Bone Density and Markers of Bone Turnover in Predicting Fracture Risk and How Changes in These Measures Predict Fracture Risk Reduction

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Surrogate markers in clinical medicine provide a useful means to assess therapeutic response to pharmacologic therapy in a wide range of chronic disease states. In the area of osteoporosis, the surrogate markers of change in bone mineral density (BMD) and bone turnover markers (BTM) provide the clinician with a means of assessing the biologic response to osteoporosis-specific pharmacologic agents. Increases in BMD and/or reductions in BTM can independently be correlated to reductions in vertebral and nonvertebral fracture risk. In managing osteoporosis patients, the BTM change at an earlier point of time after initiation of therapy and a change in BTM can provide earlier feed-back to the patient and clinician regarding issues such as compliance and a bone biologic response. An increase in BMD at 12 or 24 months after initiation of therapy is also evidence of an improvement in bone strength though with antiresorptive agents no change in BMD may also be associated with risk reduction within clinical trial sets. In this regard, changes in BMD and BTM are complimentary in their application to patient management.

Introduction

Over the past several years in the field of osteoporosis clinical management, no area has been more hotly debated than the following controversial issues—To what degree adding bone mineral to an osteoporotic skeleton with pharmacologic agents used to treat osteoporosis increases bone strength and reduces the risk for fracture?; To what degree reducing bone turnover by pharmacologic agents used to treat osteoporosis increases bone strength and reduces the risk for fracture independent of adding bone mineral?

While this paper will examine these two issues in depth, the fundamental point must be made that were it not for serial measurements of bone mineral density (BMD) and bone turnover markers (BTM), the clinical practice of osteoporosis would be relegated to guess-work.

Surrogate Markers

There are many chronic diseases where surrogate markers are used to assess the efficacy of therapy, even though the most important endpoint for treatment is the reduction in the risk for the specific clinical event. For example, the reduction in the risk for myocardial infarction is the most important outcome for the use of therapies designed to lower serum cholesterol concentrations. However, if clinicians waited for a myocardial infarction as the endpoint to assess therapeutic efficacy of pharmacologic agents designed to reduce the level of elevated serum cholesterol, one of the major risk factors for heart attacks, without measuring the reduction in the surrogate endpoint (serum cholesterol), no patient would take the medication, no health care plan would pay for the medication, and no physician would prescribe the medication. The trust in the surrogate marker as providing evidence for modifying the clinical outcome depends on the strength (power) of the pharmacologically-induced change in the surrogate marker as reflecting the change in the risk for the clinical event. In this regard, the field of osteoporosis therapies is rich in the accumulation of data that have examined the utility of two surrogate markers: BMD and BTM.

Basal BMD in the postmenopausal population has more power to predict the risk for a fragility fracture than elevated cholesterol has to predict myocardial infarction [1].

In addition, the change in antiresorptive-induced BMD may be a stronger predictor of a reduction in fragility fracture risk than is provided by the reduction in serum cholesterol mediated by anti-cholesterol lowering medications to reduce the risk for myocardial infarction [2••]. Changes in BMD and biochemical markers of BTM that are mediated by antiresorptive agents are, therefore, the two surrogate markers that have been utilized in clinical trials and in clinical practice to measure changes in bone strength [3–6].

Table 1. Non–head-to-head comparisons between changes in spinal BMD by DXA and 3-year incident fracture reduction between the antiresorptive agents

Trial	Increase in spine BMD, %	Decrease in vertebral Fx, %
FIT II	8.3	44
FIT I	7.9	47
RVE	7.1	49
RVN	5.4	41
MORE	2.6	40
PROOF	1.2	36

(*Adapted from* Faulkner [13••].)
BMD—bone mineral density; DXA—dual-energy x-ray absorptiometry; FIT—Fracture Intervention Trial; MORE—Multiple Outcomes for Raloxifene Evaluation; PROOF—Prevent Recurrence of Osteoporotic Fractures; RVE—Risedronate Vertebral European; RVN—Risedronate Vertebral North America.

