Use of Bone Alkaline Phosphatase to Monitor Alendronate Therapy in Individual Postmenopausal Osteoporotic Women

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Background: Biochemical bone markers are sensitive to the changes in bone turnover that result from treatment of postmenopausal osteoporotic women with antiresorptive therapies. Although information is available on the use of bone markers in monitoring therapy in groups of subjects, less is known regarding how these markers perform in individual patients.

Methods: Serum bone alkaline phosphatase (bone ALP) concentrations, measured with the Tandem® Ostase® assay, were used to monitor the biochemical response of bone in postmenopausal women with osteoporosis receiving either 10 mg/day alendronate therapy (n = 74) or calcium supplementation (n = 148) for 24 months.

Results: Bone ALP decreased significantly from baseline at 3 months (P < 0.0001), reaching a nadir between 3 and 6 months of alendronate therapy. The magnitude of the bone ALP decrease in the treated osteoporotic population was consistent with normalization to premenopausal concentrations. Of the 74 alendronate-treated subjects, 63 (85.1%) demonstrated a decrease from baseline in bone ALP by 6 months that exceeded the least significant change of 25%. The bone ALP decrease from baseline exceeded 25% in 72 (97%) by the end of the study.

Conclusion: The bone ALP assay is a sensitive and reliable tool that may be used to monitor the reduction in bone turnover after alendronate therapy in individual postmenopausal osteoporotic women.

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The dynamics of bone metabolism are revealed noninvasively with increasing accuracy by the use of newly identified biochemical markers of bone turnover. These markers include serum-based assays for bone alkaline phosphatase (ALP) and osteocalcin and urine-based assays for free and peptide-bound pyridinium cross-links of type I collagen. These assays offer increased sensitivity and specificity over total ALP and hydroxyproline assays and can readily detect acute fluctuations in bone metabolism (1–5). The newer biochemical markers correlate to bone remodeling indices such as calcium kinetics, strontium labeling, and bone histomorphometry and provide clinicians with tools to complement existing technology such as bone mineral densitometry to aid in the management of patients with metabolic bone disorders (6–11).

Serum bone ALP and serum osteocalcin reflect aspects of bone formation, whereas the urinary collagen cross-links are products of bone resorption. However, these bone turnover processes are intimately coupled so that the formation and resorption markers increase or decrease in the same direction and, in many cases, with similar magnitude. Exceptions to this coupling exist, such as in response to treatment with glucocorticoids, in which bone formation is acutely inhibited and bone resorption is enhanced (12), or in response to anabolic agents, in which the formation markers increase, whereas the resorption markers exhibit little change (13–16). However, when coupling is maintained, measurement of any of the bone-specific markers reflects overall bone turnover.

Similar to the use of serum total ALP measurements to monitor antiresorptive therapy in patients with Paget disease, we tested whether a new immunoassay for bone...
ALP could be used to monitor the reduction in bone turnover that results from bisphosphonate therapy in postmenopausal osteoporotic women. Our data confirm that the sensitivity of this bone ALP assay to reflect the normalization of bone turnover in response to alendronate treatment, coupled with its relatively low variability, allow reliable monitoring of the antiresorptive effect of treatment in individual osteoporotic women.

**Materials and Methods**

**Reference population.** A total of 757 apparently healthy premenopausal and postmenopausal women were included in the bone ALP reference range study. The cohort included women from three US sites and one European site. Apparently healthy premenopausal women (n = 228) with regular menses (25- to 40-day cycles), ages (mean ± SD), 40.2 ± 6.8 years (age range, 22–57 years) were enrolled. We excluded premenopausal women who were pregnant or breast feeding. Apparently healthy postmenopausal women (n = 529) with no menses for at least 6 months, ages (mean ± SD), 63.7 ± 9.2 years (age range, 45–89 years) were enrolled.

We excluded women in either group who experienced any bone fracture within the previous 6 months; any disorders known to affect bone and mineral metabolism (e.g., hypo- or hyperthyroidism or Paget disease); any abnormal renal or liver function; any prior treatment with bisphosphonate or fluoride therapy; and any treatment within the last 6 months with calcitonin, androgens, systemic corticosteroids, oral contraceptives, estrogen or progestin, or other medication known to influence bone metabolism.

The study protocol was approved by local institutional review boards at participating centers, and each subject provided written informed consent.

