CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 21, NO. 4, 2005, 545–553

0300-7995
doi:10.1185/030079905X41390

COMMENTARY

How useful are measures of BMD and bone turnover?*

Paul D. Miller[a], Marc C. Hochberg[b], Lois E. Wehren[c], Philip D. Ross[c] and Richard D. Wasnich[d]

[a] *Colorado Center for Bone Research, Lakewood, CO, USA*

[b] *University of Maryland School of Medicine, Baltimore, MD, USA*

[c] *Merck Research Laboratories, Rahway, NJ, USA*

[d] *Radiant Research-Honolulu, Honolulu, HI, USA*

Address for correspondence: **Dr Paul D. Miller, Colorado Center for Bone Research, 3190 Wadsworth Boulevard, Suite 250, Lakewood, CO 80227, USA. Tel.: +1-303-980-9985; Fax: +1-303-980-1367; email: millerccbr@aol.com**

Key words: **Bone mineral density – Bone turnover, biochemical markers – Fracture – Osteoporosis**

ABSTRACT

Measurements of bone mineral density (BMD) and biochemical markers of bone turnover are useful in the diagnosis and management of osteoporosis, as well as in research relating to the pathogenesis and treatment of the disease. Recent challenges to the utility of these measures have resulted in some confusion among both researchers and clinicians. BMD accounts for the great majority of bone strength and is the current gold standard for the diagnosis of osteoporosis, as well as for prediction of fracture risk. Although bone turnover increases sharply after menopause, biochemical markers of bone turnover have limited usefulness in fracture risk prediction. Persistently elevated bone turnover throughout the menopause is associated with structural decrements, but these cannot be measured routinely and non-invasively. In research applications, both BMD and markers of bone turnover are used to identify candidate agents in preclinical and clinical studies. In addition, head-to-head comparisons of treatments utilize these measures, because fracture endpoint trials would need to be extraordinarily large and complex. Analyses that have suggested that change in BMD or bone turnover 'explains' little of change in fracture risk with treatment appear to be flawed. Although neither can perfectly predict fracture, they are our current best alternatives.

Introduction

Measurements of bone mineral density (BMD) and biochemical markers of bone turnover have been and continue to be used commonly in clinical practice and research in osteoporosis. Recently, however, several publications have challenged the relationship of BMD changes and efficacy[1–4]. Others have suggested that the effect of suppression of bone turnover by treatment is non-linear: that suppression beyond a certain amount has no additional effect on reducing fracture risk[5]. In contrast, a recent report from the Surgeon General of the United States affirms the importance and value of these measures as surrogates for fracture efficacy in clinical trials[6]. Considerable confusion has ensued, and both clinicians and researchers have doubts about the usefulness of BMD and biochemical markers of bone turnover in the management of osteoporosis. Further, although the importance of 'bone quality' has been discussed[7], a reliable measure of bone quality that could be used by clinicians or researchers has so far not been identified. The objective of this paper is to revisit the evidence for using BMD and biochemical markers of bone turnover in clinical practice (diagnosis, prediction

* Portions of this paper were presented as a poster at the 10th annual meeting of the International Society for Clinical Densitometry, Miami, FL, USA, January 2004

of fracture risk, assessment of treatment efficacy) and drug development, to attempt to clarify some areas of confusion, and to consider possible alternative measures.

Diagnosis of osteoporosis and prediction of fracture risk

Bone mineral density

At present, measurement of BMD is the accepted gold standard for diagnosis of osteoporosis[8–13]. BMD accounts for up to 85% of the variance in bone strength[8], and exhibits a continuous association with strength, such that with each standard deviation (SD) decline in BMD the risk of fragility fracture approximately doubles[14]. Therefore, to the extent that fracture risk depends on bone strength, BMD will largely account for differences in fracture risk and will be a good surrogate measure of fracture risk. For example, the risk of fracture in an individual whose BMD is 3 SD below the population mean is 2^4 greater than the risk in an individual whose BMD is 1 SD above the mean (doubling risk four times = 16 times increased risk).

Biochemical markers of bone turnover

In contrast, biochemical markers of bone turnover (Table 1) cannot be used to make the diagnosis of osteoporosis. Biomarkers have limited usefulness in risk prediction, because associations with fracture risk have been inconsistent, are useful only in populations (not in individuals), and correlations with BMD are low[15–17]. Significant associations between high bone turnover and increased risk of fracture, for example, have been reported in some, but not all, studies[18–21].