In the pivotal clinical trials that have led to the Food and Drug Administration (FDA) registration of all antiresorptive agents for the treatment of postmenopausal osteoporosis, the primary endpoint has been vertebral fracture risk reduction over 3 years as compared with the placebo group. For the foreseeable future this most important endpoint will continue to be the primary endpoint for osteoporosis-specific pharmacologic registration, especially for agents that have novel mechanisms of action [6]. Alternatively, for agents that have already achieved FDA registration for fracture risk reduction within a class of agents (eg, the bisphosphonates), surrogate markers are accepted by the FDA and The United States Surgeon General's Office as evidence of improvements in bone strength [6,7]. As a result, weekly alendronate and risedronate along with monthly ibandronate were FDA approved for the treatment of postmenopausal osteoporosis on the evidence of surrogate marker data, not fracture data, because of the trust that exists for accepting these two surrogate markers as providing evidence for fracture risk reduction within the bisphosphonate class [8,9,10••].

Nonacceptance of BMD and BTM as Surrogate Markers

Why have BMD and BTM not been universally endorsed as providing evidence of improvements in bone strength with the use of antiresorptive agents? [11,12].

First, for individual patient management, no surrogate marker change mediated by any therapy for any chronic condition provides the clinician with the perfect ability to predict risk reduction. Therefore, many patients will still suffer a myocardial infarction even though a statin medication has significantly reduced their serum cholesterol concentration.

Second, analysis in non–head-to-head antiresorptive therapeutic studies that analyze the magnitude of change in BMD and the magnitude in fracture risk reduction between antiresorptive agents suggests that some antiresorptive agents reduce vertebral fracture incidence with little or no change in axial BMD (Table 1) [13••,14]. These analyses are non-scientific, since they are non–head-to-head analysis and the populations are not comparable [13••]. The randomization criteria for all of the antiresorptive clinical trials are different (Table 2). In addition, comparing antiresorptive agents to one another that have different mechanisms of action to inhibit bone resorption is irrational. A selective estrogen receptor modulator does not have the same mechanism of action as calcitonin or a bisphosphonate [15,16]. Even within the bisphosphonate class, there may be sufficient differences in their cellular as well as their bone–binding-affinity and pharmacokinetics to create a scenario where the mechanisms whereby bisphosphonates improve bone strength are also dissimilar [17••,18]. The result, however, of this type of inadequate scientific methodology comparing changes in BMD and bone strength in non–head-to-head clinical trials has been the explosion of scientific debate and scientific development that tries to explain why bone strength improves with the use of antiresorptive agents independent of adding bone mineral. There has been improvement in the science that has helped to explain how bisphosphonates improve bone strength independent of adding bone mineral [19•,20–23]. In addition, changes in crystal size and collagen orientation also independently contribute to bone strength (Table 3) [24–29]. Yet, we have no clinical tools available to measure these other contributions to bone strength and, therefore, must rely on the surrogate markers of BMD and BTM to assess the skeletal response to osteoporosis treatments.

Without head-to-head fracture endpoints, we will never know for certain if small differences in BMD achieved between different bisphosphonates translate into differences in fracture reduction.

The best we can achieve is using different statistical analysis to explain these relationships between the magnitude of change in BMD and the magnitude of fracture risk reduction; or to use comparison of surrogate markers within head-to-head clinical trials to provide insight into potential differences between agents. Both approaches are imperfect and have some degree of scientific merit along with some scientific flaws [30–34].

Analysis

Using statistical analysis (meta-analysis—summary statistics of many clinical trials) and statistical analysis of any given clinical trial (eg, Freedman's analysis) have provided evidence that there is a relationship between measurable increases in axial or appendicular (eg, hip) BMD measured by dual-energy x-ray absorptiometry (DXA) and the prediction of fracture risk reduction in groups of patients [2••,3, 11, 30–32].

Table 2. Differences in populations in the antiresorptive clinical trials

Trial	Change in spine BMD, %	Reduction in vertebral Fx, %	Spine T score	Baseline vertebral Fx, %
FIT II	8.3	44	-2.1	0
FIT I	7.9	47	-2.1	100
RVE	7.1	49	-2.8	100
RVN	5.4	41	-2.4	100
MORE	~3.0	30	-2.6	37
PROOF	~1.2	36	≤ -2.0	100

(*Adapted from* Faulkner [13••].)
FIT—Fracture Intervention Trial; MORE—Multiple Outcomes for Raloxifene Evaluation; PROOF—Prevent Recurrence of Osteoporotic Fractures; RVE—Risedronate Vertebral European; RVN—Risedronate Vertebral North America.

