



Monitoring Osteoporosis Therapy: Bone Mineral Density, Bone Turnover Markers, or Both?

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ABSTRACT

Monitoring the efficacy associated with antiresorptive therapy is an intuitive yet integral part of successful osteoporosis management. Although response rates to bisphosphonates in clinical trials—as judged by changes in bone mineral density (BMD)—are generally high, a small percentage of compliant patients do not respond. Accordingly, monitoring may help identify noncompliant patients and allow for other, possibly more successful, therapeutic interventions. Dual energy x-ray absorptiometry is the accepted method of assessing BMD to determine the need for treatment and to monitor its effects. Change in BMD is considered a valid intermediate end point for efficacy of fracture risk reduction. However, clinical trials have shown that the reduction in fracture risk associated with antiresorptive therapy may occur before changes in BMD become apparent. Vertebral fracture benefit is observed even among women who maintain rather than gain BMD during antiresorptive therapy. Clinical trials show that suppression of bone turnover markers after as little as 3 months of therapy is strongly associated with reductions in risk for fracture. Although formal guidelines for monitoring bone turnover markers do not yet exist, there are data to suggest that changes in these markers are valid intermediate endpoints for efficacy of fracture risk reduction that may provide valuable additional data on therapeutic success, particularly early in treatment and before changes in BMD become apparent. © 2006 Elsevier Inc. All rights reserved.

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Monitoring therapeutic efficacy associated with antiresorptive therapy is an intuitively reasonable component of managing the patient with osteoporosis. Response rates to antiresorptive therapy based on changes in bone mineral density (BMD) and bone turnover in clinical trials, even among highly compliant patients, range from approximately 70% to 85%. In clinical practice, monitoring changes in individuals can help identify both patients who do not respond to therapy and those who are noncompliant.^{1,2} Monitoring is particularly important during the first few years of treatment to establish therapeutic efficacy. Once the efficacy of a particular therapy has been established, there is no evidence to indicate that its efficacy is subsequently lost as

long as the patient remains compliant. Therefore, repeated long-term monitoring while on therapy would seem to have reduced utility.

Recent guidelines recognize the role of BMD testing in postmenopausal women in establishing the diagnosis of osteoporosis, determining the patient's risk of fracture, identifying candidates for intervention, and assessing changes in bone mass over time in treated and untreated patients.^{3,4} In addition, guidelines indicate that BMD testing may be a valuable tool to enhance acceptance of—and compliance with—treatment. The role of bone turnover marker testing in individuals in clinical practice remains controversial; however, data suggest that bone turnover marker testing may augment BMD testing, particularly when assessing fracture risk in elderly patients, assessing therapeutic response to antiresorptive agents, and identifying patients with high bone turnover to predict rapid bone loss.

This review examines the relation between BMD, bone

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turnover markers, and fracture risk. It summarizes recommendations for the timing and frequency of monitoring with bone density measurements and the selection of appropriate densitometry techniques and skeletal sites. The utility and availability of bone turnover markers for monitoring patients in clinical practice are also reviewed.

BONE MINERAL DENSITY AND FRACTURE RISK

Multiple studies have demonstrated an exponential relation between declining BMD and increasing fracture risk.⁵⁻⁹ This relation is firmly established and not considered controversial. It quickly became clear, however, that reductions in fracture risk observed with antiresorptive therapies were greater than those expected from the observed increases in bone density.¹⁰ Further, the reductions in risk were not proportional to the increases in BMD observed among the various antiresorptive agents. Although differences in clinical trial design were offered as a partial explanation for these findings, it seemed plausible that increases in BMD did not account for all of the observed fracture risk reduction seen with these agents.

Subsequent studies have established that there is a statistically significant relation between changes in BMD and fracture risk reduction, although the exact magnitude of this relation remains controversial. In a regression meta-analysis of 13 different trials of antiresorptive agents, Wasnich and Miller¹¹ found a statistically significant relation between increasing BMD at the spine or hip and the reduction in spine fracture risk. Greater increases in BMD versus placebo were associated with greater reductions in spine fracture risk, although it was clear that a small reduction in risk could still be anticipated even if BMD did not increase compared with placebo. In this analysis, the majority but not all of the reduction in risk was attributable to the increase in BMD.

Cummings and colleagues¹² performed a regression meta-analysis of 12 different trials of antiresorptive agents. As in the Wasnich and Miller meta-analysis, there was a statistically significant relation between increasing spine BMD and reduction in spine fracture risk. A small reduction in risk was also seen even when there was no increase in spine BMD compared with placebo. Unlike the Wasnich and Miller meta-analysis, however, Cummings and colleagues concluded that the majority of the reduction in spine fracture risk was not explained solely by the increase in BMD.

