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# Enhancement of Bone Mass in Osteoporotic Women with Parathyroid Hormone followed by Alendronate*

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**ABSTRACT**

Treatment of osteoporosis with PTH causes a marked increase in vertebral bone mineral density (BMD). However, this effect is rapidly reversed when the treatment is stopped. The purpose of the present study was to determine whether the bisphosphonate alendronate could preserve or enhance bone density in patients previously treated with PTH. Sixty-six postmenopausal osteoporotic women were treated for 1 yr with 50, 75, or 100 $\mu$g recombinant human PTH-(1–84) or placebo, and then were given 10 mg alendronate daily for an additional year. BMD was measured in the femoral neck, lumbar spine, and whole body. Markers of bone turnover included skeletal alkaline phosphatase, osteocalcin, and N-telopeptide.

During the first year, changes in BMD (mean ± SD) in women receiving PTH (all doses combined) were 7.1 ± 5.6% (spine), 0.3 ± 6.2% (femoral neck), and −2.3 ± 3.3% (total body). After switching to alendronate for 1 yr in women who previously had received PTH, mean changes in BMD were 13.4 ± 6.4% (spine), 4.4 ± 7.2% (femoral neck), and 2.6 ± 3.1% (whole body). In the subgroup of patients who had received the highest dose of PTH, the mean increase in vertebral BMD was 14.6 ± 7.9%. All markers of bone turnover increased during treatment with PTH and decreased to below baseline after 1 yr of alendronate.

In conclusion, sequential treatment of osteoporosis with PTH and alendronate results in an increase in vertebral bone density that is considerably more than has been reported with alendronate or estrogens alone. This combination of drugs may be a useful approach to maximizing bone density in women with vertebral osteoporosis. (*J Clin Endocrinol Metab* **85:** 2129–2134, 2000)

CURRENTLY accepted medical treatment of postmenopausal osteoporosis involves using agents that inhibit bone resorption: estrogens, bisphosphonates, or calcitonin. These drugs lead to a reduction in bone turnover, as demonstrated by a reduction in markers of both bone formation and resorption (1, 2). The effect of these drugs on bone density is maximal during the first year, resulting in total gains in bone density of less than 10% over 3 yr (3, 4). Many women with osteoporosis, however, have lost over 30% of their peak bone mass and continue to have fractures after being treated with antiresorptive drugs. An ideal therapy for osteoporosis would not only inhibit further bone loss, but would also continually stimulate new bone formation.

PTH increases trabecular bone density by stimulating bone formation (5, 6). Markers of bone formation and resorption increase during PTH treatment (7), and vertebral bone density increases by about 10% after 2 yr (8). In women previously treated with estrogen, the addition of PTH results in a mean increase in vertebral bone density of about 13% during the subsequent 3 yr, with no change in bone density in the women who remain on estrogen alone (9). It appears that estrogens are able to reduce the effects of PTH on bone resorption, but not those on bone formation (10).

One concern with PTH therapy is that its beneficial effects on bone density may decline rapidly over the first year after the medication is stopped. Therefore, it is logical to try to prevent this loss by using an antiresorptive therapy, which might consolidate the dramatic gains resulting from PTH treatment. A preliminary study has shown that cyclical therapy with the bisphosphonate clodronate was unable to maintain the improved vertebral bone density caused by intermittent cyclic PTH treatment (11). Currently, PTH must be given by sc injection, limiting its attractiveness for long-term therapy of osteoporosis. The purpose of the present study was to determine the effect of antiresorptive therapy with alendronate on vertebral, hip, and whole body bone density in osteoporotic postmenopausal women who had previously participated in a 1-yr phase 2 clinical trial involving daily injections of PTH (12).