Table 1. *Biochemical markers of bone turnover*

Resorption
Urine
N-telopeptide cross-links of type 1 collagen (uNTx)
C-telopeptide cross-links of type 1 collagen (uCTx)
Pyridinolines, free and total (Pyr)
Deoxypyridinolines, free and total (Dpd)
Serum
N-telopeptide cross-links of type 1 collagen (sNTx)
C-telopeptide cross-links of type 1 collagen (sCTx)
Cross-linked C-telopeptide of type 1 collagen (ICTP)
Tartrate-resistant acid phosphatase (TRAP)
Formation
Serum
Bone-specific alkaline phosphatase (BSAP)
Osteocalcin (OC)
Amino-terminal propeptide of type 1 collagen (P1NP)
Carboxy-terminal propeptide of type 1 collagen (P1CP)

Following menopause, turnover markers increase on average 2 or 3 SD compared to premenopausal women[22–25]. Because this increase occurs around the time of menopause, it may account for some of the initial increase in fracture risk soon after menopause and for increases seen after stopping estrogen therapy[20,24,26,27]. After this early menopausal increase, however, turnover markers remain fairly constant for the remainder of life[24], and thus appear unable to explain the substantial progressive increases in fracture risk that occur during subsequent decades. The relatively constant, albeit high, rate of turnover after menopause may partly explain why some studies have failed to detect an association between baseline marker levels and fracture risk[15–17,28]. However, the sustained high levels of bone turnover after menopause, in which the rate of bone resorption consistently exceeds bone formation, do lead to progressive declines in BMD and deterioration of microarchitecture. This process results in the irreversible loss of structural elements, and accounts for much of the increase in fracture risk with advancing age observed among untreated women.

While biochemical markers of turnover have been shown to 'predict' bone loss after menopause[29,30], they cannot be used to estimate either peak bone mass or the cumulative bone loss that has occurred in previous years. Because turnover markers cannot measure how much bone is present, they cannot be used to make the diagnosis of osteoporosis or to assess fracture risk. Consequently, the usefulness of bone turnover markers for these purposes, in the absence of BMD measurement, is somewhat uncertain at present.

Clinical risk factors

For most other risk factors the relative risk of fracture differs by two-fold or less. For example, prior fracture is associated with a doubling in risk of future fractures[31]. Moreover, age is an independent risk factor for fracture, and since BMD declines with age this leads to larger differences in risk than would be seen for the same BMD differences at any given age. Thus, an elderly woman with low BMD may have a risk of fracture that is many-fold higher than that of a young woman with high BMD. Falls are also important, but their role is independent of coexisting low BMD and difficult to quantify, especially in the elderly. The association of BMD with fracture risk is still strong after adjustment for clinical risk factors – including age and prior fracture – indicating that BMD operates independently of other risk factors and that assessment of risk factors cannot replace BMD measurement.

Evidence from bone biology

Bone resorption and formation are tightly coupled processes in young adults, but in the high turnover states

characteristic of menopause they become uncoupled, so that more bone is removed in each remodeling cycle than is replaced[32]. As this remodeling imbalance continues over time, bone mass is progressively lost and osteoporosis may ensue. Loss of structural elements of bone accompanies the loss of mass[33]. Trabeculae thin and may perforate or disappear completely; cortical bone thins and becomes increasingly porous[33,34]. Also, high turnover increases the number of resorption lacunae, or 'stress risers' – areas in trabecular bone that are thinner and thus prone to mechanical failure (fracture) when loaded (Figure 1). Furthermore, newly formed bone is relatively weak and secondary mineralization can take years to complete. When turnover is high remodeling occurs again in the same location before this process can be completed, resulting in lower mean tissue density and weaker bone. All of these processes can impair bone strength. While the complete loss of structural elements is generally irreversible, the decrease in bone strength associated with high bone turnover that results from increased stress risers and decreased bone mineralization is potentially reversible. At present, though, these structural characteristics of bone cannot be measured routinely and non-invasively.

Most therapies for osteoporosis today are anti-resorptive agents. The effect of anti-resorptive agents on fracture risk is accomplished by reducing bone resorption and the overall rate of bone turnover, thereby decreasing the number and depth of newly-activated remodeling units and allowing more complete filling and mineralization of microscopic resorption craters. Because the primary effect of these drugs is on osteoclast activity, change in markers of bone resorption (and coupled bone formation) will precede and accompany change in BMD. Increases in BMD during the first few years are believed to result from re-filling of existing resorption sites with new bone, a process that takes months, and then for completion of both primary and secondary mineralization of new bone tissue, which may take up to several years[35,36]. BMD and turnover, which we can measure, reflect the tissue level events, which we cannot measure non-invasively.

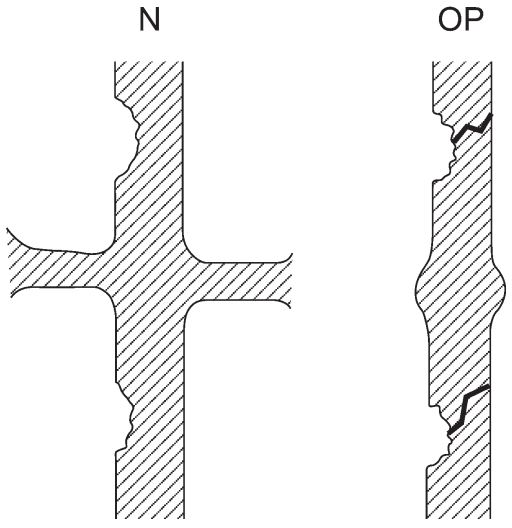

Figure 1. *Diagrammatic representation of stress risers in trabecular bone. In osteoporotic bone, in which horizontal trabeculae have been lost, (shown on the right side of the figure) stress is concentrated in the vicinity of resorption cavities, and fractures occur, as indicated by the heavy black lines. In normal bone on the left, in contrast, cross-bracing from the horizontal trabecula stabilizes the vertical trabecula, despite the presence of resorption cavities. Adapted from Parfitt (1991)[86] (Figure 1, page 5B 45S), with permission from Excerpta Medica, Inc. (note: the adapted figure shows the normal and osteoporotic trabeculae, but does not show the after-treatment trabeculae that appeared in the original article)*

