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Clinical Use of Bone Turnover Markers to Monitor Pharmacologic Fracture Prevention Therapy

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Abstract

Monitoring of drug therapies to prevent fractures is controversial. Measurement of bone turnover markers has the potential to identify those with a suboptimal response to fracture prevention medication within a few months of its commencement. However, given the imprecision of currently commercially available assays of bone turnover markers, many individual persons who are "suboptimal medication responders" are likely to be misclassified as "adequate responders" or vice versa, depending on the cut point chosen to define suboptimal and adequate response. Before bone turnover markers can be recommended for routine use in clinical practice to monitor fracture prevention therapies, three advances are needed: 1) bone marker assays with better precision; 2) research establishing optimal cut points of bone marker levels to distinguish "suboptimal responders" from "adequate responders"; and 3) research establishing the incremental fracture reduction benefit from clinical interventions for "suboptimal responders" identified from bone marker measurements.

Keywords

Bone turnover markers; Bone markers; Bone resorption; Bone formation; Least significant change; Monitoring osteoporosis therapy; Monitoring fracture prevention therapy

Introduction

Fractures related to osteoporosis continue to be a substantial public health problem. At 60 years of age, Caucasian men and women, respectively, have a 26% and 44% chance of suffering a fracture related to osteoporosis during their remaining lifetime [1]. Fractures related to osteoporosis were estimated to have a direct medical cost of $16 billion in 2005, and that cost is projected to rise to $25 billion by 2025 [2].

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Although several medications are proven to reduce the risk of osteoporotic fracture [3–6], there is controversy as to how, or if at all, patients should be monitored to assess how well such medications are working. Simply observing their fracture experience while on therapy is impractical to assess drug efficacy. First, the incidence of fractures is likely to be low over a few months to a couple of years even if the drug is not working. Second, fracture prevention medications reduce but do not eliminate the risk of fractures, and thus an incident fracture does not necessarily indicate lack of drug efficacy.

Follow-up bone densitometry to measure bone mineral density (BMD) 1 or 2 years after the commencement of fracture prevention medication has been the most common way to assess medication efficacy, and is recommended by both the International Society for Clinical Densitometry [7] and the National Osteoporosis Foundation [8]. This practice is controversial and suboptimal for several reasons. First, 1 or 2 years represent a substantial time delay before discovering that the patient has had a disappointing response to drug therapy. Second, after 2 years a substantial proportion of those on drug therapy do not have changes in BMD greater than the least significant change (LSC) of the densitometer [9]. However, most of these patients are benefiting from the medication. Post hoc analyses of the alendronate, risedronate, and teriparatide trials show that those whose bone mass does not change on drug therapy have a lower fracture risk than those assigned to placebo [10–13]. Only a minority of those taking raloxifene can expect to see any significant increases in their BMD [14]. Re-measurement of BMD is done primarily to be sure that individuals are not losing BMD on drug therapy [15]. However, randomized controlled trials would suggest that very few individuals lose sufficient bone on drug therapy to be confidently detected by bone densitometry [9], and there is no published evidence as to what proportion of patients in clinical practice lose enough BMD to be reliably detected on follow-up dual-energy x-ray absorptiometry (DXA) or that management can be improved when those individuals are correctly identified.

These medications improve bone strength and prevent fractures in part by decreasing bone turnover (in the case of antiresorptive medications) or by increasing bone turnover (in the case of anabolic agents). Changes of bone metabolism markers occur within a few weeks to a couple of months of starting drug therapy with sufficient magnitude that they have the potential to confirm a therapeutic response to the medication for individual patients and/or identify those with a suboptimal response to therapy and who may benefit by switching to a different agent [16••].

Thus, bone marker measurement to monitor pharmacologic fracture prevention therapy is attractive but controversial, with some authors advocating their use [17•, 18, 19] and others advising against their use [20, 21•, 22••]. A recent review by a joint committee of the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has summarized the evidence supporting use of bone marker measurement for management of osteoporosis [16••]. In this paper we will in three parts focus specifically on and extend that prior review regarding the potential role of bone marker in monitoring individuals after commencement of drug therapy by: 1) briefly reviewing the biology of bone turnover markers; 2) discussing a set of criteria that we propose need to be satisfied before measurement of bone turnover markers can be routinely

recommended for monitoring fracture prevention therapy; and 3) discussing the degree to which these criteria have been satisfied for each of the currently US Food and Drug Administration–approved medications to reduce fractures.

Types and Origins of Bone Turnover Markers

Markers of bone turnover are typically products of bone type I collagen degradation or synthesis, or cellular compounds produced with the activation and/or activity of osteoblasts and osteoclasts.