**Postmenopausal osteoporotic women.** This population was derived from the US portion of the Alendronate Phase III Osteoporosis Treatment Studies, described previously (17, 18). The US portion of this study enrolled 277 subjects in the placebo and 10 mg/day treatment groups. Additional inclusion criteria were introduced for the bone marker study reported here. These criteria required bone ALP determinations at baseline and at 3 and 6 months, and at least one additional bone ALP measurement at 12 or 24 months from baseline. In addition, minimum requirements for lumbar spine bone mineral density (LS-BMD) were determinations at baseline and at 24 months, and at least one additional LS-BMD measurement at 3, 6, or 12 months. Of the 277 subjects enrolled, 222 met these additional criteria: 148 of 186 (80%) subjects in the placebo group, and 74 of 91 (81%) subjects in the alendronate group. The baseline characteristics of the 222 women in the alendronate and placebo groups were similar. The mean age (± SD) for these women was 64.4 (± 6.9) years (range, 45–78 years), and they were at least 5 years postmenopause. Each subject had a LS-BMD measured with dual-energy x-ray absorptiometry that was at least 2.5 SD below the mean value for premenopausal white women (17, 18).

**TREATMENT**

Details of the alendronate treatment protocol have been published (17, 18). For the purposes of the bone marker study reported here, bone ALP and LS-BMD data are reported to the 24-month time point for the placebo and 10 mg/day alendronate groups. All subjects received a daily supplement of calcium carbonate providing 500 mg of elemental calcium.

**END POINTS**

**BMD.** The BMD of the lumbar spine (L1–L4), femoral neck, trochanter, forearm, and total body were measured with dual-energy x-ray absorptiometry, using the Hologic QDR-1000 or 1000/W (Hologic), Lunar DPX-L (Lunar), or Norland XR-26 (Norland) densitometers as described (17, 18). All BMD scans were reviewed independently by a central facility to ensure consistency across all sites. LS-BMD was the primary end point in the study.

**Bone ALP.** Bone ALP was measured in serum with a monoclonal antibody-based immunoassay (Tandem®-R Ostase®; Beckman Coulter). The performance characteristics of this assay have been established (19, 20). Results are reported in mass units, using calibration established with a preparation of bone ALP purified by immunoaffinity chromatography from SAOS-2 human osteosarcoma cells (20). The lower limit of detection of the assay is <1 µg/L; the assay within- and between-run CVs are <5% and <8%, respectively.

Serum samples were collected during the course of the study and stored frozen at −20 °C to −70 °C. Samples were subsequently shipped frozen to a central laboratory (Medical Research Laboratories, Highland Heights, KY) and stored at −70 °C before bone ALP analysis. Bone ALP was determined at the central laboratory facility after completion of the study.

**WITHIN-SUBJECT VARIABILITY**

Within-subject variability was determined by collecting nonfasting serum samples on 5 consecutive days from 17 apparently healthy postmenopausal women meeting the inclusion/exclusion criteria noted above for apparently healthy postmenopausal women. The mean (± SD) age of this study population was 58 (± 11) years (age range, 40–78 years). Serum samples were collected in the morning between 0800 and 1200, stored frozen at −70 °C and assayed for bone ALP at the completion of sample collection. The within-subject variability for healthy postmenopausal women was determined as follows: (a) the mean CV (%) for bone ALP was calculated for each individual across 5 days; (b) the mean CV (%) and standard error were calculated for the group (n = 17); and (c) the 95%
upper confidence limit for the group mean CV (\%) was calculated (group mean + 2 SE).

**SERUM SAMPLE STABILITY**

Serum samples from healthy individuals were combined to make two separate pools. These two serum pools were aliquoted and stored frozen at either −70°C or −20°C for 42 or 48 months, respectively. Stability was determined by removing an aliquot at least twice a month and assaying for bone ALP, using the Tandem-R Ostase assay. Over the 42- to 48-month period, 105 and 117 bone ALP measurements, respectively, were performed to assess stability.

**STATISTICAL ANALYSIS**

Comparisons between healthy premenopausal and postmenopausal women and untreated postmenopausal osteoporotic women (at baseline) were performed using the unpaired Student t-test. The group changes in bone ALP and BMD from baseline across time in the alendronate treatment study were evaluated by analysis of variance.

The Z-score was defined as the number of standard deviations from the bone ALP mean of apparently healthy premenopausal women. The bone ALP concentrations in the premenopausal population followed gaussian distribution (P = 0.1223).