Table 3. Components contributing to bone strength

Structural properties*
- Geometry—size, shape
- Microarchitecture—trabecular architecture, cortical thickness/porosity

Material properties*
- Mineral—mineral-to-matrix ratio, crystal size
- Collagen—type, crosslinks
- Microdamage/microfracture

*Affected by bone turnover rate.
(*Adapted from* Jarvinen *et al.* [20].)

Meta-analysis shows more of a linear relationship (Fig. 1) [30,31] for changes in axial BMD and reduction in vertebral fracture risk and an exponential relationship between changes in hip BMD and reduction in nonvertebral fracture risk (Fig. 2) [32].

Individual (Freedman-type) analysis has shown a wide range of relationships between the magnitude of change in axial BMD and the magnitude of vertebral fracture risk reduction [2••]. Even within the bisphosphonate class, the degree to which the change in axial BMD induced by bisphosphonates to the magnitude of axial fracture risk reduction ranges from 18% to 28%. This relationship is neither proportional nor linear. Nevertheless even within this type of statistical analysis (Freedman analysis), there is agreement that some relationship exists—adding bone mineral by use of antiresorptive therapy adds strength to bone. This is accomplished by first reducing the remodeling space and second by secondary mineralization. Both mechanisms add more mineral to bone contributing to the increase in bone strength.

Clinical Practice

In clinical practice it is not fair to extrapolate results derived from meta-analysis to individual (Freedman analysis) to comparator trials (Fosamax vs Actonel [FACT] I—alendronate vs risedronate or FACT II—teriparatide vs alendronate) [35••,36••]. The fundamental scientific basis which provides the power of evidence derived from meta-analysis is that all data-points are included (eg, all data must be included in the meta-analysis that is available to compare the relationship between the two comparators) [37]. In the case of BMD and fracture risk, all clinical trials that have data for the change in BMD and the change in risk must be included to validate the strength of a meta-analysis. Extrapolating the results of a well-designed meta-analysis to individual or comparator trials undermines the scientific principle on which meta-analysis results rest. As soon as one removes from a meta-analysis two clinical trials to make a comparison of those clinical trials and make the same conclusion(s) that were made within the meta-analysis that included all the available data-points, the conclusion(s) become invalid.

Therefore, conclusions derived from meta-analysis cannot be extrapolated to individual clinical trial data or comparator trial data. In the same manner, data analyzed from individual clinical trials (Freedman analysis) also cannot be used to make clinical management decisions because of the highly variable results reported in Freedman analysis, even within the same dataset, depending upon the choice of covariates and site of BMD measurement chosen to calculate risk reduction [2••,34].

In clinical practice, the most important reason for serial BMD measurement is not to necessarily see an increase in BMD but to be certain the BMD does not decline beyond the least significant change (LSC) [38,39]. In most clinical trials, few treated participants lost BMD; yet, in clinical practice, patients do lose bone on treatment. Clinical trial patients are different from clinical practice patients [40]. Clinical trial patients are highly pre-selected not to have secondary conditions that are seen in many clinical practice patients that may mitigate the BMD response to osteoporosis-specific pharmacologic therapies (eg, celiac disease, vitamin D deficiency, and so on) [41]. Clinical trial patients are highly compliant and see specialized research personnel very frequently. Clinical practice patients have none of these selections or extra encouragement. Measuring BMD and finding a loss of BMD in treated clinical practice patients uncovers a host of possible unrecognized