Discovery and development of new treatments

Current standard practice

A routine approach to developing treatments for chronic conditions is to identify risk factors and determine if their modification is plausible. For osteoporosis, age, low BMD, and history of prior fracture are the most consistent and strongest predictors of fracture risk[8,37,38]. Age and history of prior fracture cannot be modified, so pharmacologic research has focused on maintaining or improving BMD to reduce fracture risk. As noted above, high bone turnover has been proposed as another modifiable risk factor, since it appears to be a contributing factor to progressive declines in BMD and microarchitecture (including increased stress risers and under-mineralized bone), and has been associated with fracture risk in some studies.

Effects on bone turnover and BMD are the only options currently available that can reasonably be used on a large scale in drug development to quantitate treatment effects. Preclinical studies that evaluate prospective agents in animal models utilize effects on bone turnover and BMD to measure efficacy and to evaluate likely dose ranges. In humans, measures of biochemical markers of bone turnover are used to establish an initial dose range, because they respond quickly to anti-resorptive therapy. Studies using a BMD endpoint, which must be longer in order to reliably detect change, are used to select the dose to be used in fracture trials.

Possible alternatives

What other clinical properties could be measured? Histomorphometry of an iliac crest biopsy, either 2- or 3-dimensional, permits evaluation of some structural

properties of bone, but the relationship of these to bone strength and fracture risk remains somewhat unclear[39]. Histomorphometry has a well-established role to identify osteomalacia (a condition characterized by increased osteoid and decreased mineralization rates), marrow fibrosis or other qualitative abnormalities of bone. In non-clinical studies measurement of trabecular bone volume by histology is useful, whereas this has limited value in clinical studies, because variability of histomorphometric measures is relatively large, and the procedures are invasive, tedious, and cumbersome[40]. As a consequence, it is difficult to conduct such studies and to demonstrate and replicate significant findings. Thus, the primary clinical use of these examinations to date has been to exclude toxicity by establishing that normal-appearing bone is formed in response to treatment.

Although the Food and Drug Administration (FDA) and other regulatory agencies generally require evidence of fracture reduction in osteoporotic patients in order to grant a 'treatment' indication to a new agent, supporting evidence of positive effects on BMD and bone turnover are necessary elements in an application. However, after a therapeutic agent has received a treatment indication, demonstrating sustained comparable effects on bone turnover and BMD may be adequate for approval of alternate formulations (such as weekly dosing) and indications (such as prevention of bone loss or osteoporosis). The underlying assumption is that lowering turnover and maintaining BMD will prevent consequent loss of bone structural elements and progressive increase in fracture risk[41–43]. The lowest dose that prevents bone loss in the great majority of subjects is generally chosen.

Indicators of anti-fracture efficacy

Approval of new treatments for osteoporosis has depended, in the past, on demonstration of efficacy as measured by fracture reduction. Now that effective treatments are available, the ethics of conducting placebo-controlled trials, especially those with fracture endpoints, are under debate. The prevailing opinion of ethicists seems to be that new agents should be evaluated in comparison to current treatments to demonstrate equivalence, non-inferiority, or superiority[44].

Head-to-head trials of two active treatments are often used to demonstrate that the agents are equivalent or that one is superior to the other. Unfortunately, extremely large studies would be necessary to detect meaningful differences (or to confirm similarities) between therapeutic agents using fracture endpoints, because fractures are simply too infrequent, even in high-risk populations[45]. Moreover, such trials must be conducted with extraordinary attention to detail (further increasing difficulty and cost), because errors in conduct multiply their potential for bias in estimating equivalence or superiority[46]. Trials in lower-risk populations would need to be even larger and of longer duration, because the incidence of low-trauma fractures is lower in patients with osteopenia than in patients with osteoporosis[47]. As a consequence, the total number of fractures would be expected to be smaller and the proportion of all fractures that result from substantial trauma (sufficient to fracture normal bone), rather than from low BMD, would be greater[47].

Change in BMD or markers of bone turnover and fracture risk

One possible alternative for the class of anti-resorptive agents, which share the primary operational mechanism of inhibiting bone resorption and reducing the rate of bone turnover, is to use changes in BMD and/or biochemical markers of bone turnover during therapy as surrogate endpoints. A number of analytic methods have been used in attempts to evaluate BMD and turnover changes for this purpose; differences in interpretation and differences in results among studies have led to confusion and controversy.

