−0.45[a]	−0.49[b]	−0.09
Group 2	0.21	0.07	−0.03
Group 3	−0.46	−0.23	−0.20
Radius shaft			
Group 1	−0.32	−0.08	−0.39
Group 2	−0.45	−0.48	−0.46
Group 3	−0.61[b]	−0.58[b]	−0.65[b]
QCT			
Group 1	−0.28	−0.06	−0.03
Group 2	0.28	0.41	0.34
Group 3	0.26	0.16	0.11

[a] $P < 0.05$.
[b] $P < 0.01$.

Because there might be clinical utility if early changes in markers predict subsequent changes in BMD, we also examined associations between the percent change in each marker during the first 6 months of randomly assigned therapy and the percent change in BMD across the entire study period. Once again, there were several moderately strong associations between changes in markers and changes in BMD. Associations between percent change in BMD and the change in bone formation markers across the entire treatment period were often stronger than similar associations with the 6-month percent change in bone formation markers (data not shown, available upon request).

Discussion

In this study, administration of alendronate, a potent inhibitor of bone resorption, reduced the ability of once-daily teriparatide administration to increase levels of serum P1NP, OC, and NTX, biochemical markers used to reflect activity of osteoblasts and osteoclasts (17). These findings suggest that alendronate impairs the ability of teriparatide to stimulate new bone formation in men and are consistent with our previous report that alendronate impairs the ability of teriparatide to increase BMD of the lumbar spine and femoral neck in men (14). Similar results have been reported in a shorter study comparing the effects of alendronate, PTH, or both in postmenopausal women (15).

Our objective was to determine whether bone resorption is required for teriparatide to increase bone formation. A previous study had demonstrated that 6 wk of daily teriparatide treatment failed to increase bone resorption (as reflected by urinary excretion of NTX and free deoxypyridinoline) in postmenopausal women who had received alendronate for an average of 11 months (18). To prevent teriparatide-induced increases in bone resorption, we administered alendronate for 6 months before initiating teriparatide administration. By and large, we accomplished our goal. Mean serum NTX levels, used to reflect bone resorption, never exceeded baseline levels in the men who received combination therapy, indicating that bone resorption was not elevated above normal in those men. Despite this, mean serum OC and P1NP levels clearly increased above baseline in these men, although the increases in these bone formation markers were dramatically attenuated compared with the increases in OC and P1NP in men treated with teriparatide alone. These findings indicate that alendronate attenuates the ability of teriparatide to increase bone formation and strongly suggest that bone resorption plays an important role in the anabolic actions of PTH on bone. It should be noted, however, that serum NTX levels did increase modestly, reaching pre-alendronate baseline levels, when teriparatide was added to alendronate, indicating that alendronate did not completely block the ability of teriparatide to stimulate bone resorption. It is unclear whether the anabolic capacity of teriparatide would have been attenuated further if alendronate had totally blocked teriparatide's ability to stimulate bone resorption.

Several other studies have examined the effects of PTH plus antiresorptive agents in humans. Three randomized, controlled studies reported that teriparatide increases BMD in postmenopausal women taking estrogen or estrogen-progestin replacement therapy (19–21). Because none of