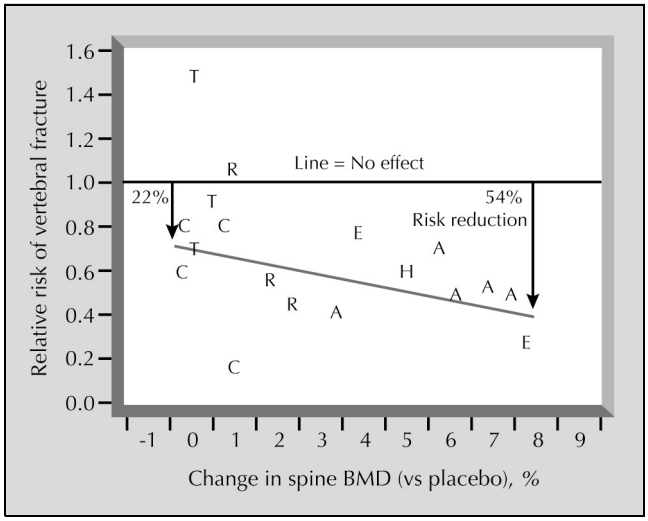

Figure 1. Relationship between changes in spinal BMD and incident vertebral fracture risk reduction in clinical trials—a meta-analysis. BMD—bone mineral density.

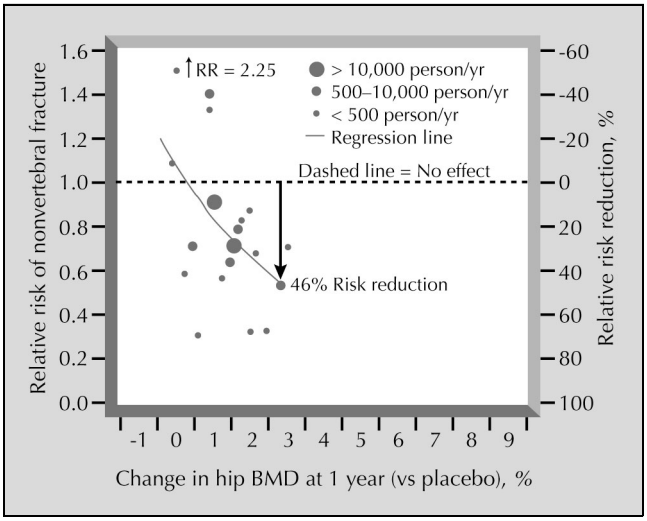

Figure 2. The relationship between antiresorptive induced increases in hip BMD and incident reduction of nonvertebral fractures. BMD—bone mineral density.

medical conditions in addition to compliance and persistent issues; and, a loss of BMD on therapy leads to a greater risk for future vertebral fractures than maintaining BMD [4].

The same fundamental principles regarding the usefulness of BMD in fracture risk prediction and/or predicting risk reduction with treatment can be said of the use of BTM. Baseline BTM that are elevated predict a greater risk for hip, vertebral, and nonvertebral fracture in the postmenopausal population [42,43] ; and reductions in BTM with antiresorptive agents predict in groups of patients, fracture risk reduction independent of changes in BMD [44•,45•].

If BTM are elevated in postmenopausal women, and may be associated with higher rates of bone loss and greater risk for fracture than a postmenopausal woman with normal bone resorption markers, it must also be kept in mind that there are other causes of high BTM beyond postmenopausal rapid bone loss. High bone turnover can be seen in hyperthyroidism, hyperparathyroidism, multiple myeloma, Paget's disease, metastatic cancer to bone, recent bone fracture, immobilization, and space travel. An elevated bone formation marker, such as bone specific alkaline phosphatase is also seen in osteomalacia but not in myeloma. For unclear reasons there is an uncoupling between the high bone resorption seen in myeloma (normal resorption markers) and the elevated bone formation markers. Therefore, high levels of BTM require a differential diagnosis but then if felt to be a result of high bone turnover related to estrogen deficiency, then the implications are higher rates of loss and greater risk for fracture.

Bone Turnover

As our understanding of bone turnover has increased, so has the data that as postmenopausal women age, their bone turnover increases and that this greater increase in turnover may be associated with a greater degree of bone fragility [46]. In addition, evidence has accumulated that the goal of antiresorptive pharmacologic therapy is to reduce bone turnover into the normal pre-menopausal range, if not into the lower half of the normal pre-menopausal range. In this regard there is current debate about the relationship between the magnitude of suppression of bone turnover induced by antiresorptive agents and the magnitude of fracture risk reduction. Data from the risedronate clinical trials have suggested that below a certain level of reduction in bone turnover measured by the resorption marker, N-telopeptide, there is no greater reduction in incident vertebral fracture risk (eg, a threshold level exists) [44•]; while data from the alendronate clinical trials suggest that the greater the reduction in the bone turnover marker, bone specific alkaline phosphatase, the greater the reduction in incident vertebral fracture risk [45•]. Why the discrepancies? Part of the answer lies into why it is scientifically unsound to compare changes in BMD with changes in fracture risk reduction without head-to-head fracture trials—randomized populations are not the same and surrogate markers only reflect part of the bone strength story. Part of the answer lies in the low frequency of fracture events at the lower ranges of bone turnover levels (eg, reduced statistical power to detect true threshold or no-threshold effects). Nevertheless, it is clear that there is some relationship between the magnitude of reduction in bone turnover markers and the magnitude of fracture risk reduction—both incident vertebral fracture and nonvertebral fracture events [32,43].