Change in BMD measured by dual-energy X-ray absorptiometry (DXA) seems to underestimate fracture reduction associated with anti-resorptive treatment[48]. Nonetheless, for anti-resorptive agents, changes in BMD and bone turnover are robust, graded predictors of fracture risk reduction: in at-risk populations, the greater the change, the larger the reduction in fracture risk[1,21,49,50]. Although one report suggested that decreases in bone turnover beyond a certain point had no greater benefit on reducing vertebral fracture risk[5], a larger study found no evidence of such a plateau for either vertebral or non-vertebral fracture[21] (Figure 2). Because this area is so controversial, the findings deserve further scrutiny and perspective.

Two meta-regression analyses of anti-resorptive agents reported that reductions in vertebral fracture risk were twice as large for agents that produced the largest BMD increases at the spine or hip, compared to agents that had little or no effect on BMD[1,50]. Some have interpreted this as suggesting that about 50% of vertebral fracture risk reduction is attributable to change in BMD. A similar meta-regression analysis of nonvertebral fracture risk found that agents that had little or no effect on BMD (or on bone turnover) did not reduce the risk of nonvertebral fractures, and that fracture risk reductions increased progressively in proportion to the magnitude of changes in BMD and turnover[49].

These results suggest that changes in BMD (and/or bone turnover) might be responsible for a majority of

the therapeutic effect on fracture risk. On the other hand, some analyses have suggested that the proportion of vertebral fracture risk reductions during treatment that are 'explained' by BMD is as low as 4 to 10%[2,3,51,52], whereas others reported values as high as 83%[53]. Why does such a wide range of estimates exist? Which is correct? Which, if any, is appropriate for clinical use?

Surrogate markers

Ideally, the surrogate marker should lie directly in the causal pathway between treatment and outcome and mediate the effect of treatment on clinical outcome, and measured changes in the surrogate should reflect these effects. Freedman *et al*. proposed a statistical technique for validating the usefulness of surrogates[54]. Because the low estimates cited above were calculated using Freedman-type analysis, and because of the increasing reliance on fracture surrogates, it is useful to examine the method in greater detail.

In the Freedman-type analyses by Shih *et al*.[53], data from one clinical trial, in which treatment with alendronate was associated with a statistically significant increase in BMD, decrease in bone turnover, and reduction in risk of fracture, were examined using 24 separate statistical models (Tables 2 and 3). Depending only on the choice of covariates and site of BMD measurement that are entered into the equation for predicting fracture risk reduction, the proportion of the risk reduction 'explained' by change in BMD during treatment ranged from 3% to 83%. In 18 of the models, BMD accounted for 60% or more of treatment-related vertebral fracture risk reductions. Others have also reported highly variable results using the Freedman analysis, even within one set of data, depending on which variables were included in the mathematical model[55–57].

Treatment decisions are unlikely to be based on considerations such as the proportion of treatment effect 'explained', since the concept lacks practical

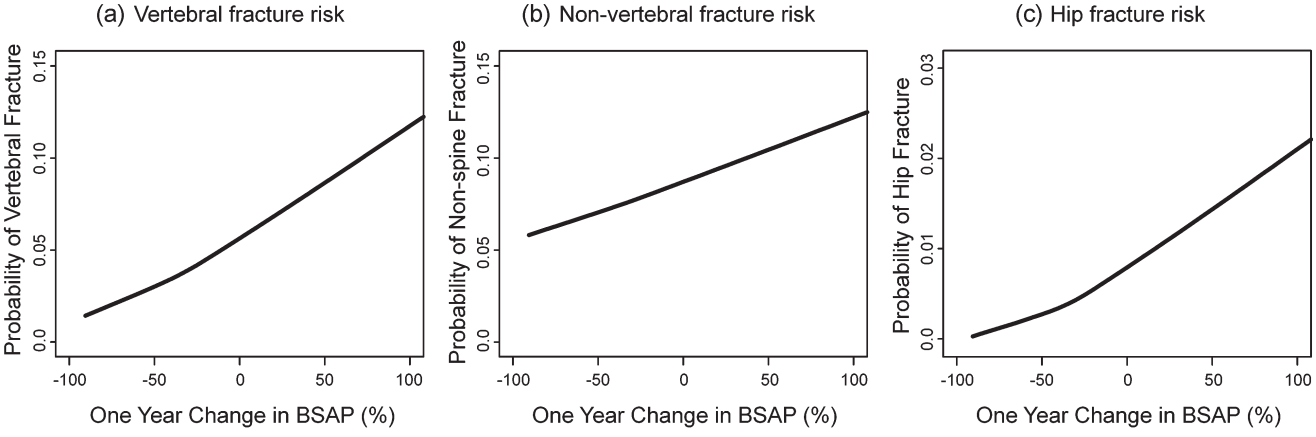

Figure 2. *Relation between change in biochemical marker of bone turnover (bone-specific alkaline phosphatase, BSAP) and fracture risk among women treated with alendronate. The mean (SD) one-year change in BSAP was 13.7 (4.4) ng/ml. (a) Vertebral; (b) non-vertebral and (c) hip fracture risk. Regardless of whether the association of BSAP with vertebral, non-vertebral, or hip fracture is considered, the relation is continuous. There is no evidence of a threshold or plateau for the relationship between decreases in bone turnover and vertebral fracture risk. The authors gratefully acknowledge Dr. Douglas Bauer for providing this figure*