The critical difference or least significant change is defined as the minimum significant difference (P ≤0.05) between two consecutive bone ALP measurements in the same subject and uses the formula described by Soletormos et al. (21) and others (22) to account for both procedural and within-subject variability:

\[
\sqrt{2} \times Z \times \sqrt{CV_p^2 + CV_a^2}
\]

in which CV<sub>p</sub> is the within-subject variability, CV<sub>a</sub> is the assay imprecision, and Z is the Z-statistic, which equals 1.96 for a two-tailed analysis at 95% confidence. Within-subject variability was determined as described above. The assay imprecision (CV<sub>a</sub>) of 7.4% was based on between-run precision data reported previously (19, 20).

**RESULTS**

**EXPECTED VALUES**

Bone ALP was evaluated in three groups: apparently healthy premenopausal women, apparently healthy postmenopausal women, and postmenopausal osteoporotic women selected on the basis of low bone mass. Compared with premenopausal women, the bone ALP mean increased 1.5-fold in postmenopausal women (P = 0.0001) and twofold in postmenopausal osteoporotic women (P ≤0.0001; Table 1). The bone ALP mean increased 1.3-fold in the osteoporotic group vs postmenopausal women (P ≤0.001). The bone ALP upper limit (mean + 2 SD) for healthy premenopausal women is 14.5 µg/L. Among the 529 healthy postmenopausal women in this study, 32.5% (172 of 529) demonstrated bone ALP concentrations that equaled or exceeded 14.5 µg/L, whereas twice that proportion (67.1%, 149 of 222) exceeded 14.5 µg/L in the postmenopausal osteoporotic group.

**CRITICAL DIFFERENCE**

The mean within-subject CV for bone ALP determined daily over a 5-day period in 17 postmenopausal women was 4.2% (data not shown). On the basis of these data, the 95% upper confidence limit for the within-subject CV was 4.8%. Using the formula described in Materials and Methods, we calculated the critical difference, i.e., the difference between two determinations for bone ALP that may be considered to have clinical significance with 95% confidence, to be 25%.

**HUMAN SERUM SAMPLE STABILITY**

Bone ALP stability was determined in serum samples aliquoted and stored frozen at −20°C for up to 48 months or stored frozen at −70°C for up to 42 months. No loss of immunoreactivity was observed over this period at either temperature (data not shown). These results support the use of this assay in studies, such as the one reported here, in which samples have been stored frozen before analysis.

**MONITORING ALENDRONATE THERAPY—LS-BMD**

The time course of LS-BMD changes from baseline for the group receiving 10 mg of alendronate and the placebo group is plotted in Fig. 1B. An increase in LS-BMD over baseline for the alendronate group was observed at all time points. A slight decline in LS-BMD was observed at 24 months for the calcium-supplemented placebo group. The LS-BMD in the alendronate group was significantly different from the placebo group at all time points.

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**Table 1. Bone ALP concentrations in healthy premenopausal and postmenopausal women and in postmenopausal osteoporotic women.**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean, µg/L</th>
<th>SD, µg/L</th>
<th>Increase over the pre-MP&lt;sup&gt;a&lt;/sup&gt; mean</th>
<th>Proportion above the pre-MP upper limit,&lt;sup&gt;a&lt;/sup&gt; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal women</td>
<td>228</td>
<td>8.7</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>529</td>
<td>13.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.7</td>
<td>52%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Postmenopausal osteoporotic women</td>
<td>222</td>
<td>17.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.6</td>
<td>101%</td>
<td>67.1%</td>
</tr>
</tbody>
</table>

<sup>a</sup> pre-MP, premenopausal.
<sup>b</sup> pre-MP upper limit (mean + 2 SD) = 14.5 µg/L.
<sup>c</sup> P ≤0.0001 vs premenopausal women.
<sup>d</sup> P ≤0.0001 vs premenopausal women, and P ≤0.001 vs postmenopausal women.
The increase in LS-BMD was most rapid during the first year of alendronate treatment and continued to increase throughout the study. As reported previously, significant increases over baseline BMD were also observed for this study at the femoral neck and trochanter, and in total body BMD \( (17, 18) \). In this 10-mg treatment group, all alendronate-treated subjects responded to therapy based on increased LS-BMD by the 2-year time point.