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## Subjects and Methods

### *Subjects*

To be eligible for this study, women had to be at least 5 yr postmenopausal, aged 50–75 yr, and have a vertebral bone mineral density (BMD) at least 2.5 SD below the mean for young women. Because the

dose of PTH was not adjusted for body weight, they must have weighed no more than 25% above their ideal body weight. Subjects must have been in generally good health, with no diseases known to contribute to osteoporosis and no diseases of the lumbar spine that would compromise interpretation of vertebral BMD. Subjects could not have been treated for osteoporosis with calcitonin during the previous 4 months, with estrogens or cyclical editronate during the previous 6 months (and no more than 2 cycles of etidronate at any time), with fluoride during the previous 12 months, or with bisphosphonates other than editronate at any time. The 66 women in the present study were part of a larger cohort of 206 women who originally entered a 1-yr study of PTH treatment of osteoporosis (12). Of the 161 patients who completed the randomized, multicentered first year of the study, 75 entered the 1-yr open extension with alendronate. Sixty-six patients completed the second year and formed the basis for this report (19, 12, 17, and 18 patients in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively). Of the 28 patients who had whole body bone density determinations, 8, 6, 5, and 9 patients were in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively.

The study protocol for the first year of the study was approved by the institutional review board for each center. The study protocol for alendronate treatment during the second year of the study was approved by the Queen Elizabeth II health sciences research ethics committee and by other local institutional review boards where required. All women provided written informed consent.

### *Protocol*

The first year of the study was a randomized, double blind, multicentered trial in which women were randomized to receive daily sc injections one of three doses (50, 75, or 100 $\mu$g) of recombinant human PTH-(1–84) (Allelix Biopharmaceuticals, Inc., Mississauga, Canada) or placebo. The second year of the study was an open label trial at 7 of the original 18 sites, in which all women received 10 mg alendronate, orally, each morning with a glass of water on an empty stomach and were instructed not to consume anything else for at least 30 min. All participants were also given daily dietary supplements of 500 mg calcium carbonate and 400 IU vitamin D.

BMDs of the lumbar spine and femoral neck were measured using either Lunar Corp. or Hologic, Inc., densitometers at baseline (2 measurements) and after 3, 6, 12, 18, and 24 months. A subgroup of 30 patients also had whole body densitometry at baseline and 12 and 24 months. Follow-up densities for each patient were assessed on the same machine as the original measurements. Quality control and central analysis of the bone density measurements were provided by the University of California Osteoporosis and Arthritis Research Group. Markers of bone formation (serum osteocalcin and skeletal alkaline phosphatase) and of bone resorption [urinary N-terminal collagen telopeptide (NTx)] were measured in 46 of the patients after 12, 18, and 24 months in the laboratory of one of the authors (C.J.R.). Osteocalcin was measured using a two-site immunoradiometric assay (kit DSL-7600, Diagnostics Systems Laboratories, Inc., Webster, TX). Skeletal alkaline phosphatase was measured using the Tandem-R Ostase Immunoradiometric Assay (Hybritech, Inc., San Diego, CA). NTx was measured using an enzyme-linked immunosorbent assay (Osteomark, Ostex International, Inc., Seattle, WA). Specimens were obtained from fasting morning blood or urine. All samples from an individual patient were measured in the same assay run. The mean intraassay coefficients of variation were 3.2% for NTx, 7.1% for osteocalcin, and 4.0% for skeletal alkaline phosphatase.

### *Statistical analysis*

Analysis was performed for all patients who completed the 2-yr study. Results are expressed as the mean ± SD unless otherwise noted. Statistics were performed using StatView (Abacus Concepts, Berkeley, CA) on a MacIntosh computer. Group means were compared using ANOVA, followed by Fisher's protected least significant difference test for *post-hoc*, pairwise comparisons. Comparisons within groups over time were made using a repeated measures ANOVA. $P < 0.05$ was considered statistically significant.

## Results

### *BMD*

The BMD results are expressed as percent changes from baseline to account for differences among densitometers from different manufacturers. The results are shown graphically in Fig. 1. During the first year, the mean vertebral bone density increased by 1.3%, 4.3%, 6.9%, and 9.2% in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively ($P <$ 0.0001). During the second year, in which patients received 10 mg alendronate daily, there was a further increase in the mean vertebral bone density of 5.7%, 6.3%, 6.2%, and 4.9%, respectively ($P$ = NS for the percent change in BMD among the four groups during the second year). After 2 yr of treatment, patients who originally received placebo or 50, 75, or 100 $\mu$g PTH showed increases in vertebral bone density of 7.1 ± 5.3%, 11.3 ± 5.7%, 13.4 ± 5.0%, and 14.6 ± 7.9%, respectively. Patients who originally received 100 or 75 $\mu$g PTH had a greater improvement in bone density than those who had received placebo ($P$ = 0.0004, 0.0032, and 0.0796 for the 100, 75, and 50 $\mu$g groups, respectively). Eight patients had an increase in the vertebral spine bone density greater than 20% during the study (four in the 100 $\mu$g PTH group, three in the 75 $\mu$g PTH group, and one in the 50 $\mu$g PTH group).