In clinical practice the advantages of serial BTM determinations are that they provide earlier assessment of a bone biological effect of the osteoporosis-specific pharmacologic agent that has the effect on bone turnover. In addi-

tion a certain magnitude of biomarker change is needed to insure that the biomarker change is greater than the LSC for the biomarker assay precision-error, and once such a change is seen, it implies that the patient is taking the medication, the medication is being absorbed, and that the drop in BTM beyond the LSC is predictive, to some degree, of a reduction in fracture risk. Alternatively, if there is no or little change in the bone turnover marker, the clinician should raise the questions surrounding poor compliance, proper dosing instructions being followed, adequate absorption of (especially) the fastidiously absorbed oral bisphosphonates, or some secondary process that could mitigate the bone biological effect of the drug (vitamin D deficiency, and so on). Patients like early feed-back that a medication is being effective, especially for often an asymptomatic disease requiring chronic intervention.

Parathyroid Hormone

The issue(s) of the utilization of bone density and bone turnover for determining the efficacy of the anabolic agent, low dose daily parathyroid hormone (PTH) are even more uncertain. Most of the data acquired has been with the use of teriparatide (1-34 recombinant human PTH) in clinical trials of postmenopausal women and elderly men [47–52].

Administering PTH induces an impressive increase in axial BMD, and in a head-to-head comparator trials examining teriparatide (20 μg/day) to alendronate (10 mg/day) there was a significantly greater increase in spinal BMD as measured by DXA with teriparatide than the increase induced by alendronate [36••]. Nevertheless, just as in the FACT trial, there are no prespecified fracture data, so it remains unknown in this PTH versus alendronate study translates into differences in bone strength.

The hip BMD as measured by DXA increases as well as with PTH, though as in most osteoporosis-specific pharmacologic trials, the magnitude of the hip BMD increase is less than the more cancellous bone of the axial skeleton. Hip BMD increases with PTH are generally more than observed with agents that have not been shown to reduce the risk for nonvertebral fractures (raloxifene and calcitonin). The forearm BMD as measured by DXA declines with the administration of teriparatide [48]. Yet, forearm bone strength increases. Why? PTH increases bone strength in part by increasing bone size due to its effect to add new bone to the periosteum [53–55, 56••], and thereby, increasing the cross-sectional moment of inertia [56••]. BMD as measured by DXA is a derived equation: BMD = bone mineral content (BMC)/Area. Therefore, as bone area increases the calculated areal BMD may decline even though BMC also increases with PTH. In studies in cynomegalus monkeys where peripheral quantitative computed tomography (QCT) was measured, the bone volumetric area increases and biomechanical testing of bone strength shows that strength also increases [57]. Therefore, areal BMD by DXA may be misleading in monitoring the effect of PTH on bone, especially cortical bone sites where the increase in bone area may be greater than the PTH-induced increase in BMC. In the future, we may utilize central as well as peripheral QCT technologies as the preferred technology to monitor response to PTH.

With regard to BTM in clinical practice and their usefulness in monitoring PTH there is growing evidence that certain biochemical markers of bone formation (BFM) may provide evidence of an early anabolic effect of PTH [58•,59]. Bone formation markers such as bone specific alkaline phosphatase and serum osteocalcin rise early (within 1 month) of PTH administration. Perhaps even more sensitive as a BFM is serum P1NP or P1CP (procollagen 1 N-Telopeptide and C-Telopeptide). P1NP is the most robust BFM that increases rapidly with PTH administration and there is preliminary evidence that the rise in P1NP is correlated ($r = 0.6$) with an increase in BMD 6 or 12 months after PTH initiation; and, is associated with an improvement in bone formation as assessed by double tetracycline-labeled quantitative bone histomorphometry [51,59].