**MONITORING ALENDRONATE THERAPY—SERUM BONE ALP**

In the group receiving 10 mg of alendronate, the bone turnover marker serum bone ALP decreased 35.5% from baseline at 3 months, decreased 45.7% from baseline at 6 months, and remained at this concentration after 12 and 24 months of treatment (Fig. 1A). All time points were statistically different from baseline \( (P \leq 0.0001) \). In contrast, in the calcium-supplemented placebo group, the mean percentages of change in bone ALP from baseline were smaller and transient (Fig. 1A). Serum bone ALP decreased by 11.4% at 3 months, remained at that concentration at 6 months, and subsequently increased to baseline values by 24 months. In the placebo group, the mean percentages of change in bone ALP were statistically different from baseline at 3, 6, and 12 months \( (P \leq 0.0001) \), but not different from baseline at 24 months \( (P = 0.9003) \).

By 3 months of alendronate therapy, the mean bone ALP decreased to within 1 SD of the mean bone ALP established for healthy premenopausal women (Fig. 2). The mean \( (\pm SD) \) bone ALP decreased from 17.0 \( (\pm 4.6) \) \( \mu g/L \) at baseline to 8.9 \( (\pm 2.8) \) \( \mu g/L \) after 6 months of alendronate therapy. This 6-month mean bone ALP value

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was indistinguishable from the mean (± SD) bone ALP of the premenopausal population reported in Table 1 \( (P = 0.6032) \).

When the alendronate group was stratified into quarters on the basis of baseline bone ALP values, the mean bone ALP for all quarters decreased to within 1 SD of the mean of premenopausal women after 6 months of treatment and remained within that range for the treatment duration (Fig. 3). At 3 months, only the quarter with the highest baseline bone ALP did not demonstrate a mean bone ALP decrease to within 1 SD of the premenopausal mean.

In this postmenopausal osteoporotic population, the correlation between baseline bone ALP and either baseline LS-BMD or LS-BMD increase after 24 months of alendronate therapy did not reach statistical significance. The percentage of increase in LS-BMD after 24 months for the combined alendronate and placebo groups correlated with the percentage of decrease in bone ALP at 3 months \( (r = 0.4282; P \leq 0.0001) \) and 6 months \( (r = 0.4945; P \leq 0.0001) \). However, when a similar analysis was used, no significant correlation existed when the placebo and alendronate groups were analyzed separately.

To assess the biochemical response to therapy in individual postmenopausal osteoporotic women, two criteria were applied: a ≥25% decrease in bone ALP from baseline after 6 months of treatment (biochemical responders) and a bone ALP value that fell below the mean + 1 SD (11.6 µg/L) determined for healthy premenopausal women (normalizers).

Of the 74 alendronate-treated postmenopausal osteoporotic women, 63 (85.1%) of the subjects had bone ALP concentrations that decreased ≥25% from baseline by 6 months (biochemical responders). Of these 63 biochemical responders, 60 (95%) demonstrated bone ALP values that normalized by 6 months, i.e., decreased from baseline to within 1 SD of the premenopausal mean. The three responders whose bone ALP did not normalize by 6 months had baseline bone ALP values >20 µg/L (Z-score >3.9) and demonstrated >40% reduction from baseline in bone ALP after 6 months of alendronate therapy.

The decrease in bone ALP from baseline did not exceed 25% by 6 months in 11 of 74 (14.9%) subjects in the alendronate group. However, the bone ALP response was apparent but delayed because in 9 of the 11 subjects, the bone ALP decrease was sustained and exceeded 25% by 24 months of therapy. In total, 72 of the 74 (97.3%) alendronate-treated postmenopausal osteoporotic women demonstrated a bone ALP response.

When the same biochemical response criteria were applied to the 148 women in the calcium-supplemented placebo group, 36 of 148 (24.3%) of the subjects had bone ALP concentrations that decreased ≥25% from baseline by 6 months. By 24 months, the number of subjects in the placebo group classified as biochemical responders decreased substantially (17 of 148, 11.5%). Thus, at the 6-month time point, the sensitivity and specificity of bone ALP in this study was determined to be 85.1% and 75.7%, respectively.

