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Antifracture Efficacy of Antiresorptive Agents Are Related to Changes in Bone Density

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ABSTRACT

There is a current debate about the extent to which antifracture efficacy of antiresorptive drugs are related to changes in bone mineral density (BMD). *In vitro* studies show that most of the variability in bone strength is related to BMD, and prospective studies have shown that low BMD is an important predictor of fracture risk. It seems that higher levels of bone turnover are also associated with increased fracture risk. Over the short term, a reduction in activation frequency or resorption depth would lead to fewer (and/or shallower) resorption sites and refilling of existing sites initially. There is also evidence that inhibiting resorption allows bone to respond to mechanical demands, preferentially thickening critical trabeculae, and this may help compensate for reduced connectivity. Each of these mechanisms would increase BMD and would disproportionately improve bone strength. Over the long term, maintaining bone mass and preventing loss of structural elements would result in progressively greater differences in BMD and fracture risk over time, relative to untreated women. The conceptual model predicts that both the short- and long-term antifracture efficacy of antiresorptive drugs will depend on the extent to which treatment can increase and maintain BMD. To examine this issue, we compiled data from clinical trials of antiresorptive agents and plotted the relative risk of vertebral fractures against the average change in BMD for each trial. The confidence intervals are large for individual trials, and there was substantial variability in antifracture efficacy at any given level of change in BMD. Overall, however, trials that reported larger increases in BMD tended to observe greater reductions in vertebral fracture risk. Poisson regression was used to quantify this relationship. The model predicts that treatments that increase spine BMD by 8% would reduce risk by 54%; most of the total effect of treatment was explained by the 8% increase in BMD (41% risk reduction). These findings are consistent with the short-term predictions of the conceptual model and with reports from randomized trials. The small but significant reductions in risk that were not explained by measurable changes in BMD might be related to publication bias, measurement errors, or limitations of current BMD technology. (*J Clin Endocrinol Metab* **85:** 231–236, 2000)

IN THE PAST 10 years, a number of publications have reported reductions in vertebral fracture risk related to antiresorptive treatments. Although vertebral fracture is the primary outcome of these clinical trials, bone density is also reported as a surrogate measurement of bone strength. Increases in bone density are typically a secondary outcome measurement of therapeutic efficacy.

The prognostic implications of diminished BMD are well characterized; irrespective of fracture type and bone density measurement site, there is a consistent doubling of fracture risk for each SD reduction of BMD (1, 2). However the nature of the relationship between increasing BMD and decreasing fracture risk has not been well characterized. It is not known whether a one SD increase in BMD, resulting from antiresorptive treatment, results in a 50% reduction in fracture risk. In fact, it has been reported that the observed reductions in fracture risk cannot be fully explained by the changes in bone density (3).

Recognizing that increases in BMD may not fully explain fracture reduction, the objective of this study is to quantitate and characterize the relationship between vertebral fracture risk and BMD changes associated with antiresorptive treatments.

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Materials and Methods

To explore this issue, we surveyed review articles and recent abstracts to identify clinical trials of antiresorptive drugs such as alendronate, calcitonin, estrogen, etidronate, and tiludronate. Only randomized, placebo-controlled studies of postmenopausal women were considered. Trials that compared calcium or vitamin D to placebo were excluded because most of the trials of pharmacologic agents provided calcium and/or vitamin D to participants, so their effects are above and beyond those of calcium or vitamin D. Furthermore, studies of vitamin D were excluded because vitamin D may have nonskeletal benefits independent of BMD changes in vitamin D-deficient populations, and effects of vitamin D have generally been demonstrated in vitamin D-deficient populations rather than community-dwelling women (4, 5).

Poisson regression was used to examine associations between change in BMD and reduction in fracture risk (relative to the placebo group in each trial) across all trials. A variable ("Intercept") for treatment assignment was also included in models to estimate the reduction in fracture risk that could not be explained by change in BMD, representing the Y-intercept when change in BMD equals zero. The Poisson model is appropriate for binary outcomes such as fracture incidence and takes the sample size and number of fracture events into consideration, giving greater weight to larger studies. The relative risk (RR) expresses the fracture incidence in the treatment group relative to the placebo group in each trial, pooled across all studies. The vertebral fracture definition differed somewhat between studies. However, we do not believe this is a significant limitation, as any differences would apply to both the placebo and treatment groups in a particular trial. Moreover, all of the larger trials (6–11) used similar criteria, including a review of fractures at a single radiological center (University of California–San Francisco, San Francisco, CA). Indicator variables identified each trial as a covariate to compensate for the fact that several trials involved more than one treatment or dose; this also adjusts for differences between trials other than change in BMD, such as trial duration and potential differences in baseline characteristics. A sensitivity analysis was performed by elim-

inating trials from the model, one at a time, to examine the resulting effect on the associations with treatment and change in BMD.