BFM use in monitoring PTH may provide the clinician and his/her patient early feed-back as to a "response" to PTH much in the manner that the early drop in bone resorption markers may provide early feedback in the utilization of antiresorptive (anti-remodeling) pharmacologic agents. There is no data as of this paper that has correlated any change in PTH-mediated increases in BMD or BFM to fracture risk reduction.

There has been preliminary data that have also examined the bone effects of PTH in combination with antiresorptive agents that may offer some insight into the interactions between PTH as an anabolic agent and antiresorptive agents. Most of the data that is published on this issue is preliminary-observational or short-term, without any fracture data [48–51,60]. Most of the data that suggests that prior or concomitant use of raloxifene or alendronate may mitigate the bone biologic response to PTH relies heavily on BFM changes (increases) that are consistently mitigated by the presence of an antiresorptive agent. However, changes in BMD measured by DXA in the two prospective studies [49,50] have indicated no mitigation of the axial BMD response by combination therapy and in the study by Black *et al.* [50], there was a significantly greater increase in total hip BMD with combination therapy. In the study by Finkelstein *et al.* [49] there was a significantly greater increase in total body BMD with combination therapy. Both of these studies showed greater effects with PTH monotherapy as measured by central (axial) QCT; yet there is no data in any osteoporosis literature that has examined what pharmacologically induced changes in BMD as measured by QCT mean relative to changes in bone strength. There are preliminary prospective raloxifene data that suggest that combination therapy with raloxifene and alendronate in treatment naive postmenopausal women causes a

significantly greater increase in total hip BMD than monotherapy [61]. Therefore, it is too soon to know if there is any mitigation of PTH effect by prior or concomitant use of an antiresorptive agent and these interactions merit in depth additional investigations. One thing seems to be clear, after discontinuation of PTH, an antiresorptive agent is needed to retain the gains in BMD that are induced by PTH [62,63].

Glucocorticoid-induced Osteoporosis

Though the focus of this paper has been on postmenopausal osteoporosis postmenopausal osteoporosis, a few brief comments are pertinent about glucocorticoid-induced osteoporosis (GIOP).

Basal BMD is a poor indicator about the risk for fracture in acute, high-dose GIOP or chronic low-dose GIOP [64–66]. In fact the World Health Organization criteria used for the diagnosis of osteoporosis cannot be applied to GIOP and the well recognized and quantified relationship between low BMD and fracture risk defined in postmenopausal osteoporosis also cannot be applied to GIOP. Patients may fracture with normal BMD and/or T-scores who receive glucocorticoids as opposed to the well-defined risk relationship observed in postmenopausal osteoporosis or age-related bone loss. Bisphosphonates have very favorable effects in the treatment of glucocortocoid-induced bone loss [67-72]. Therefore, guidelines provided by The American College of Rheumatology are correct in their strategies to reduce fracture risk in patients receiving high dose or chronic low-dose glucocorticoids [73••]. The same type of usefulness of BTM previously outlined for postmenopausal osteoporosis also cannot be used to guide clinical management decisions for GIOP. BTM are very inconsistent in their predictability of rates of bone loss, fracture risk prediction, or response to therapeutic agents utilized for the treatment of GIOP as they may be for postmenopausal osteoporosis [74••].

Conclusions

Both BMD measurements as well as measurements of biochemical markers of bone turnover (BTM) provide highly useful information for clinicians managing patients with postmenopausal osteoporosis.

Neither surrogate marker is perfect in its application of individual clinical patient management, for diagnosis or for decisions regarding therapeutic response. Nevertheless, just as the development of a new incident fracture on treatment may not necessarily represent "treatment-failure", changes in surrogate markers may not always reflect changes in bone-strength that might be mediated by treatment.

It is how the clinician interprets any change in a surrogate marker in deciding if an osteoporosis-specific pharmacologic agent is effective. All are imperfect sciences—as is bone biology in its essence. Nevertheless, not to utilize surrogate markers in clinical practice management in osteoporosis would remove the only methods clinicians have to assess therapeutic response and engage in constructive patient dialogue.

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