During the first year, the mean femoral neck bone density changed by −1.0%, −1.0%, 2.3%, and −0.7% in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively. The femoral neck bone densities at the end of the first year were not significantly different from baseline in any of the groups, nor were the groups significantly different from each other. During the second year, the femoral neck bone density increased by 4.2%, 5.5%, 2.8%, and 4.5% in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively. At the end of the second year, two of the four groups were significantly increased compared to baseline ($P$ = 0.089, 0.009, 0.019, and 0.124 for the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively).

During the first year, mean whole body bone density changed by 0.7%, −0.6%, −3.5%, and −2.8% in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively ($P$ = 0.0267 for the three PTH groups compared to placebo). During the second year, whole body bone density increased by 2.6%, 3.2%, 5.2%, and 6.1% in the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively. At the end of 24 months there was no significant difference in whole body bone density among the four groups. However, three of the four groups were significantly increased compared to baseline ($P$ = 0.007, 0.048, 0.402, and 0.023 for the placebo and 50, 75, and 100 $\mu$g PTH groups, respectively).

### *Bone marker results*

For analysis of bone marker levels, results from patients in the three PTH-treated groups were combined and compared to those in patients who received placebo (Fig. 2). After 1 yr of PTH treatment, all three markers were significantly increased compared to those in placebo-treated patients. After an additional year of alendronate treatment, all three markers decreased to below the levels seen in the placebo group before starting alendronate.