Results

The studies that reported vertebral fracture data are summarized in Table 1. The RR of vertebral fracture is plotted against the change in BMD (relative to placebo) for each trial in Figs. 1 and 2. Although the 95% confidence intervals (CI) were not reported for all studies, the CI are roughly inversely related to the person-years of follow-up in each trial, and there is much greater uncertainty around the smaller studies than for larger studies. For example, the RR and CI for vertebral fractures in the Vertebral Fracture Arm of the Fracture Intervention Trial (FIT) was 0.53 (0.41, 0.68), and we can be confident that alendronate has an antifracture efficacy of at least 32% (difference between the upper limit of the CI and 1.0) (10). Although certain other trials reported reductions in fracture risk that seemed to be large in comparison to the small increases in BMD, the CI were often large, and there is little confidence that the true effect is as large as reported. Furthermore, there are other studies that reported much lower antifracture efficacy (or even an apparent increase in risk) for an equivalent change in BMD. These observations are likely related to the small sample size of many trials, which makes the results unstable.

Given the large variability in antifracture efficacy among reports for a specified level of change in BMD plus the large confidence intervals around most of these estimates, it is difficult to gauge whether large reductions in fracture risk can truly occur when BMD increases are small, or if these findings are simply due to chance. To explore this further, Poisson regression was used to obtain a "best fit" of the data. The model predicts that the reduction in vertebral fracture risk improves as a function of change in BMD (Table 2 and line plots in Figs. 1 and 2). The model also predicts a small (20% to 22%) but significant decrease in risk (Intercept) when there is no measurable increase in BMD (RR = 0.80 to 0.78, Table 2). The predicted RR of vertebral fracture for a treatment that increases spine BMD by 8% (approximately the maximum increase reported) is the product of the treatment effect explained by the 8% BMD gain (RR = 0.59) and the effect not explained by changes in BMD (Intercept; RR = 0.78), yielding a total effect of RR = 0.46, representing a 54%

TABLE 1. Summary of vertebral fracture incidence and BMD data used in analyses

Reference	Duration (yr)	Agent and dose	Vertebral fracture cases (n)	Person-yr	Spine BMD[a] (%)	Hip BMD[a] (%)
11	4.2	Placebo	78	8971	1.5	−1.6
		Alendronate 5/10	43	8971	8.3	3.4
10	2.9	Placebo	145	2822	1.8	−1.7
		Alendronate 5/10	78	2822	8.0	3.0
8	3	Placebo	22	1065	−0.8	−1.3
		Alendronate (5, 10, or 20/5)	17	1578	6.8	3.5
16	2	Placebo	6	180	0.56	−1.51
		Alendronate 1	4	162	1.21	0.30
		Alendronate 2.5	3	170	4.10	−0.01
		Alendronate 5	4	170	6.23	1.89
44	3	Placebo	32	552	1.03	−0.60
		Etidronate	28	588	5.08	1.44
36	2.88	Placebo	25[b]	58	−2.7	—
		Etidronate	10[b]	58	5.3	
37	1	Placebo	12	34	0.2	1.4
		HRT-transdermal	7	34	5.3	2.6
14	1	Placebo	18	45	0.96	−0.71
		Raloxifene 60	21	43	1.78	0.95
		Raloxifene 120	20	45	2.07	0.47
6	2.9	Placebo	263	7705	0	0
		Raloxifene 60	169	7705	2	2
		Raloxifene 120	139	7705	2.5	2.5
15	2	Placebo	6	80	1.0	—
		Calcitonin 50	2	80	2.1	
		Calcitonin 100	0	86	2.1	
		Calcitonin 200	2	82	2.1	
7	5	Placebo	70	1385	0.7	0
		Calcitonin 100	59	1385	1.2	0
		Calcitonin 200	51	1385	1.2	0
		Calcitonin 400	61	1385	1.6	0
9	2	Placebo	4	318	−0.5	—
		Tiludronate 50	6	318	−0.2	
		Tiludronate 200	3	318	0.1	
9	3	Placebo	62	1839	0.7	—
		Tiludronate 50	48	1839	0.2	
		Tiludronate 200	59	1839	1.4	

[a] Percent change, relative to baseline.
[b] Number of vertebral fractures, not number of women.
HRT, Hormone replacement therapy; —, not available.
All doses in milligrams.