The relation between increasing hip BMD and reduction in non-spine fracture risk was evaluated in a meta-analysis of 18 trials of antiresorptive agents by Hochberg and colleagues.¹³ Once again, a statistically significant relation between increasing BMD and declining fracture risk was demonstrated. Greater increases in BMD predicted greater decreases in fracture risk. Unlike the meta-analyses examining the relation between increasing BMD and reducing spine fracture risk, in the Hochberg study no significant

reduction in non-spine fracture risk was seen in the absence of a significant increase in hip BMD.

The relation between the increase in BMD and the reduction in fracture risk has also been examined by looking at individual trials or at multiple trials of a single antiresorptive agent. An analysis of the prospective Fracture Intervention Trial (FIT) included 2,984 women recruited for the Vertebral Fracture Arm (VFA) and Clinical Fracture Arm (CFA) who received alendronate; larger increases in total hip or spine BMD at the end of 12 and 24 months of therapy were associated with a substantially lower incidence of new vertebral fractures at the end of the trial. This suggested that greater increases in BMD on therapy were associated with greater decreases in spine fracture risk.¹⁴

Watts and colleagues¹⁵ looked at this same relation between increasing BMD and reducing spine fracture risk by pooling data from the 2,047 women receiving 2.5 mg or 5 mg of risedronate daily from the North American Vertebral Efficacy with Risedronate Therapy (VERT-NA) trial, the Multinational VERT trial (VERT-MN), and the Hip Intervention Program (HIP) trial.¹⁵ Although this analysis showed greater reductions in spine fracture risk in women who gained BMD on therapy compared with those who lost BMD on therapy, it could not be shown that greater gains in BMD on therapy resulted in greater reductions in spine fracture risk.

The simple maintenance of BMD on therapy would also appear to be of benefit in reducing fracture risk. In FIT, subjects who were compliant (defined as taking $\geq 70\%$ of the study drug, alendronate, for 3 to 4 years), but who had a measured decline of 0% to 4% in BMD at the lumbar spine, nevertheless had 60% reduction in vertebral fracture risk compared with patients who received placebo.¹⁶ A measured decline of $\leq 3\%$ is generally considered indicative of no real change in BMD.¹⁷ However, subjects with $\geq 4\%$ loss in BMD and those who lost any BMD at both the hip and spine did not benefit from alendronate.¹⁶ Together, these data imply that compliant patients who maintain BMD after 1 to 2 years of therapy still receive substantial benefit from treatment.

The exact percentage of spine fracture risk reduction that can be attributed to increased BMD during antiresorptive therapy is controversial. In the Watts group study, an analysis of the relation between increases in spine BMD on risedronate therapy and reductions in spine fracture risk suggested that only 18% of the reduction in risk was attributable to the increase in BMD.¹⁵ In an analysis of a slightly different group of women from the VERT-NA and VERT-MN trials using the same statistical methodology, the reduction in spine fracture risk attributable to the increase in BMD appeared to be 28%, not 18%.¹⁸ Shih and colleagues¹⁹ also performed multiple statistical analyses of data from the 2 arms of the FIT of alendronate. Depending on the arm of the trial, the skeletal site chosen to evaluate the change in BMD, and the time at which the change in BMD was measured, the estimates for the percentage of the

reduction in spine fracture risk attributable to the increase in BMD varied from <10% to >80%.

From these analyses, it is clear that there is a statistically significant relation between increasing BMD due to antiresorptive therapy and decreasing fracture risk. However, this relation may not be the same for reductions in spine fracture risk compared with non-spine fracture risk. Small reductions in spine fracture risk are predicted even in the absence of demonstrable increases in BMD, but it is not clear that this is the case for reductions in non-spine fracture risk. The exact magnitude of the reduction in risk attributable to the increase in BMD remains controversial, as the result is clearly dependent on how each analysis is performed. It would also seem clear from the analyses by Hochberg and coworkers¹⁴ of the FIT of alendronate and the analysis by Watts and colleagues¹⁵ of the VERT and HIP trials of risedronate that it is far better to gain BMD on therapy than to lose it.