Osteocalcin levels after 1 yr of PTH treatment (27.4 ± 3.9

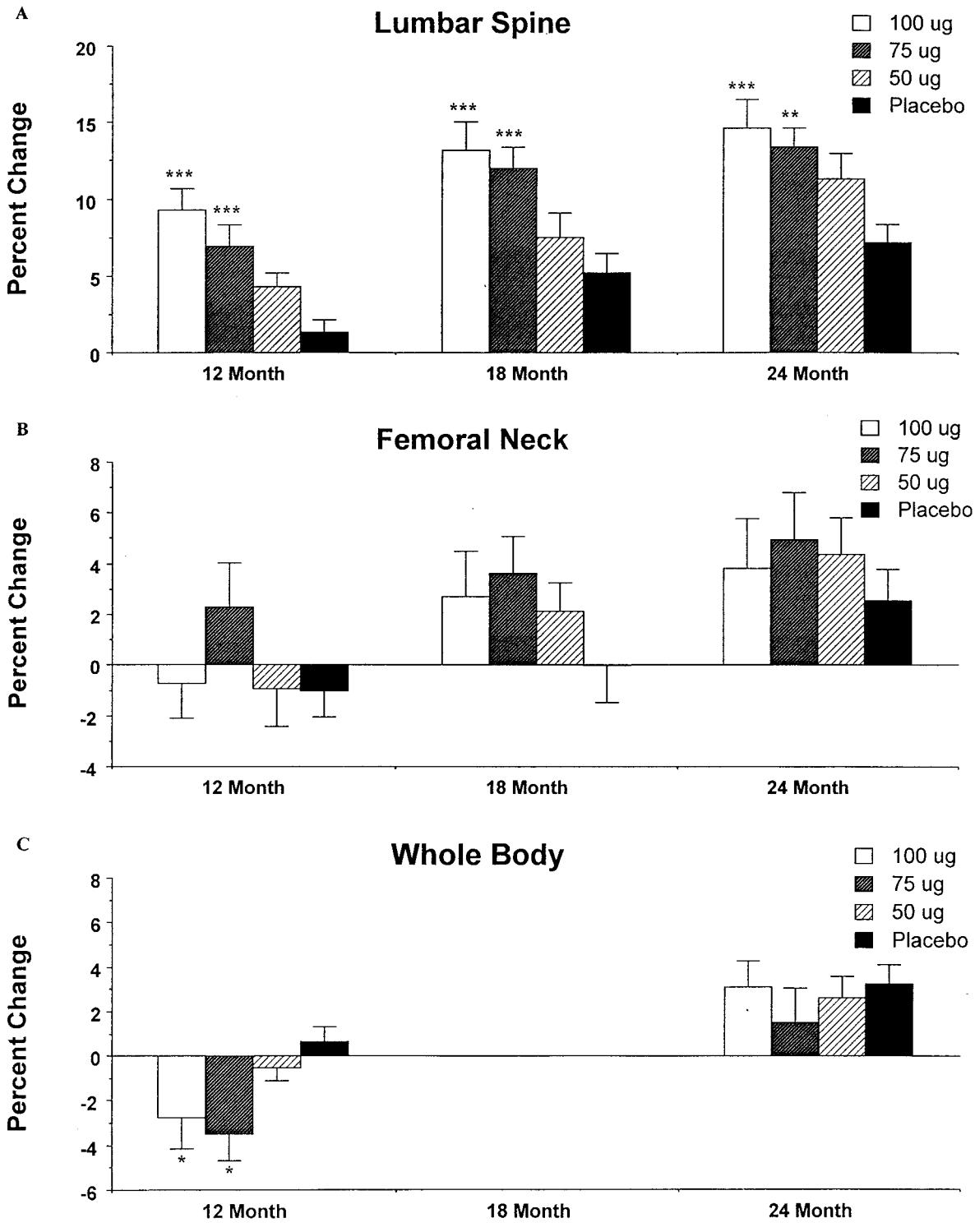


FIG. 1. BMD (percent change from baseline; mean ± SEM) in postmenopausal women given 100, 75, or 50 $\mu$g PTH or placebo during the first year followed by 10 mg alendronate daily during the second year. Month 12 data represent the changes observed after 1 yr of PTH or placebo. Month 18 and month 24 data represent the changes observed after an additional 6 and 12 months of alendronate treatment, respectively. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (compared to placebo/alendronate group).

nmol/L) were significantly higher than those in the placebo-treated patients (12.4 ± 2.3 nmol/L; $P = 0.03$). After 12 months of alendronate treatment, osteocalcin levels in the PTH-treated patients decreased to 5.5 ± 0.4 nmol/L ($P <$ 0.0001 compared to baseline and compared to the placebo-treated group before alendronate).

Skeletal alkaline phosphatase levels after 1 yr of PTH treatment (29.7 ± 3.0 $\mu$g/L) were significantly higher than those