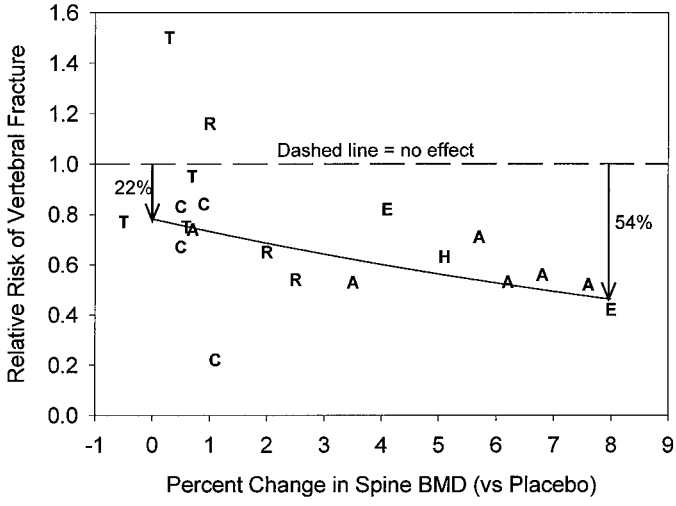

FIG. 1. RR of new vertebral fracture *vs.* change in spine BMD (*vs.* placebo) for randomized controlled trials of antiresorptive agents listed in Table 1. The *solid line* represents the Poisson regression results (see text and Table 2). A, alendronate; C, calcitonin; E, etidronate; H, hormone replacement (estrogen); R, raloxifene; T, tiludronate.

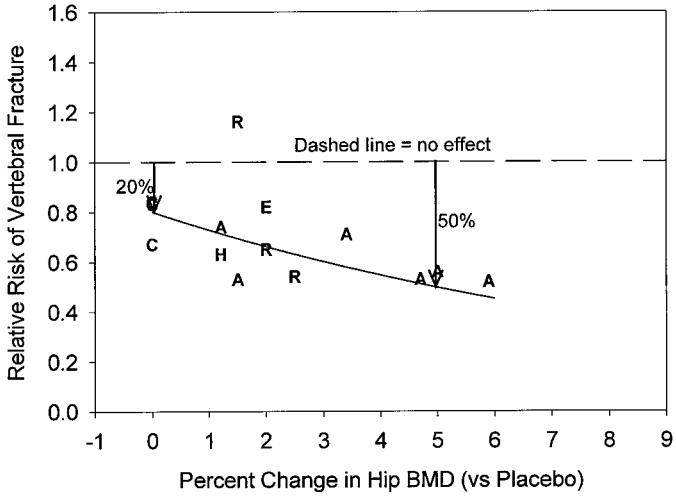

FIG. 2. RR of new vertebral fracture *vs.* change in hip BMD (*vs.* placebo) for randomized controlled trials of antiresorptive agents listed in Table 1. The *solid line* represents the Poisson regression results (see text and Table 2). A, alendronate; C, calcitonin; E, etidronate; H, hormone replacement (estrogen); R, raloxifene; T, tiludronate.

risk reduction. For hip BMD, the maximum reported BMD change was ~5%; the model predicts that this would yield a total effect of (0.80)(0.62) = 0.50, a fracture risk reduction of 50%. The contributions of BMD changes to the total effects on fracture risk are further illustrated in Figs. 3 and 4. It is obvious that for an agent that produces a large increase in BMD (*e.g.* 8% at the spine *vs.* placebo), changes in BMD account for most of the total (50–54%) reduction in fracture risk.

The regression results were robust; dropping individual trials singly from the model had little effect on the associations. One exception was the raloxifene trial (6); when this study was omitted, the estimated treatment effect not

TABLE 2. Associations of BMD increases and treatment effects not explained by BMD (Intercept) with risk of vertebral fractures

Variable	RR (95% CI)
Spine BMD[a]	0.59 (0.43, 0.80)
Intercept[b]	0.78 (0.69, 0.89)
Hip BMD[a]	0.62 (0.46, 0.83)
Intercept[b]	0.80 (0.68, 0.94)

Poisson regression was used with vertebral fracture as the outcome variable and both treatment (intercept) and change in BMD (at the spine or hip) as predictor variables; there were two regression models.

[a] RR shown represents the predicted effect of an 8% increase in spine BMD or a 5% increase in hip BMD; the total effect of the increase in BMD during treatment equals the product of the two RRs (change in BMD and intercept).