BONE TURNOVER MARKERS AND FRACTURE RISK

Increased bone turnover has been proposed as a potential risk factor for osteoporotic fractures because it may increase bone loss and cause microarchitectural deterioration of bone tissue.²⁰⁻²² Bone is constantly being remodeled in a cyclic process by which osteoclasts resorb bone tissue and osteoblasts produce new bone matrix that is subsequently mineralized. Bone loss occurs when the balance of the remodeling process shifts toward excess resorption. Bone remodeling, or bone turnover, activity is reflected in serum or urine levels of various biochemical markers. Serum markers of bone formation include bone alkaline phosphatase, osteocalcin, and the C- and N-terminal propeptides of type I collagen. Urine bone resorption markers include breakdown products of type I collagen such as pyridinium crosslinks (pyridinoline [PYR], deoxypyridinoline [D-PYR]) and the C- and N-telopeptides of type I collagen (CTx and NTx). These biochemical products of bone formation and bone resorption are collectively called biochemical markers of bone turnover. Although levels of these markers are a dynamic reflection of rates of bone remodeling, they do not provide information on the existing level of BMD. Consequently, they cannot confirm the presence or absence of osteoporosis and are not a substitute for BMD testing.

In 1996, Garnero and colleagues²³ demonstrated that elderly women with elevated levels of the bone resorption markers urinary CTx and D-PYR had an increased risk for hip fracture that was independent of BMD. The relation between markers of bone turnover, age, and fracture risk was also examined in an age-stratified random sample of 351 women.²⁰ Among postmenopausal women, levels of biochemical markers of bone turnover were positively associated with age; depending on the marker used, the prevalence of elevated turnover among postmenopausal women >50 years old ranged from 9% to 42%. In this sample,

osteoporosis was significantly associated with high bone turnover and prior osteoporotic fracture.

Recent meta-analyses provide further evidence that bone turnover—rather than just increases in BMD—has a strong influence on fracture risk. In the meta-analyses from Wasnich and Miller¹¹ and from Cummings and colleagues,¹² the small reductions in spine fracture risk seen in the absence of an increase in BMD compared with placebo suggest an independent role of the reduction in bone turnover in the spine fracture risk reduction achieved with antiresorptive agents. The Hochberg group meta-analysis noted earlier showed a statistically significant relation between reduction in non-spine fracture risk and reduction in bone turnover.¹³ Greater reductions in turnover predicted greater reductions in non-spine fracture risk. The Hochberg model estimated that 70% reduction in markers of bone resorption or 50% reduction in markers of bone formation compared with placebo would result in 40% and 44% reductions in the risk of non-spine fracture, respectively.

These data suggest that increased bone turnover is an important determinant of fracture susceptibility. Similarly, reductions in bone turnover during antiresorptive therapy reduce fracture risk. Trials of antiresorptive agents indicate that reductions in vertebral fracture risk are observed within 1 year of therapy. This effect occurs too rapidly to be solely the result of increases in BMD.^{24,25} In trials of postmenopausal women on risedronate, reductions in incidence of vertebral fracture of 61% to 65% were observed after 1 year of therapy, well before significant changes in BMD were detectable.^{24,25} When combined with findings from the separate meta-analyses of Wasnich and Miller¹¹ and Cummings and colleagues,¹² which suggested that reductions in spine fracture risk could be expected in the absence of increases in BMD compared with placebo, and the suspected deleterious effects of high bone turnover on bone architecture, it has been reasonably assumed that these early reductions in spine fracture risk are attributable to suppression of bone turnover.

GUIDELINES FOR MONITORING BONE MINERAL DENSITY IN PATIENTS BEING TREATED FOR OSTEOPOROSIS

Measurement Sites

Current osteoporosis guidelines are in general agreement regarding preferred skeletal sites for diagnosing osteoporosis and monitoring changes in BMD (Table 1).^{26,27} The North American Menopause Society (NAMS) indicates that the total hip is the preferred site for BMD testing, particularly in women aged ≥ 60 years in whom spinal measurements may be unreliable.⁴ NAMS proposes that spine BMD may be a useful measure of bone loss, particularly in early postmenopausal women, because this population tends to lose bone faster in the spine than in the hip. The American Association of Clinical Endocrinologists (AACE) guidelines recommend BMD measurement at either the lumbar

Table 1 Guidelines for monitoring changes in bone mineral density

	American Association of Clinical Endocrinologists	North American Menopause Society	International Society of Clinical Densitometry
Preferred sites	Lumbar spine Proximal femur	Total hip in most women Spine may be considered in younger women	Spine and hip
Preferred technique	DXA	DXA	DXA
Frequency	Normal baseline BMD: every 3–5 yr Osteoporosis prevention: every 1–2 yr until stability is documented; thereafter, every 2–3 yr Osteoporosis therapy: annually until stability is achieved, and every 2 yr thereafter	Untreated: every 5 yr Treated: every 2 yr	Treated patients: yearly until therapeutic effect is established; longer intervals thereafter