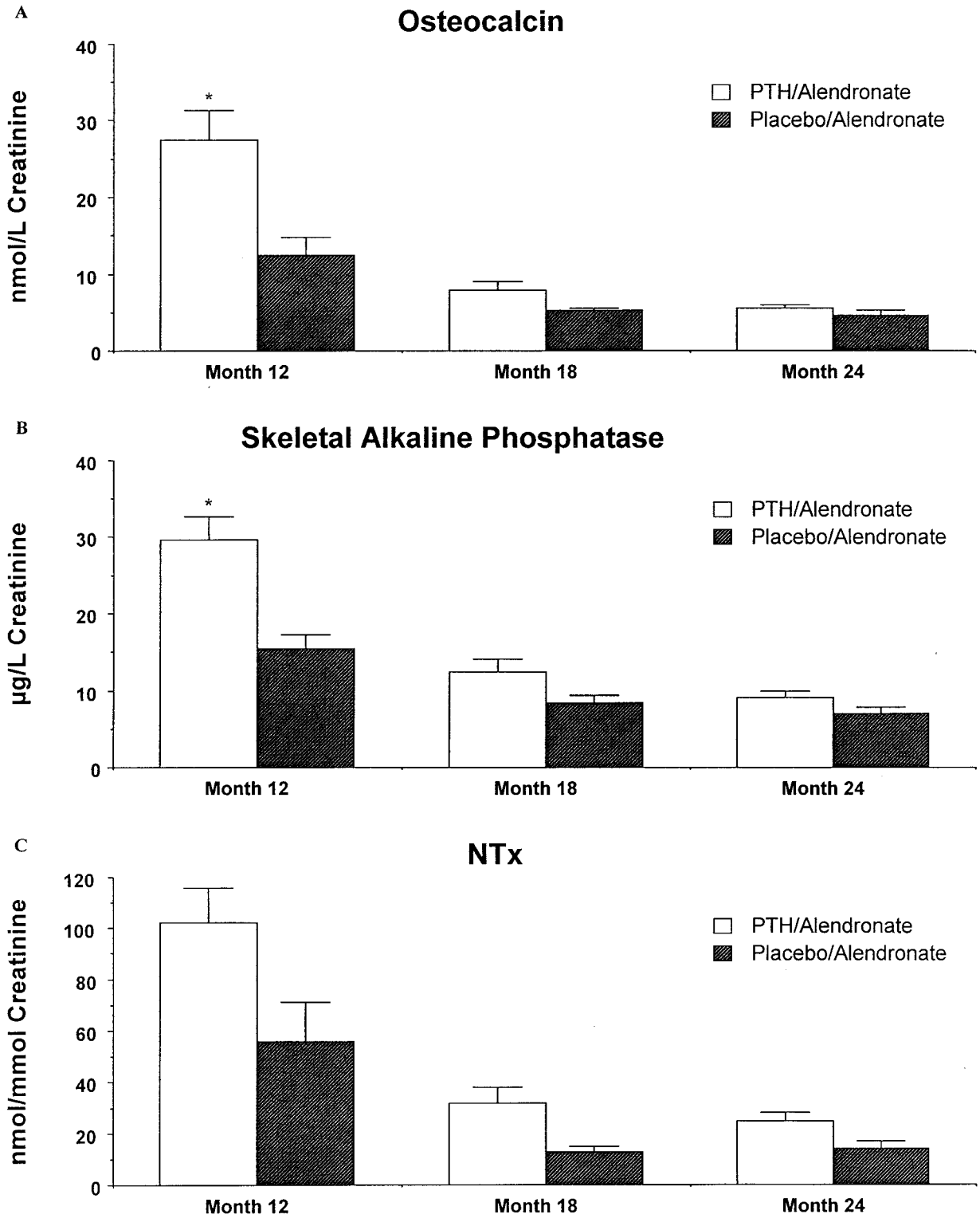


FIG. 2. Markers of bone turnover (mean ± SEM) in postmenopausal women given 100, 75, or 50 $\mu$g PTH or placebo during the first year followed by 10 mg alendronate daily during the second year. For the purposes of these analyses, the results were combined for the three PTH doses. *, $P < 0.05$ (compared to placebo/alendronate group).

in the placebo-treated patients (15.4 ± 1.9 $\mu$g/L; $P = 0.01$). After 12 months of alendronate treatment, levels in the PTH-treated patients decreased to 9.1 ± 0.8 $\mu$g/L ($P < 0.0001$ compared to baseline and compared to the placebo-treated group before alendronate).

NTx levels after 1 yr of PTH treatment (102 ± 14 nmol/

**TABLE 1.** Baseline features of study subjects

| | |
|---|---|
| 0.82 ± 0.13 | |
| Age (yr) | 64 ± 5 |
| Ht (cm) | 162 ± 49 |
| Wt (kg) | 48 ± 18 |
| BMI (kg/m$^2$) | 32 ± 8 |
| *t*-score: lumbar spine | −3.2 ± 0.6 |
| *t*-score: femoral neck | −2.4 ± 0.8 |
| Serum creatinine (mmol/L) | 0.82 ± 0.13 |

Values are the mean ± SD.

L·mmol/L creatinine) were higher than those in the placebo-treated patients (56 ± 15 nmol/L·mmol/L creatinine; $P = 0.06$). After 12 months of alendronate treatment, levels in the PTH-treated patients decreased to 25 ± 3 ($P < 0.0001$ compared to baseline and $P = 0.0010$, compared to the placebo-treated group before alendronate).