The 36 subjects in the placebo group classified as biochemical responders at 6 months were further analyzed. These women had significantly less baseline calcium intake (572 vs 902 mg/day; \( P = 0.0016 \)) and significantly higher baseline bone ALP concentrations (20.5 vs 16.8 µg/L; \( P = 0.0010 \)) when compared with the remainder of the placebo group. Furthermore, these biochemical responders in the placebo group lost less bone, especially at the earlier time points. When compared with the 112 nonresponders, the LS-BMD decrease for the 36 biochemical responders was significantly less at 3 months \( (0.87\% \pm -0.42\%; P = 0.0133) \) and 6 months \( (1.44\% \pm 0.15\%; P = 0.0175) \); however, the difference did not reach significance at 12 months \( (-0.44\% \pm -0.73\%; P = 0.65) \) or 24 months \( (-0.15\% \pm -0.96\%; P = 0.2083) \), although the trend was still apparent.
Discussion

Our study indicates that measurements of serum bone ALP effectively monitor the biochemical response of bone to alendronate treatment in individual postmenopausal osteoporotic women. The criteria established in this study to assess a biochemical response were modeled after those commonly used for monitoring response to antiresorptive therapy with total ALP in patients with Paget disease (23–26). In Paget disease and postmenopausal osteoporosis, a desired effect of antiresorptive therapy is to normalize increased bone turnover. In our study of postmenopausal women with osteoporosis, baseline bone turnover, as assessed using serum bone ALP, was double that observed in premenopausal women (Table 1). After 6 months of alendronate therapy, serum bone ALP was reduced by ~50% to concentrations that were indistinguishable from those observed in the premenopausal population. These results are similar to those reported previously for the bone ALP response to alendronate (27) and suggest that by 6 months of alendronate treatment a new steady state in bone turnover is achieved, similar to that observed in healthy premenopausal women.

The bone marker data analyzed by treatment groups, although informative, provide little insight into the use of the bone marker in individual subjects. When the responder criterion based on critical difference values established in this study (≥25% bone ALP decrease from baseline at the 6-month time point) was used, the majority (85%) of the alendronate-treated women were identified as biochemical responders and demonstrated bone ALP values that normalized to premenopausal concentrations. Normalization of bone ALP occurred irrespective of the baseline bone ALP value (Fig. 3), suggesting that those women with the highest bone turnover demonstrated the greatest biochemical response, as has been observed in other studies (27–30). The reduction and normalization of bone turnover in our study produced an increase in LS-BMD after 2 years of alendronate therapy, although the correlation between the percentage of decrease of bone ALP and the percentage of increase of LS-BMD did not reach significance. This is contrasted by reports using estrogen replacement therapy, in which a statistically significant relationship was observed between the decrease in bone markers, including bone ALP, after therapy and the 1- or 2-year BMD increase in postmenopausal women without (28, 29) or with (30) established osteoporosis. The difference in the results between our study with alendronate and the estrogen studies may be related to differences between in the mechanism of action of the drugs, the populations studied, and/or the superior homogeneity of the bone turnover and BMD response induced by the more potent bisphosphonate compound. Although the correlation between the magnitude of the bone marker decrease at 6 months and the magnitude of the bone density increase at 1 or 2 years of estrogen therapy reached statistical significance, the practical utility for individual patients is diminished given the weak correlations reported.

In our analysis, 11 of the 74 subjects in the alendronate group did not meet the responder criterion established in this study for bone ALP at 6 months. However, 9 of these 11 subjects showed sustained bone ALP decreases from baseline after therapy initiation, which after 24 months of alendronate therapy exceeded 25% (data not shown). These results suggest that the biochemical response of bone to alendronate as determined using bone ALP, although delayed, was evident in these subjects. The reason for the delayed yet apparent reduction in bone turnover in response to alendronate in these subjects is unclear because their baseline characteristics and 2-year LS-BMD response were indistinguishable from the remainder of the alendronate group. This observation highlights the need to repeat the bone ALP measurement in alendronate-treated patients who do not demonstrate at least a 25% decrease in 6 months.

A small but significant decrease in bone ALP concentrations was also observed for the 500 mg/day calcium-supplemented placebo group (Fig. 1A and Fig. 2). This bone ALP decrease was transient, and the ALP concentration returned to baseline values by 24 months. Those classified as biochemical responders to the calcium supplementation as assessed using bone ALP had lower calcium intake at baseline and tended to lose less bone during the 2-year follow-up. Our results support those of others who have shown that calcium supplementation decreases bone turnover, with a subsequent positive effect on the rate of bone loss and the greatest benefit observed for those women with the lowest calcium intake (31–35).