BMD = bone mineral density; DXA = dual energy x-ray absorptiometry.
Adapted from *Endocr Pract*,³ *Menopause*,⁴ and *J Clin Densitom*.^{26,27}

spine or the proximal femur.³ In 2002, the International Society for Clinical Densitometry (ISCD) recommended the posteroanterior (PA) spine as the preferred site with the total hip as an alternative site.²⁸ All 3 organizations agree that tests at peripheral sites such as the wrist or heel are useful for the assessment of fracture risk but should not be used for diagnosis or monitoring.^{3,4,28}

Techniques

The various guidelines are also in general agreement that dual energy x-ray absorptiometry (DXA) is the preferred technique for monitoring changes in BMD during therapy just as it is the preferred technique for diagnosis of osteoporosis.^{3,4,26,28} Other techniques such as quantitative ultrasound, radiographic absorptiometry, or single-energy x-ray absorptiometry are not recommended because they can only be used to measure BMD in the peripheral skeleton, such as the wrist, heel, or hand. Similarly, although DXA is the preferred technique for monitoring therapy, DXA measurements of the wrist, heel, or hand are not used for this purpose. Instead, such measurements of the peripheral skeleton by any technique are solely used for the prediction of fracture risk or for diagnosis of osteoporosis in exceptional cases when the spine or proximal femur cannot be measured with DXA.

Frequency of Testing

There is some variation among the guidelines with regard to the frequency of repeat measurements. According to the ISCD, measurements are rarely justified more frequently than yearly.^{26,28} Once efficacy has been established, less frequent intervals are deemed appropriate. Similarly, the

AACE suggests that postmenopausal women receiving treatment for osteoporosis have yearly measurements until stability is demonstrated and at 2-year intervals thereafter.³ In contrast, the NAMS suggests that the initial follow-up measurement not be made for 2 years.⁴

These suggested intervals are based on the observed rates of change with currently available antiresorptive agents and the reproducibility of DXA BMD testing. The reproducibility or precision of DXA BMD testing is excellent, but not perfect. Even when an individual is repeatedly measured within minutes of the original test, the BMD results will not be identical because the test is not perfectly reproducible.¹⁷ For a physician to conclude that a real biologic change in BMD has occurred, a change must be observed that sufficiently exceeds the precision error of the test. This is called the least significant change. When DXA testing is properly performed, changes of $\geq 3\%$ at the PA spine and total hip are considered indicative of real biologic change. Changes $< 3\%$ in either direction suggest stability or no real change in bone mass. With current antiresorptive therapies, changes of $\geq 3\%$ are generally not reached in the spine before 1 year and are not reached at the total hip until 2 years of treatment have been completed.

In accordance with the ability of current BMD technologies to detect clinically relevant changes, Medicare covers repeat BMD testing every 23 months in women and men aged ≥ 65 years being monitored to assess the response to or efficacy of a US Food and Drug Administration (FDA)-approved osteoporosis drug therapy.²⁹ The Current Procedural Terminology (CPT) code 76075 refers to ≥ 1 DXA measurement of BMD made at the spine or proximal femur. To indicate that the efficacy of an approved therapy for

Table 2 Biochemical markers of bone turnover used in clinical practice in the United States

Marker	Sample	Laboratory availability
Bone alkaline phosphatase	Serum	++
Osteocalcin	Serum	—
C-telopeptides of type I collagen	Serum/urine	+
Deoxypyridinoline	Urine	+++
Crosslinked N-telopeptides of type I collagen	Urine	+++
Pyridinoline	Urine	+

+++ = broad availability; — = limited availability.

Adapted with permission from *J Clin Densitom*.³⁰**Table 3** Proposed reference ranges for biochemical markers of bone turnover

Marker	Mean or Median	Upper Limit of Reference Range
Bone alkaline phosphatase (U/L)	18.3	29.6
Bone alkaline phosphatase ($\mu\text{g/L}$)	8.5	14.3
C-telopeptides of type I collagen ($\mu\text{g/mmol}$)	220	476
Free deoxypyridinoline (nmol/mmol)	5.0	7.4
Crosslinked N-telopeptides of type I collagen (nmol BCE/mmol)	35	65

BCE = bone collagen equivalent.

Adapted with permission from *J Clin Densitom*.³⁰

osteoporosis is being monitored, the CPT code V67.59 may also be used in conjunction with the appropriate *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis code. Most private healthcare plans provide coverage for BMD testing to monitor the therapeutic response to therapy, but they generally will not reimburse testing for this indication more often than every 2 years.