these studies included a group of subjects treated with teriparatide alone, however, it is not possible to determine whether postmenopausal hormone therapy augments, does not affect, or reduces the ability of teriparatide to increase BMD. Moreover, because hormone therapy failed to prevent teriparatide-induced increases in bone resorption in these women, the role that bone resorption plays in the anabolic effects of teriparatide could not be assessed (21). In women on long-term alendronate therapy a 6-wk course of teriparatide increased markers of osteoblast activity without increasing markers of osteoclast activity (18). Once again, however, the lack of a group of subjects treated with teriparatide alone makes it impossible to determine whether alendronate reduced the ability of teriparatide to increase bone formation activity. Teriparatide increased bone formation and BMD less in postmenopausal women previously treated with alendronate than in postmenopausal women previously treated with raloxifene (22). Because alendronate is a more potent antiresorptive agent than raloxifene and has a much longer biological half-life, this finding is also consistent with the notion that antiresorptive agents mitigate the anabolic effects of teriparatide. This study also raises the question whether different classes of antiresorptives, such as bisphosphonates, hormone therapy, selective estrogen receptor modulators, or antibodies against receptor activator of nuclear factor-κB ligand (RANKL), may affect PTH action differently. Finally, in a 6-month study, total hip BMD increased slightly more when teriparatide was given together with raloxifene, although changes in lumbar spine and femoral neck BMD were similar (23). The short duration of this study limits interpretation of its findings.

The mechanisms whereby alendronate attenuates the anabolic action of teriparatide is unknown, although some mechanisms have been proposed. PTH could exert its anabolic effect on bone either indirectly via a mechanism that requires it to increase osteoclastic bone resorption or via a direct stimulatory effect on osteoblastic bone formation. Bone resorption may release preformed growth factors adsorbed to bone matrix such as IGF-I, TGF-β, or basic fibroblast growth factor (24). If these locally released growth factors cause or enhance the anabolic action of PTH, suppressing bone resorption would impair the anabolic actions of PTH as observed in our subjects. Osteoclasts may also activate osteoblasts by direct intercellular communications, as has been established for osteoblastic regulation of osteoclast formation (25). In contrast, PTH might stimulate bone formation independently of its effects on bone resorption, either by reducing osteoblast apoptosis (26) or by increasing the local production of IGF-I or other growth factors that stimulate osteoblast activity (27–29). Bisphosphonates reduce the number and activity of osteoblasts (30). In the presence of alendronate, there may be fewer osteoblasts available for stimulation by PTH or the activity of individual osteoblasts could be impaired. Thus, although our data strongly suggest that bone resorption is required, at least in part, for the anabolic actions of PTH, we cannot exclude the possibility that these results are due to direct effects of alendronate on osteoblasts.

Levels of bone turnover markers peaked after 6 months of treatment with teriparatide monotherapy and then declined toward baseline. This pattern is similar to that which we (12) and others (9, 10, 21, 31–34) have reported previously in humans. The mechanism for this delayed PTH resistance is unknown, although it could reflect a depletion of osteoblast precursors, a decrease in osteoblast sensitivity to teriparatide, changes in teriparatide absorption, changes in teriparatide metabolism, or other factors. Interestingly, although teriparatide-induced increases in markers of osteoblast activity were attenuated by alendronate, these markers continued to increase gradually throughout the study period in men receiving combination therapy. Thus, the formation markers in the teriparatide-treated groups were converging by the end of the study period, a finding that was not apparent in a similar shorter study (15). If combination therapy were continued even longer, it is possible that osteoblast activity would eventually be similar to or even surpass levels in men treated with teriparatide monotherapy. Such putative effects and the long-term consequences of combination therapy on BMD and fractures warrant additional study.

No consistent pattern of associations was observed between changes in markers of bone turnover and changes in BMD. In men treated with teriparatide alone, increases in bone turnover markers were most strongly associated with changes in hip and radius shaft BMD. In men treated with teriparatide plus alendronate, increases in markers of bone turnover were best associated with changes in spine and radius shaft BMD. In women with postmenopausal osteoporosis, changes in the serum carboxyl-terminal propeptide of type 1 procollagen after 1 month of teriparatide therapy and P1NP after 3–6 months were the best predictors of subsequent increases in lumbar spine BMD (32, 34). Similar associations have been reported between bone turnover markers and changes in spine BMD with teriparatide administration in postmenopausal women on chronic estrogen and glucocorticoid therapy (33) and in men (9). We did not find any advantage of measuring early changes in bone turnover *vs.* cumulative changes in bone turnover for predicting changes in BMD. Additionally, markers used to assess osteoblast activity offered no consistent advantage over a marker used to assess osteoclast activity in predicting changes in BMD in response to teriparatide, and none of the associations was strong. Thus, although measurements of bone turnover markers provide valuable insight into teriparatide pharmacotherapy, these markers are unlikely to provide important clinical information in individual patients treated with teriparatide monotherapy or with combination therapy.