Markers of Bone Resorption

When bone is resorbed, the N-terminal and C-terminal products of bone type 1 collagen peptide chains, called N-telopeptides (NTX) and C-telopeptides (CTX), are released in this process, and can be measured in either serum or urine. Lysine and hydroxylysine amino acids within the collagen peptide chains are converted to ketoimine compounds that subsequently are converted to nonreducible deoxy-pyridinium and pyridinium cross-links [23]. These cross-links are released during bone collagen degradation yielding pyridinoline and deoxypyridinoline cross-links. During osteoclastogenesis, the enzyme tartrate-resistant acid phosphatase is synthesized and released, and also rises with osteoclastic number and activity. RANK ligand (RANKL [receptor activator of nuclear factor-κB ligand]), a cytokine essential for osteoclastogenesis, is a marker of bone resorption activity.

Markers of bone resorption, especially the bone collagen degradation products, have marked diurnal variation. Serum and urine levels of these markers are highest in the early morning (3–7 AM) and fall to a nadir in the early afternoon hour with an amplitude as high as 50% of their 24-h mean level [24]. Food intake decreases bone resorption markers [25], and thus these markers need to be assessed while fasting.

The coefficients of variation for recently developed serum assays for β CTX are more precise than older tests with coefficients of variation ranging from 3.8% to 5.7% [26]. The commonly recommended least significant change (LSC) for use in an individual person to detect a change with only a 5% chance of type 1 error (stating there is a change when in fact there is not) is 2.8 times the interassay coefficient of variation. Thus, the upper bound of the LSC for serum CTX with the newer assays would be approximately 16% [26]. For the older CTX assays and for urine NTX, respectively, the LSCs are stated to be approximately, respectively, 30% and 60% [17•].

Markers of Bone Formation

Type 1 bone collagen is first synthesized as a propeptide, and propeptide fragments (procollagen 1N-terminal propeptide [P1NP] and procollagen 1C-terminal propeptide [P1CP]) cleaved during post-transcription modulation reflect bone formation activity. Bone-specific alkaline phosphatase (BSAP) is an enzyme produced by activated osteoblasts that appears to have a role in calcium hydroxyapatite deposition on bone. Osteocalcin is a bone matrix protein manufactured by osteoblasts but also released from bone during bone resorption, and thus reflects both osteoblastic activation and bone resorption activity. Automated assays to measure P1NP and osteocalcin have been developed with interassay

coefficients of variation of, respectively, 4.4% to 9.2%, and 4.7% to 7.2%, suggesting the upper bounds of the LSC for P1NP and osteocalcin, respectively, of 25% and 20% [26].

Markers of bone formation have less diurnal variation than bone resorption markers, with a difference between nadir and peak levels about 12% for bone alkaline phosphatase but lower for P1NP. The diurnal variation of serum osteocalcin is higher (difference between nadir and peak levels estimated in one study at 19%) [27]. Food intake has a lower effect on bone formation than on resorption markers [28].

Importantly, bone turnover marker levels increase substantially within a couple of weeks after acute fractures, reflecting the processes of fracture repair and healing, and can stay somewhat elevated up to a year or more following a fracture [29]. Systemic glucocorticoids depress markers of bone formation, but have a two-phase effect on bone resorption, increasing resorption acutely but returning to normal or low levels with chronic use [30, 31]. Renal insufficiency impairs the excretion of some but not all bone turnover markers.

Monitoring of Drug Therapy to Treat Osteoporosis and Reduce Fractures

The most promising clinical application for measurement of bone turnover markers in clinical practice is monitoring of drug therapy used to treat osteoporosis and prevent fractures. As for any diagnostic test, we propose that routine use of bone monitoring of pharmacologic fractures should be recommended only if there is a reasonable pretest probability of a test result that would warrant a change to a different management strategy. For such an approach to be evidence based, we propose six criteria that need to be satisfied before use of a bone marker can be recommended for routine clinical use (Table 1), especially in the form of formal guidelines:

1. At the individual patient level, treatment-related changes in bone marker levels have to be sufficiently large relative to the imprecision of the test that apparent changes in the bone marker level can confidently be ascribed to the medication. The most common measure of the magnitude of bone marker change required to satisfy this criterion is the LSC.
2. There has to be significant between-person heterogeneity in treatment-related changes of bone markers. If all patients show similar changes in the bone marker level, then the bone marker cannot distinguish adequate from suboptimal responses to the medication.
3. There must be evidence that short-term changes in the bone marker during the first few months of therapy are associated with long-term fracture reduction benefit.
4. There is a sufficient clinically significant difference in fracture rates among those above and below a chosen cut point of bone marker change such that a change of management strategy (eg, changing to a different medication) is a reasonable consideration for those whose bone marker values do not change beyond the cut point.