[b] RR shown represents the predicted risk of fracture given a 0% increase in BMD.

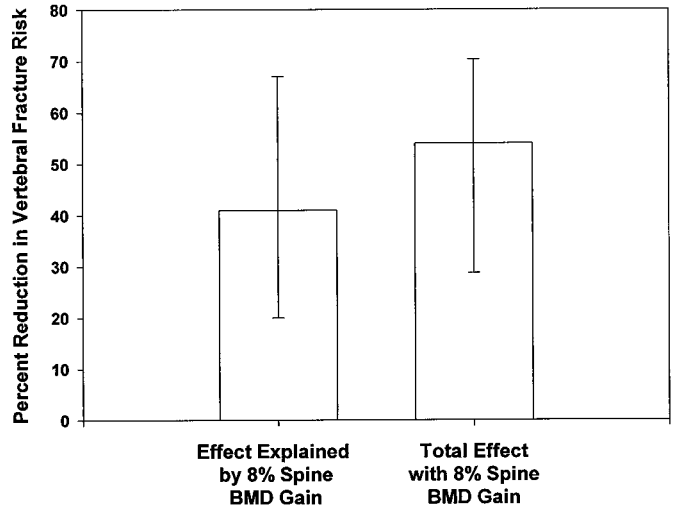

FIG. 3. Total percentage of reduction in risk of new vertebral fracture ("Total Effect with 8% Spine BMD Gain"), and the contribution attributed to an 8% gain in spine BMD (*vs.* placebo), based on the Poisson regression results. Vertical lines indicate 95% CI. Measurable increases in BMD during treatment will reduce fracture risk in proportion to the magnitude of BMD change. The value shown for BMD (41%; difference between 0.59 and 1.0) is based on the approximate maximum (8%) spine BMD change observed in clinical trials (Table 2). The total reduction in risk (54%) is calculated as the product of the RR for BMD changes and the RR for Intercept [1.0 − (0.78*0.59)]; it is not a simple sum of the two values. The difference between the two bars shown represents the reduction in risk that could not be explained by changes in BMD.

explained by BMD (Intercept) decreased to 13–14% (RR = 0.86–0.87) and was no longer significant in either model; thus, changes in BMD seemed to explain all of the observed reductions in risk. Changes in spine and hip BMD remained statistically significant in all models, except change in hip BMD increased slightly (RR = 0.65) and became nonsignificant when one calcitonin trial (7) was omitted; Intercept was also not significant in this model. We also tried dropping the two tiludronate trials, but the effect on the associations was again negligible. Excluding the six alendronate trials resulted in an even stronger association for changes in BMD and a weaker association for the Intercept (which lost significance in the model that included hip BMD).

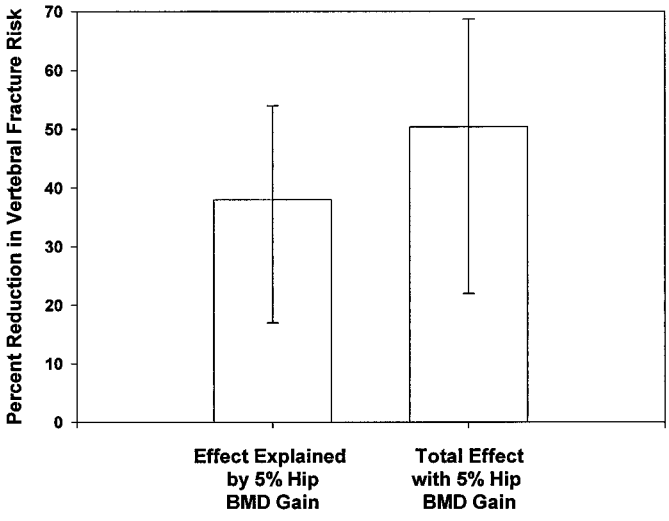

FIG. 4. Total percentage of reduction in RR of new vertebral fracture ("Total Effect with 5% Hip BMD Gain") and the contribution attributed to a measured 5% gain in hip BMD (*vs.* placebo), based on the Poisson regression results. *Vertical lines* indicate 95% CI. Measurable increases in BMD during treatment will reduce fracture risk in proportion to the magnitude of BMD change. The value shown for BMD (38%; difference between 0.62 and 1.0) is based on the approximate maximum (5%) hip BMD change observed in clinical trials (Table 2). The total reduction in risk (50%) is calculated as the product of the RR for BMD changes and the RR for Intercept [1.0 –(0.80*0.62)]; it is not a simple sum of the two values. The difference between the two bars shown represents the reduction in risk that could not be explained by changes in BMD.