The dose of teriparatide employed (37 μg) was higher than that currently approved by the U.S. Food and Drug Administration (20 μg) but similar to the dose used in many clinical studies of teriparatide (10–13, 35). Alendronate might impair the ability of a lower dose of teriparatide to increase bone turnover even more. If so, antiresorptive agents might reduce the anabolic effect of teriparatide in clinical practice more dramatically than reported previously (14).

In summary, alendronate impairs the ability of teriparatide to increase bone turnover in osteoporotic men. This finding suggests that bone resorption plays a role in the ability of teriparatide to increase bone formation. After an initial period of dramatic stimulation, bone turnover declines with continued teriparatide monotherapy. Daily injections of teriparatide initially increase indices of bone formation and resorption much more in men receiving teriparatide monotherapy than in men receiving combination therapy, but this

large initial difference dissipates as teriparatide therapy is prolonged. The long-term consequences of these differing patterns of bone turnover merit additional investigation.

Acknowledgments

We thank Ms. Anjali Rao and Ms. Anya Lepp for their meticulous administration of the study protocol and data management, Ms. Robbin Cleary and Ms. Sarah Zhang for performing the bone density measurements, and the nursing and dietary staff of the Mallinckrodt General Clinical Research Center for their dedicated care of the patients.

Received January 27, 2006. Accepted May 3, 2006.

Address all correspondence and requests for reprints to: Joel S. Finkelstein, M.D., Endocrine Unit, Bulfinch 327, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: jfinkelstein@partners.org.

This work was supported by 5 P50 AR44855 and K24 DK02759 (to J.S.F.), K23 RR016310 (to B.Z.L.), and M01-RR-1066 from the National Center for Research Resources, General Clinical Research Centers Program.