GUIDELINES FOR MONITORING BONE TURNOVER IN PATIENTS BEING TREATED FOR OSTEOPOROSIS

Biochemical markers of bone turnover are particularly attractive as a means of monitoring therapeutic efficacy because significant suppression of bone turnover occurs far more rapidly than detectable changes in BMD. These markers reach a nadir within 3 to 6 months of initiation of therapy in clinical trials. It must be noted, however, that the imprecision of measuring bone turnover using markers is far greater than that of measuring BMD using DXA. Additionally, formal guidelines do not exist, and cutoff values for the use of markers of bone turnover are uncertain.

USE OF BONE MARKERS IN CLINICAL PRACTICE

Desirable levels of bone turnover markers are generally considered to be those within the premenopausal range. However, the true premenopausal range for the various markers is controversial. Opinion-based guidelines developed in 1999 by Miller and colleagues³⁰ provided preliminary guidance for use of markers in clinical practice; however, it should be noted that these guidelines are not endorsed by any major medical society at this time. Miller and colleagues suggested that therapeutic efficacy was indicated by a decrease of 20% to 50% from baseline, depending on which marker was being used; if a baseline level was unavailable, a marker level within the premenopausal range could be considered evidence of efficacy. Biochemical markers of bone turnover that are available for use in clinical practice and potential cutoff values for the upper limit of the premenopausal range are summarized in **Table 2** and **Table 3**. It should be noted that these reference ranges may vary by laboratory and by the type of assay used. As suggested in Table 2, not all markers are widely available. Both urinary N-telopeptide and bone alkaline phosphatase are useful markers and are generally clinically available. Marker variability can be reduced by performing specimen collection at approximately the same time each morning and by performing duplicate measurements (i.e., measurements made 1 or 2 days apart from which an average value is calculated).

Guidelines from the National Osteoporosis Foundation (NOF), NAMS, and AACE observe that bone turnover markers may provide valuable additional information to assist in the assessment of fracture risk and therapeutic response, and in identifying patients with high bone turnover.^{3,4,31} However, specific guidance on how to use them in the management of individual patients is lacking.

Reimbursement for biochemical markers of bone turnover varies among private insurers in the United States. Measurements for collagen crosslinks (PYR, NTx, CTx) are potentially reimbursable by Medicare using CPT code 82523. Because of the imprecision in marker measurements, Medicare will allow duplicate measurements to be done at baseline.³² Reimbursement will also be considered for a follow-up marker 3 months after the baseline value has been obtained and again 12 months after the 3-month assessment. Measurements may be considered for reimbursement annually thereafter. CPT codes for other markers may be found in the current issue of the American Medical Association (AMA) CPT code book.

SUMMARY

Fracture risk is strongly related to BMD. Declining BMD is exponentially associated with increasing fracture risk. Increases in BMD during antiresorptive treatment are significantly associated with reduction in fracture risk, although it is clear that not all of the reduction in risk is attributable to the increase in BMD. Nevertheless, monitoring changes in BMD in patients receiving treatment for osteoporosis to

assess therapeutic efficacy is integral to the osteoporosis treatment paradigm.

Although studies suggest that greater increases in BMD are associated with greater reductions in fracture risk, it is important to emphasize that the stability of BMD on therapy appears to confer fracture protection compared with placebo treatment. Thus, a lack of change in BMD on therapy should not be construed as treatment failure. Other studies, however, clearly suggest—in terms of fracture risk reduction—that it is better to gain BMD on therapy than to lose it. Some of these same studies suggest that reductions in spine fracture risk can be seen in the absence of demonstrable gains in BMD compared with placebo. These data, as well as data indicating that spine fracture risk reductions occur before significant BMD increases are observed, suggest that improvements in bone microarchitecture related to suppression of bone turnover are an important determinant of the reduction in spine fracture risk.

Several major organizations have published guidelines for monitoring changes in BMD during therapy. These guidelines are in general agreement regarding the skeletal sites to use for monitoring, the preferred techniques used for monitoring, and the frequency at which repeat measurements of BMD should be conducted. The organizations responsible for these BMD guidelines are also in general agreement that markers of bone turnover may provide valuable additional data over and above those obtained from BMD. In particular, the measurement of biochemical markers may be useful for determining response to therapy earlier than with bone densitometry. However, formal guidelines covering the use of markers for this purpose in individual patients do not yet exist. The level or magnitude of change of any given marker that indicates therapeutic efficacy remains controversial. Therefore, in spite of their promise in the rapid assessment of therapeutic efficacy, biochemical markers currently have limited applicability in the care of most women at risk for osteoporosis. For most women, a DXA spine and/or proximal femur study remains the most appropriate diagnostic modality for diagnosing osteoporosis, monitoring therapeutic effectiveness, and identifying those individuals who are not compliant with or who do not respond to therapy.

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