## Discussion

In humans, PTH markedly increases cancellous bone density in areas such as the vertebrae while causing no change or a modest reduction in sites primarily composed of cortical bone. There is some evidence that this apparently negative effect of PTH may be associated with increased subperiosteal bone formation in cortical sites, and that the bone loss is not seen after longer treatment periods, especially if estrogen therapy is given concurrently (9, 10). However, our study is the first to demonstrate that alendronate can reverse this loss (as seen in whole body BMD) and cause further significant gains at all sites measured regardless of whether the patient had been treated with PTH. Alendronate not only maintains the PTH-induced improvement in vertebral bone density, but also causes a further increase in vertebral BMD similar to that seen in the alendronate-treated patients not previously given PTH. In patients who received the largest dose of PTH (100 μg/day) for 1 yr followed by 1 yr of alendronate treatment (10 mg/day), vertebral bone density increased by 14.6 ± 7.9%, which is far greater than that previously found with antiresorptive therapy alone. During the second year, alendronate increased both femoral neck and whole body BMD, such that after 2 yr these parameters were similar between patients who had originally received PTH and those who had received placebo. It thus appears that alendronate is able to reverse any negative effects PTH may have on cortical bone density.

Other studies suggest that the ability of an antiresorptive agent to maintain PTH-induced gains in bone density depends on the potency of the agent and the dose given. In a study using sequential therapy with PTH, followed by the bisphosphonate clodronate (400 mg/day for 1 month, repeated every 3 months), clodronate was not able to preserve the PTH-induced increases in bone density (11). In the rat, bisphosphonates, but not estrogen, have been shown to maintain cancellous bone density in the proximal tibia of rats previously treated with PTH (13). On the other hand, in women, estrogens appear to maintain PTH-induced gains in BMD. In premenopausal women, PTH prevented bone loss caused by hypogonadism induced by a GnRH agonist (14), and the beneficial effects of PTH were maintained when the GnRH agonist therapy was stopped, and the women returned to a eugonadal state. Similarly, in postmenopausal women receiving chronic estrogen and glucocorticoid treatment, 1 yr of PTH treatment improved vertebral and hip BMD, and this improvement was maintained 1 yr after PTH was stopped (15).

In designing this study, we hypothesized that PTH would increase the number of bone-remodeling units, effectively increasing the remodeling space. This may be an explanation for the absence of change in BMD at the femoral neck and a decrease in mean whole body BMD at the highest PTH doses. Therapy with a potent antiresorptive agent such as alendronate may not only exert its effect by reducing bone turnover, but also may decrease the previously enlarged remodeling space. Such a concept, however, had previously been tried unsuccessfully with calcitonin. In that study, PTH was given cyclically for 28 days every 3 months, followed by calcitonin (75 U, sc, daily) for the subsequent 42 days. Calcitonin was unable to further increase BMD or decrease markers of bone resorption compared to PTH alone (8). On the other hand, previous studies suggest that beneficial results could be obtained when PTH and estrogens were given concurrently (9, 16). In a controlled, randomized study of women who had already received estrogen for at least 2 yr, the addition of PTH over the subsequent 3 yr increased bone density by 13% in the lumbar spine, by 2.7% in the hip, and by 8.0% in the total body (9). Antiresorptive agents may enhance PTH's beneficial effect on cancellous bone and prevent the negative effects of PTH on cortical bone. One might expect, therefore, that PTH would have a similar beneficial effect in eugonadal, premenopausal women and in eugonadal men. In fact, a recent study did find that PTH enhanced both vertebral and hip BMD in men with idiopathic osteoporosis (17).

The bone marker results in this study confirm previous findings that PTH increases both bone formation and resorption, whereas alendronate decreases these parameters. The previous use of PTH did not inhibit the ability of alendronate to suppress these markers. In a recent study, in which PTH was given to women already receiving alendronate, markers of bone formation were increased, whereas markers of bone resorption remained suppressed (18).

In summary, 1 yr of PTH, followed by 1 yr of alendronate, increased vertebral bone density more than has been reported in studies of antiresorptive agents alone. This study provides evidence that the effect of PTH on bone density can be optimized when a potent antiresorptive agent is used either concurrently or after PTH treatment. Further studies will be needed to determine which option is best. Although animal studies indicate that PTH also improves cancellous bone strength (5, 19), and preliminary human studies suggest that PTH reduces vertebral fracture risk (9), these findings will need to be confirmed in large scale human trials. Finally, the possibility that repeated cycles of PTH treatment may lead to progressive gains in bone mass offers the hope that it may be possible to normalize bone density in osteoporotic patients.

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