References

1. **Finkelstein JS** 2004 Osteoporosis. In: Goldman, L, Ausiello, D, eds. Cecil textbook of medicine. 22nd ed. Philadelphia: Saunders; 1547–1555
2. **Melton LJ** 1999 Epidemiology of fractures. In: Orwoll, ES, ed. Osteoporosis in men. The effects of gender on skeletal health. San Diego: Academic Press; 1–13
3. **Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA** 1999 Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. Proc Natl Acad Sci USA 96:133–138
4. **Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW, Dequeker J, Favus M, Seeman E, Recker RR, Capizzi T, Santora AC, Lombardi A, Shah RV, Hirsch LJ, Karpf DB** 1995 Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 333:1437–1443
5. **Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE** 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348:1535–1541
6. **Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, Ettinger B** 1998 Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med 339:733–738
7. **Ringe JD, Faber H, Dorst A** 2001 Alendronate treatment of established primary osteoporosis in men: results of a 2-year prospective study. J Clin Endocrinol Metab 86:5252–5255
8. **Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A** 2000 Alendronate for the treatment of osteoporosis in men. N Engl J Med 343:604–610
9. **Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP** 2000 Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab 85:3069–3076
10. **Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA** 2003 The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17
11. **Finkelstein JS, Klibanski A, Schaefer EH, Hornstein MD, Schiff I, Neer RM** 1994 Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. N Engl J Med 331:1618–1623
12. **Finkelstein JS, Klibanski A, Arnold AL, Toth TL, Hornstein MD, Neer RM** 1998 Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1–34): a randomized, controlled trial. JAMA 280:1067–1073
13. **Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH** 2001 Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441
14. **Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM** 2003 The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 349:1216–1226
15. **Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ** 2003 The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 349:1207–1215
16. **Rosenthal DI, Ganott MA, Wyshak G, Slovik DM, Doppelt SH, Neer RM** 1985 Quantitative computed tomography for spinal density measurement. Factors affecting precision. Invest Radiol 20:306–310
17. **Bikle D** 1997 Biochemical markers in the assessment of bone disease. Am J Med 103:427–436
18. **Cosman F, Nieves J, Woelfert L, Shen V, Lindsay R** 1998 Alendronate does not block the anabolic effect of PTH in postmenopausal osteoporotic women. J Bone Miner Res 13:1051–1055
19. **Reeve J, Mitchell A, Tellez M, Hulme P, Green JR, Wardley-Smith B, Mitchell R** 2001 Treatment with parathyroid peptides and estrogen replacement for severe postmenopausal vertebral osteoporosis: prediction of long-term responses in spine and femur. J Bone Miner Metab 19:102–114
20. **Roe EB, Sanchez SD, DelPuerto GA, Pierini E, Bacchetti P, Cann CE, Arnaud CD** 1999 Parathyroid hormone 1–34 (hPTH 1–34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis: results from a placebo-controlled randomized trial. J Bone Miner Res 14:S137
21. **Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, Dempster D, Cosman F** 1997 Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet 350:550–555
22. **Ettinger B, San Martin J, Crans G, Pavo I** 2004 Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 19:745–751
23. **Deal C, Omizo M, Schwartz EN, Eriksen EF, Cantor P, Wang J, Glass EV, Myers SL, Krege JH** 2005 Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. J Bone Miner Res 20:1905–1911
24. **Oreffo ROC, Mundy GR, Seyedin S, Bonewald LF** 1989 Activation of the bone derived latent TGF-β complex by isolated osteoclasts. Biochem Biophys Res Commun 158:817–823
25. **Martin TJ, Sims NA** 2005 Osteoclast-derived activity in the coupling of bone formation to resorption. Trends Mol Med 11:76–81
26. **Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC** 1999 Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest 104:439–446
27. **Canalis E, Centrella M, Burch W, McCarthy TL** 1989 Insulin-like growth factor I mediates selective anabolic effects of parathyroid hormone in bone cultures. J Clin Invest 83:60–65
28. **McCarthy TL, Centrella M, Canalis E** 1989 Parathyroid hormone enhances the transcript and polypeptide levels of insulin-like growth factor I in osteoblast enriched cultures from fetal rat bone. Endocrinology 124:1247–1253
29. **Kream BE, Petersen DN, Raisz LG** 1990 Parathyroid hormone blocks the stimulatory effect of insulin-like growth factor-I on collagen synthesis in cultured 21-day fetal rat calvariae. Bone 11:411–415
30. **Vaisman DN, McCarthy AD, Cortizo AM** 2005 Bone-specific alkaline phosphatase activity is inhibited by bisphosphonates: role of divalent cations. Biol Trace Elem Res 104:131–140
31. **Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, Dore RK, Correa-Rotter R, Papaioannou A, Cumming DC, Hodsman AB** 2002 A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 87:4528–4535
32. **Chen P, Satterwhite JH, Licata AA, Lewiecki EM, Sipos AA, Misurski DM, Wagman RB** 2005 Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. J Bone Miner Res 20:962–970
33. **Lane NE, Sanchez S, Genant HK, Jenkins DK, Arnaud CD** 2000 Short-term increases in bone turnover markers predict parathyroid hormone-induced spinal bone mineral density gains in postmenopausal women with glucocorticoid-induced osteoporosis. Osteoporos Int 11:434–442
34. **McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, Donley DW, Dalsky GP, Eriksen EF** 2005 Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med 165:1762–1768
35. **Slovik DM, Rosenthal DI, Doppelt SH, Potts JT, Daly MA, Campbell JA, Neer RM** 1986 Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1–34) and 1,25-dihydroxyvitamin D. J Bone Miner Res 1:377–381