An important attribute to consider when evaluating the reliability of a biochemical marker for use in long-term patient monitoring is within-subject and assay variability. These parameters are used to determine the least significant change, or critical difference, needed for a marker to distinguish a true clinical response from normal variation in serial measurements in an individual (21). Major sources of within-subject variability include within-day (diurnal) and biological variation. The diurnal and biological variability of serum bone ALP is approximately one-half of that observed for the urinary assays for peptide-bound collagen cross-links (22, 36–39). These differences are partially attributed to the liver rather than to kidney clearance of bone ALP from circulation and the relatively long half-life (1–2 days) of bone ALP in serum (40–42). Our critical difference estimate (25%) in healthy postmenopausal women is similar to (22) or slightly higher than (43) the critical difference reported previously for serum bone ALP. For comparison, a critical difference of 25% for serum bone ALP is comparable to the critical difference of 31% determined for prostate-specific antigen, a serum-based analyte, measured by immunoassay,
widely used to detect and to monitor the treatment of prostate cancer (44).

Similar bone ALP and total ALP response profiles were observed in the alendronate group. However, the bone ALP change was twice that observed for the total ALP measurement (data not shown). This is as expected considering that total ALP measurements are less specific to bone than measurements of the bone isoenzyme. In conditions such as osteoporosis and renal osteodystrophy and in other conditions in which bone metabolic changes are often subtle, the use of the more bone-specific test confers clinical advantages (45–47). However, for patients with conditions that typically produce more marked bone metabolic changes, including bone metastases and Paget disease, the two assays have been shown to provide similar clinical discrimination (48–50).

The response profiles of the biochemical markers of bone turnover differ with different treatment protocols. The responses of bone ALP and other bone markers to 10 mg/day alendronate are rapid and substantial: by 3 months for the urinary peptide-bound collagen cross-links and by 4 to 6 months for the serum-based bone formation markers, including bone ALP and osteocalcin, a nadir is reached that is maintained throughout the treatment duration (27). When the same bone markers are used to monitor, for example, estrogen replacement therapy, the bone marker response is less rapid and less substantial than for 10 mg/day alendronate therapy (22, 28). The markers are likely reflecting the relative potency of the drugs to affect bone metabolic processes, a hypothesis that is supported by the greater BMD increase observed after 2 or 3 years with alendronate therapy compared with estrogen replacement therapy (17, 18, 22, 27, 28).

In this study, all alendronate-treated women responded to therapy, based on an increase in LS-BMD after 24 months of therapy. Therefore, without any treatment nonresponders in this study, we were unable to determine whether monitoring with bone ALP could distinguish treatment responders from treatment nonresponders in the 74 alendronate-treated women. Thus, the clinical and economic value of monitoring therapy can be questioned if it is assumed that all postmenopausal women respond to alendronate. However, in a controlled clinical study such as the one reported here, patient adherence to the protocol is monitored closely. Such is not the case in practice. Thus, the placebo group serves as a surrogate for those noncompliers who would not be expected to show the same biochemical (and bone density) response to therapy as those who took alendronate as instructed.

It should be pointed out that treatment response was based on an increase in LS-BMD after 24 months without any consideration of the least significant change required for bone density measurements to distinguish a true clinical response from measurement error. However, bone density testing currently is the most commonly used procedure to assess fracture risk and to monitor osteoporosis therapy in postmenopausal women. Therefore, a direct comparison of the bone marker results to bone density is warranted. The effectiveness of either monitoring tool to identify those postmenopausal women on therapy who sustain osteoporotic fractures remains to be determined.

The importance of confirming a significant reduction and normalization of bone turnover after antiresorptive drug therapy was summarized in a recent report by Riggs et al. (51). These authors proposed that the vertebral fracture rate can be decreased substantially either by inhibiting high bone turnover and the resulting destruction of the microarchitectural integrity of cancellous bone with antiresorptive drugs or by inducing large increases in vertebral BMD in response to bone formation-stimulating compounds. Furthermore, these authors suggested that normalization of high bone turnover by antiresorptive therapy decreases the vertebral fracture rate independently of changes in vertebral BMD. These results emphasize the importance of monitoring antiresorptive therapy using bone markers with good sensitivity and specificity to provide timely assurance that the desired reduction and normalization of bone turnover has been achieved.

In conclusion, we have shown that bone ALP provides a sensitive and accurate means to monitor the reduction in bone turnover in response to alendronate therapy in individual postmenopausal osteoporotic women. This marker should be useful for those patients for whom this information is needed for optimal clinical care.

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