Table 2. *Percent of vertebral fracture risk reduction 'explained' by BMD (95% CI) at 1 year*

BMD sites	With or without baseline of each BMD site	Vertebral fracture arm		Clinical fracture arm	
		BMD actual value	BMD % change from baseline	BMD actual value	BMD % change from baseline
L-spine	W	26.5% (7.7 to 57.5%)	27.8% (9.0 to 59.4%)	9.6% (–23.9 to 53.5%)	11.2% (–21.9 to 56.6%)
	W/O	16.5% (7.6 to 32.8%)	18.8% (2.8 to 43.5%)	14.0% (5.3 to 39.6%)	6.1% (–27.2 to 46.2%)
Total hip	W	25.8% (11.4 to 50.8%)	23.1% (9.5 to 46.2%)	8.4% (–15.2 to 42.0%)	8.3% (–15.4 to 41.8%)
	W/O	10.6% (3.3 to 22.1%)	20.8% (8.6 to 41.5%)	16.0% (7.1 to 44.2%)	3.0% (–20.3 to 29.8%)
Trochanter	W	28.3% (13.3 to 54.8%)	24.3% (10.3 to 48.3%)	11.1% (–10.3 to 45.8%)	10.9% (–10.5 to 45.5%)
	W/O	13.6% (5.4 to 27.2%)	20.2% (8.9 to 39.9%)	16.9% (7.8 to 46.4%)	5.4% (–15.8 to 33.2%)
Combination	W	46.3% (23.0 to 89.1%)	45.2% (22.5 to 87.1%)	14.6% (–23.1 to 68.4%)	16.3% (–21.0 to 71.5%)
	W/O	19.2% (9.3 to 37.1%)	36.4% (16.8 to 71.3%)	19.8% (8.9 to 54.6%)	8.7% (–28.1 to 55.0%)

Table 3. *Percent of vertebral fracture risk reduction 'explained' by BMD (95% CI) at end of study (3–4 years)*

BMD sites	With or without baseline of each BMD site	Vertebral fracture arm		Clinical fracture arm	
		BMD actual value	BMD % change from baseline	BMD actual value	BMD % change from baseline
L-spine	W	22.3% (–2.6 to 56.5%)	29.7% (5.7 to 66.0%)	27.4% (–8.0 to 91.2%)	21.5% (–14.8 to 80.6%)
	W/O	25.6% (14.4 to 47.7%)	20.4% (–1.5 to 50.7%)	24.7% (10.8 to 66.7%)	22.2% (–13.7 to 81.9%)
Total hip	W	79.0% (49.8 to 137.5%)	74.8% (46.7 to 130.6%)	72.9% (34.5 to 205.6%)	71.9% (33.4 to 203.6%)
	W/O	26.0% (15.0 to 46.7%)	77.2% (49.3 to 133.7%)	42.0% (22.7 to 155.6%)	74.0% (35.8 to 208.0%)
Trochanter	W	78.0% (49.1 to 135.8%)	71.8% (44.6 to 125.7%)	68.1% (30.3 to 194.2%)	68.6% (30.6 to 195.3%)
	W/O	31.5% (18.8 to 55.8%)	71.5% (45.1 to 124.5%)	45.3% (24.5 to 124.6%)	72.2% (33.9 to 203.9%)
Combination	W	80.1% (45.9 to 145.5%)	82.5% (48.6 to 147.4%)	64.1% (23.6 to 171.4%)	61.2% (20.3 to 167.7%)
	W/O	35.0% (20.9 to 62.8%)	78.8% (47.1 to 140.3%)	44.3% (23.7 to 115.7%)	66.6% (25.7 to 178.9%)

clinical meaning. Thus, the Freedman method is not a valid or useful means of assessing the association between BMD or turnover and fracture risk in order to make clinical management decisions.

Finally, participants are likely to have similar responses to the treatment in any single study, and the dynamic range of response is limited. As a consequence, it may be more useful to look at associations by pooling studies to examine responses over a wider range, as was done in the meta-regression analyses[1,49,50], rather than limiting analyses to a single study. Analyses similar to that done by Hochberg and colleagues have been used in studies of other chronic diseases to evaluate the relationship between surrogates and clinical outcomes and to predict their efficacy.

Findings from clinical trials of anti-resorptive agents

Examples from the clinical trial literature of anti-resorptive agents are consistent with predictions based on these meta-regression analyses. For example, raloxifene has a relatively modest effect on BMD and bone turnover markers, and has shown a significant reduction in vertebral, but not non-vertebral, fracture risk in placebo-controlled trials[58]. Only potent anti-resorptive agents such as alendronate and risedronate, which have shown substantially greater effects on BMD and turnover, have demonstrated reduction in the risk of both vertebral and non-vertebral fractures[59–61].