Discussion

Bone density is an important risk factor for fractures, and there is no evidence that should dissuade us from continuing to use BMD for evaluating fracture risk of our patients (1, 2, 12). In fact, many clinical trials use low BMD as an entry criterion, to ensure that a sufficient number of participants will have fractures during follow-up to provide adequate statistical power for detecting a treatment effect *vs.* placebo (6, 8–11, 13–16). Most of the variation in bone strength among individuals and the declines in bone strength with age are explained by bone density (17–20). This is true for the hip and vertebrae, and for samples of cortical and trabecular regions within these sites.

Although the relation of baseline BMD with fracture risk is well-established, how would changes in BMD during antiresorptive treatment relate to bone strength and fracture risk? There are at least three mechanisms: 1) over the short term, a reduction in activation frequency would lead to fewer (and possibly shallower) resorption sites and refilling of existing sites (21); 2) there is evidence that inhibiting excessive resorption allows compromised bone to respond to mechanical demands (38), preferentially thickening critical trabeculae, and helping to compensate for reduced connectivity (22, 23). The amount of bone resorbed is less than the amount subsequently formed, leading to continued positive bone balance and increases in BMD beyond the 1–2 yr needed to refill existing resorption sites in some studies (21, 22, 24–26); 3) Part of the effect of antiresorptive agents to increase BMD is more complete mineralization of bone tissue due to the reduction in the rate of bone turnover (27, 28).

Each of these three mechanisms would increase BMD and would disproportionately improve bone strength. Over the long term, maintaining bone mass and preventing loss of structural elements would result in progressively greater differences in BMD and fracture risk over time, relative to untreated women. Thus, one would predict that both the short- and long-term antifracture efficacy of antiresorptive drugs will depend on the extent to which treatment can increase BMD and prevent the bone loss that would occur without treatment. Accordingly, the agents that have been tested in clinical trials were selected on the basis of their effects on BMD; there was no *a priori* reason to think that they would influence bone strength by other mechanisms.

The relative contributions of these three mechanisms may vary with time after initiation of antiresorptive treatment, as excess resorption sites are gradually refilled. The magnitudes of associations with bone strength and, therefore, reductions in fracture risk may differ for these three types of BMD increases. Furthermore, the association of BMD increases with fracture risk may be stronger than observed for static (baseline) measures of BMD, for reasons outlined below.

Increases in BMD and decreases in marker levels have been documented during treatment with certain antiresorptive agents. However, some observers have questioned the use of BMD for evaluating treatment efficacy and, by inference, for monitoring response to treatment, because BMD increases do not seem to fully explain the observed reductions in fracture risk. For example, Cummings *et al.* (3) have proposed that changes in BMD account for only a fraction of the antifracture efficacy of antiresorptive drugs. It has also been proposed that some agents might reduce fracture risk substantially while having little or no effect on BMD (6, 7).

The observation by Cummings *et al.* (3) that changes in BMD during treatment do not seem to explain all of the antifracture efficacy is not surprising—nor is it unexpected. Even if changes in BMD are responsible for all of the antifracture effect, it may not be possible to demonstrate this empirically because of measurement errors or failure of changes at a single skeletal site to reflect changes at other sites. Similarly, the actual increases in trabecular bone mass may be much greater than is apparent from areal BMD measurements, and the relationship between such changes in BMD during treatment and fracture risk may be much stronger than expected from the relationship of baseline BMD and fracture risk (19, 29). Thus, measured BMD changes may seem to underestimate improvements in bone strength, but may nonetheless be proportional to reductions in fracture risk.

It is not necessary that changes in BMD during treatment explain all of the antifracture effect; as long as antifracture efficacy is roughly proportional to changes in BMD, such changes will be of clinical value. For comparison, the extent to which measured changes in serum cholesterol seem to underestimate the observed reductions in coronary heart disease varies depending on the type of measurement (HDL, LDL, and so forth) and whether the effects of measurement errors and other factors are considered (30, 31). Nevertheless cholesterol measurements are used for monitoring response to treatment.