Effects on bone turnover can be measured within weeks or months of initiating treatment, effects on BMD within months, and effects on fracture risk follow soon after effects on BMD, also within months[62–67]. The maximal effect of treatment on bone turnover is realized within the first 3 (resorption) to 6 (resorption-coupled formation) months of treatment, while BMD at sites with substantial trabecular content continues to increase for years (up to at least 10 years with alendronate[68] and at least 5 to 7 years with risedronate[69,70]) depending on the agent and the site of BMD measurement. Much of the initial reduction in fracture risk, especially spine fracture, may be accounted for by early changes in bone turnover and BMD, followed later by additional increases in BMD as the new bone matrix becomes fully mineralized. Thus, increases in BMD during the first 6 months may primarily represent refilling of existing remodeling sites – although these BMD increases are relatively small, they translate into disproportionately large increases in bone strength. Decrease in the proportion of 'immature', incompletely mineralized bone may contribute to increased bone strength. Long-term non-vertebral fracture reduction may depend more on continued accrual of bone (or prevention of bone loss relative to untreated patients) than on turnover effects, still bearing in mind that reduction in turnover mediates increases in BMD.

Effects of discontinuation of treatment

The role of BMD and bone turnover in fracture risk is further exemplified by examining the resolution of effect when treatment is discontinued. When hormone therapy is stopped, bone turnover increases almost immediately, to levels at or higher than pre-treatment baseline[27,71]. BMD is lost at high rates, comparable to those seen immediately after menopause[71,72]. It seems plausible to suggest that this sudden increase in skeletal metabolic activity, which would produce increased numbers of resorption cavities to act as stress risers and the higher proportion of immature, incompletely mineralized bone would decrease average mineralization, could be associated with an increased fracture risk, and some data suggest that this is so[73,74]. Are aspects of bone structure likely to be simultaneously affected? Yes, of course, and these changes, which we cannot currently measure *in vivo*, are likely to contribute to the increased risk of fracture. In contrast, among women who discontinued alendronate after up to 5 years of treatment, bone turnover increased slightly but, on average, remained within the normal premenopausal range, BMD remained stable at the spine and total body (loss at the total hip was significant and averaged

1.8%), and no significant increase in fracture risk was observed during the next 5 years[68]. However, this study was small, so confidence intervals around the estimates are wide, and a small increase in fracture risk after discontinuation cannot be ruled out. In each of these instances, observations of turnover and BMD correlate well with fracture experience.

It must also be remembered that BMD as measured by our current techniques is not capturing a simple, single property of bone, but rather represents a summary measure of several properties that contribute to bone strength: the amount of bone present, the amount of mineral present (a reflection of the extent of mineralization), and, to some extent, the size of the bone, because BMD is an areal measure. One can argue, as Delmas and Seeman[4] did recently, that the site at which bone is formed will importantly affect strength, so bone formed at a stress riser may have a greater effect than would bone formed at another site; however, regardless of where the bone is formed, it will have an effect on measured BMD. Change in BMD and change in fracture risk will not show a one-to-one correlation, for all the reasons previously described. Nevertheless, a strong and consistent correlation does exist.

Given the evidence summarized above, many currently accept changes in BMD and turnover markers as indicators of therapeutic efficacy[48]. For example, the criterion for therapeutic equivalence of weekly versus daily dosing for alendronate and risedronate was based on equivalent BMD changes on a background of continued stable reductions in bone turnover[75,76], and results from head-to-head trials with BMD and bone turnover endpoints have also been interpreted as providing information about relative therapeutic efficacy[77–85].

Conclusions

In summary, bone turnover markers and BMD are measures that serve a wide range of purposes in research and clinical practice. They remain an important means of evaluating and comparing treatment efficacy, in the absence of adequate fracture endpoint trials. In his recent report, the U.S. Surgeon General specifically recommended their use in clinical trials of therapeutic agents[6]. Although neither BMD nor bone turnover is a perfect predictor, useful alternatives do not, at present, exist for either the researcher or the clinician.