Our finding that larger increases in BMD are associated

with greater antifracture efficacy is concordant with our conceptual model. It is also supported by a recent report from the Fracture Intervention Trial; larger increases in BMD during treatment with alendronate were associated with lower risk of vertebral fractures (32). Women with BMD increases of at least 3% during the first 12–24 months had approximately half the incidence of new vertebral fractures compared with the small proportion of women whose BMD did not measurably increase during the first year or two of treatment. It is plausible to expect increases in BMD to correlate with increases in bone strength when the newly formed bone tissue is normal, as observed using antiresorptive agents (29). However, one cannot assume that an agent that increases BMD will also reduce fracture risk, especially if bone quality is impaired. This is illustrated by fluoride treatment, which is associated with increases in BMD, but no corresponding increase in bone strength in an animal model (33) and no decrease in fracture incidence when all data from several clinical trials are considered (34, 35).

There are several limitations to our analysis. One is the possibility of publication bias; small trials that had little or no effect on BMD, but which found an apparent reduction in fracture risk simply by chance may have been published more often than similar trials that failed to find a significant effect on fractures. Assuming 2 years of follow-up with an annual incidence of 6.5% in the placebo group, a sample size of at least 2000 (placebo plus treatment groups combined) is required to provide 90% statistical power to detect a 32% reduction in fracture incidence on treatment (13). In this light, many of the published trials were grossly underpowered; one trial of calcitonin had observed only 10 women with new vertebral fractures in a total sample size of 164 women (15), and some other studies had even fewer participants (36, 37). Thus, it is unlikely that such small trials would have found a significant reduction in fracture risk other than by chance. Such publication bias might cause the relationship between change in BMD and antifracture efficacy to be underestimated, so that changes in BMD do not seem to account for the entire reduction in risk. Publication bias might also explain why the model predicts an apparent risk reduction for treatments that do not increase BMD.

Another limitation is that not all clinical trials reported fracture results, and we may have missed some studies. However, it is unlikely that we would have missed a large study that would have had a significant effect on the results. Our analysis also assumes that all antiresorptive agents act primarily by reducing the rate of bone turnover and that the resulting increases in BMD and bone strength would accrue via the same mechanisms. At present, there are no convincing data to suggest otherwise. Our findings were either strengthened or remained unchanged when either the tiludronate or the alendronate trials were excluded, and when individual trials were excluded from the analyses. Thus, the results are highly robust and suggest that the findings are not attributable to the influence of a single agent.

The changes in hip BMD were measured at the femoral neck for three studies and total hip for the other six studies with hip BMD. This is unlikely to be a significant limitation because two of the three studies were small (16, 37) and would, therefore, have little influence on the findings. Moreover, changes in femoral neck BMD during treatment are similar in magnitude to those for total hip (10, 11). The similarity of the hip and spine findings is also reassuring. Finally, as noted earlier, there are numerous reasons why current BMD methodology may not accurately reflect how changes in bone strength (and fracture risk) are related to measured changes in BMD. As a result, measured BMD changes may underestimate antifracture efficacy even if the mechanism truly depends on increases in BMD.

What might one predict over the long term? By the end of 2 yr, one would expect the slowing of bone turnover rate to have exerted its full effect on the number of resorption sites. However, BMD continues to increase beyond 2 years during treatment with alendronate and etidronate, even though turnover marker levels do not continue to decrease progressively beyond 6 (to 12) months (24, 25). Maintaining low marker levels into the future may not have a progressively greater benefit on fracture risk, compared to placebo. However, maintaining BMD, or increasing it, would be expected to have a progressively larger antifracture benefit with time (relative to placebo), since the untreated women will tend to lose BMD (and bone structure) progressively.

In conclusion, the available data suggest that antiresorptive therapies that produce larger increases in BMD tend to have greater antifracture efficacy. This relationship may have been underestimated due to measurement errors, publication bias, or other factors. Also, one cannot conclude that treatments that produce larger increases in BMD will be efficacious—the effects on bone strength may differ depending on the location and quality of newly formed bone tissue, which may differ between agents. However, the results support the theory that clinically important degrees of antifracture efficacy cannot be attained without an adequate, concomitant increase in BMD.

Note Added in Proof

A large (n = 2458) trial of risedronate (5 mg) was recently published (Harris ST, *et al.* Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. J Am Med Assoc. 1999; 282:1344–1352). The relative risk of vertebral fracture was reduced by 41%, and BMD increased 4.3% at the spine and 2.8% at the hip (*vs.* placebo) during an average follow-up of 2.5 yr. Including these data in the Poisson regressions had no effect on the results, except that the association for spine BMD (relative risk, 0.60; 95% CI, 0.44, 0.81) was slightly different than shown in Table 2 (all other numbers were unchanged). Thus, our conclusions remain unchanged.

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