References

1. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 2002;112:281-9
2. Black DM, Sarkar S, Mitlak B, Knickerbocker R, Cummings SR. What proportion of the effects of raloxifene (RLX) on vertebral fracture risk can be directly attributed to its bone mineral density (BMD) effects? J Bone Miner Res 1999;14(Suppl 1):S158 [Abstract]
3. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res 2002;17:1-10
4. Delmas PD, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone 2004;34:599-604
5. Eastell R, Barton I, Hannon RA, Chines AA, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res 2003;18:1051-6
6. U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004
7. Bouxsein ML. Bone quality: where do we go from here? Osteoporos Int 2003;14(Suppl 5):S118-27
8. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. Osteoporos Int 1998;8(Suppl 4):S1-88
9. U.S. Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002;137:526-8
10. Working Party Writing Group. Osteoporosis: clinical guidelines for prevention and treatment. Update on pharmacological interventions and an algorithm for management. London: Royal College of Physicians; 2001. pp.1-14
11. Sambrook PN, Seeman E, Phillips SR, Ebeling PR. Preventing osteoporosis: outcomes of the Australian Fracture Prevention Summit. Med J Aust 2002;176(Suppl):S1-16
12. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. Can Med Assoc J 2002;167(Suppl):S1-34
13. National Institute for Clinical Excellence. TA087 Osteoporosis – secondary prevention – guidance. Available from www.nice.org.uk/page.aspx?o=241348 [Accessed March 9th, 2005]
14. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Br Med J 1996;312:1254-9
15. Adachi JD. The correlation of bone mineral density and biochemical markers to fracture risk. Calcif Tissue Int 1996;59(Suppl 1): S16-9
16. Akesson K, Ljunghall S, Jonsson B, Sernbo I, Johnell O, Gardsell P, et al. Assessment of biochemical markers of bone metabolism in relation to the occurrence of fracture: a retrospective and prospective population-based study of women. J Bone Miner Res 1995;10:1823-9
17. Melton LJI, Crowson CS, O'Fallon WM, Wahner HW, Riggs BL. Relative contributions of bone density, bone turnover, and clinical risk factors to long-term fracture prediction. J Bone Miner Res 2003;18:312-8
18. Akesson K, Vergnaud P, Gineyts E, Delmas PD, Obrant KJ. Impairment of bone turnover in elderly women with hip fracture. Calcif Tissue Int 1993;53:162-9
19. Garnero P, Hausherr E, Chapuy M-C, Marcelli C, Grandjean H, Muller C, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. J Bone Miner Res 1996;11:1531-8
20. Melton LJ III, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. J Bone Miner Res 1997;12:1083-91
21. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, et al. Change in bone turnover and hip, non-spine and vertebral fracture in alendronate-treated women: the Fracture Intervention Trial. J Bone Miner Res 2004;19:1250-8
22. Hassager C, Colwell A, Assiri AMA, Eastell R, Russell RGG, Christiansen C. Effect of menopause and hormone replacement therapy on urinary excretion of pyridinium cross-links: a longitudinal and cross-sectional study. Clin Endocrinol 1992;37:45-50

23. Slemenda C, Hui SL, Longcope C, Johnston CC. Sex steroids and bone mass: a study of changes about the time of menopause. J Clin Invest 1987;80:1261-9
24. Garnero P, Sornay-Rendu E, Chapuy M-C, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. J Bone Miner Res 1996;11:337-49
25. Garnero P, Shih WJ, Gineyts E, Karpf DB, Delmas PD. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. J Clin Endocrinol Metab 1994;79:1693-700
26. Ross PD, Knowlton W. Rapid bone loss is associated with increased levels of biochemical markers. J Bone Miner Res 1998;13:297-302
27. Wasnich RD, Bagger YZ, Hosking D, McClung MR, Wu M, Yates J, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. Menopause 2004;11:622-30
28. Bauer DC, Sklarin PM, Stone KL, Black DM, Nevitt MC, Ensrud KE, et al. Biochemical markers of bone turnover and prediction of hip bone loss in older women: the Study of Osteoporotic Fractures. J Bone Miner Res 1999;14:1404-10
29. Johansen JS, Riis BJ, Delmas PD, Christiansen C. Plasma BGP: an indicator of spontaneous bone loss and of the effect of oestrogen treatment in postmenopausal women. Eur J Clin Invest 1988;18:191-5
30. Riis BJ, Rodbro P, Christiansen C. The role of serum concentrations of sex steroids and bone turnover in the development and occurrence of postmenopausal osteoporosis. Calcif Tissue Int 1986;38:318-22
31. Klotzbuecher C, Ross P, Landsman P, Abbott T, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 2000;15:721-39
32. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling: emerging insights into the pathophysiology of osteoporosis. N Engl J Med 1995;332:305-11
33. Recker RR, Barger-Lux MJ. Bone remodeling findings in osteoporosis. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis, 2nd edn. San Diego, CA: Academic Press; 2001. pp.59-70
34. Mosekilde L. Age-related changes in bone mass, structure, and strength – effects of loading. Z Rheumatol 2000;59(Suppl 1):1-9
35. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone 2000;27:687-94
36. Heaney RP, Yates AJ, Santora AC. Bisphosphonate effects and the bone remodeling transient. J Bone Miner Res 1997;12:1143-51
37. Siris ES, Miller PD, Barrett-Connor E, Faulkner K, Wehren LE, Abbott T, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 2001;286:2815-22
38. Kanis JA, Johnell O, Oden A, Dawson A, de Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989-95
39. Hauge EM, Mosekilde LE, Melsen F, Frydenberg M. How many patients are needed? Variation and design considerations in bone histomorphometry. Bone 2001;28:556-62
40. Hodgson SF, Johnson KA, Muhs JM, Lufkin EG, McCarthy JT. Outpatient percutaneous biopsy of the iliac crest: methods, morbidity, and patient acceptance. Mayo Clinic Proc 1986; 61:28-33
41. Thomsen JS, Ebbesen EN, Mosekilde L. Relationships between static histomorphometry and bone strength measurements in human iliac crest bone biopsies. Bone 1998;22:153-63
42. Thomsen JS, Ebbesen EN, Mosekilde L. Static histomorphometry of human iliac crest and vertebral trabecular bone: a comparative study. Bone 2002;30:267-74
43. Borah B, Dufresne TE, Chmielewski PA, Gross GJ, Prenger MC, Phipps RJ. Risedronate preserves trabecular architecture and increases bone strength in vertebra of ovariectomized minipigs as measured by three-dimensional microcomputed tomography. J Bone Miner Res 2002;17:1139-47
44. Ellenberg SS. Scientific and ethical issues in the use of placebo and active controls in clinical trials. J Bone Miner Res 2003;18: 1121-4
45. Kanis JA, Oden A, Johnell O, Caulin F, Bone HG, Alexandre J-M, et al. Uncertain future of trials in osteoporosis. Osteoporos Int 2002;13:443-9
46. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. Br Med J 1996;313:36-9
47. Kanis JA, Alexandre J-M, Bone HG, Abadie E, Brasseur D, Chassany O, et al. Study design in osteoporosis: a European perspective. J Bone Miner Res 2003;18:1133-8
48. Khosla S. Surrogates for fracture endpoints in clinical trials. J Bone Miner Res 2003;18:1146-9
49. Hochberg MC, Greenspan SL, Wasnich RD, Miller PD, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab 2002;87:1586-92
50. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 2000;85:231-6
51. Sarkar S, Reginster J-Y, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. J Bone Miner Res 2004;19:394-401
52. Cummings SR, Black DM, Pearson JB, Karpf DB, Harris F, Genant HK, et al. How much of the reduction in risk of vertebral fractures by alendronate is explained by increased spine BMD? J Bone Miner Res 1999;14(Suppl 1):S159 [Abstract]
53. Shih J, Bauer DC, Orloff J, Capizzi T, Thompson D, Oppenheimer L, et al. Proportion of fracture risk reduction explained by BMD changes using Freedman analysis depends on choice of predictors. Osteoporos Int 2002;13(Suppl 3):S38-9
54. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med 1992;11:167-78
55. Wang Y, Taylor JMG. A measure of the proportion of treatment effect explained by a surrogate marker. Biometrics 2002;58:803-12
56. Lin DY, Fleming TR, de Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Stat Med 1997;16:1515-27
57. Bycott PW, Taylor JMG. An evaluation of a measure of the proportion of the treatment effect explained by a surrogate marker. Control Clin Trials 1998;19:555-68
58. Cranney A, Tugwell P, Zytaruk N, Robinson V, Weaver B, Adachi J, et al. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:524-28
59. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23:508-16
60. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:517-23
61. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C, et al. IX. Summary of meta-analysis of therapies for postmenopausal osteoporosis. Endocr Rev 2002;23:570-8
62. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41
63. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82
64. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA 1999;282:637-45
65. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282: 1344-52

66. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333:1437-43
67. Reginster J-Y, Minne HW, Sorensen OH, Hooper M, Roux C, Brandt ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 2000;11:83-91
68. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99
69. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone 2003;32:120-6
70. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 2004;75:462-8
71. Greenspan SL, Emkey RD, Bone HG, Weiss SR, Bell NH, Downs RW Jr, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:875-83
72. Tremollieres FA, Pouilles J-M, Ribot C. Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women. Osteoporos Int 2001;12:385-90
73. Dufresne TE, Chmielewski PA, Manhart MD, Johnson TD, Borah B. Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional microcomputed tomography. Calcif Tissue Int 2003;73:423-32
74. Yates J, Barrett-Connor E, Barlas S, Chen Y-T, Siris ES. Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. Obstet Gynecol 2004;103:440-6
75. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging Clin Exp Res 2000;12:1-12
76. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71:103-11
77. Downs RW Jr, Bell NH, Ettinger MP, Walsh BW, Favus MJ, Mako B, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. J Clin Endocrinol Metab 2000;85:1783-8
78. Dursin N, Dursin E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract 2001;55:505-9
79. Hosking D, Adami S, Felsenberg D, Andia JC, Valimaki M, Benhamou L, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Curr Med Res Opinion 2003;19:383-94
80. Sambrook PN, Geusens P, Ribot C, Solimano JA, Ferrer-Barriendos J, Gaines K, et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (EFficacy of FOSAMAX versus EVISTA Comparison Trial) International. J Intern Med 2004;255:503-11
81. Luckey M, Kagan R, Greenspan S, Bone H, Kiel DP, Simon J, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause 2004;11:405-15
82. Ravn P, Bidstrup M, Wasnich RD, Davis JW, McClung MR, Balske A, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the Early Postmenopausal Intervention Cohort Study. Ann Intern Med 1999;131:935-42
83. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA 2003;289:2525-33
84. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. J Clin Endocrinol Metab 2000;85:720-6
85. Rosen CJ, Hochberg M, Bonnick S, McClung M, Miller P, Broy S, et al. Treatment with once-weekly alendronate 70 mg compared to once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized, double-blind study. J Bone Miner Res 2004;20:141-51
86. Parfitt AM. Use of bisphosphonates in the prevention of bone loss and fractures. Am J Medicine 1991; 91(Suppl 5B): 42S-46S

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Paper CMRO-2922_3, *Accepted for publication*: 25 February 2005
Published Online: 17 March 2005
doi:10.1185/030079905X41390