5. The precision of the test is sufficiently good such that "suboptimal responders" can be differentiated from "adequate responders" with no more than modest misclassification.

6. Finally, ideally there would be evidence that clinical intervention(s) for those identified as "suboptimal responders" reduces their risk of fractures compared with no further intervention.

Alendronate

In the FIT of alendronate versus placebo, the magnitude of reduction of BSAP and P1NP over 1 year have both been shown to be associated with the magnitude of vertebral fracture reduction, and BSAP reduction also predicts fewer non-spine and hip fractures over 3 to 4.5 years of follow-up [32]. The proportions of those on alendronate who had greater than 15% and greater than 30% reductions of BSAP were, respectively, 80% and 56%. Moreover, those who had a reduction in BSAP greater than 30% of the baseline value had significantly lower incidence of hip and non-spine fractures on alendronate compared to those with less than 30% change of BSAP. Thus, for alendronate, BSAP is a marker that fits criteria 1 through 3 (Table 1).

However, the appropriate cut point of bone turnover change that one would choose to identify "suboptimal responders" to alendronate remains unclear, and needs to be chosen mindful of how this would influence management. Presumably, if the decrease in BSAP on alendronate was less than that chosen cut point, that would lead to a change of drug therapy (eg, to a parenteral bisphosphonate or denosumab). An approach that emphasizes detection of suboptimal responders with high sensitivity would choose a high cut point of BSAP decrease, but this would come at the expense of low specificity. For example, according to data from the FIT, if those with less than a 30% decrease in BSAP are considered to be suboptimal responders, then 44% would be considered to be suboptimal responders and switched to different medications [32]. However, the proportion of those who truly do not experience a reduction of fracture incidence relative to what they would have experienced without the drug is likely much smaller [10]. Thus, at this cut point, there is likely to be a substantial number of those who are indeed having fracture reduction benefit from the drug that would be misclassified as "suboptimal responders" [22••].

With a lower cut point of at least a 15% reduction of BSAP, 20% of those taking alendronate would be considered nonresponders according to FIT data [32] and would be switched to other, more expensive medications. In this case, the emphasis would be lower sensitivity to identify nonresponders in exchange for higher specificity, but given the imprecision of the test [22••] significant numbers of "suboptimal responders"may be classified as "adequate responders" and vice versa. Much more study is required to establish what might be the appropriate cut point to assess suboptimal response, and at this time criterion 4 is only partially fulfilled for BSAP monitoring of alendronate treatment and criterion 5 is not fulfilled. There is no evidence that switching to any other medication would reduce the incidence of fractures in those who do not have a reduction of BSAP on alendronate, and thus criterion 6 is not satisfied.

Risedronate

In the randomized trials of risedronate versus placebo [33, 34], fasting morning urine C-telopeptide and N-telopeptide were assessed at both baseline and 3 to 6 months later for a subset of 669 women. The percentage decrease in both urine CTX (median, 60%) and urine NTX (median, 51%) was associated with the reduction of incident vertebral fractures on alendronate versus placebo [35, 36].

These findings were confirmed in the IMPACT trial, which treated 2302 osteoporotic postmenopausal women with risedronate 5 mg daily for 1 year [37••]. All participants had serum CTX and urine NTX measured at baseline and at 10 weeks and 22 weeks after baseline, with an LSC of 30% calculated for both. Seventeen percent and 31% of participants did not suppress their bone resorption activity beyond the LSC level for, respectively, serum CTX and urine NTX. The incidence of nonvertebral fracture was significantly higher (4.3%) among those who did not have a decrease of serum CTX beyond the LSC compared to those who did (1.7%), although this comparison was adjusted for other fracture risk factors such as BMD, age, or prior fracture, and fractures occurring before the follow-up marker measurement were not excluded. Importantly, this difference in nonvertebral fracture incidence between those with higher compared to those with lower decreases in bone turnover was as great in the subset with very high medication compliance (percent days covered ≥80%), indicating that at least with risedronate true suboptimal response to the medication may occur independent of compliance.

This study makes a reasonable case that bone markers can be used to monitor response to an oral bisphosphonate, but again three issues remain before this could be recommended for routine clinical use. First, it remains unclear what cut point of change in bone turnover should be chosen to define suboptimal response. Second, if a cut point of 30% decrease in bone marker level is chosen it remains unclear what proportion are misclassified given imprecision of the tests. Third, it remains unclear if switching “suboptimal responders” to a different pharmacologic agent would lower fracture incidence compared with staying on risedronate. Thus, current evidence indicates that criteria 1 through 3 are satisfied for use of terminal telopeptides to monitor risedronate therapy, but criterion 4 is only partially satisfied, and criteria 5 and 6 are not satisfied.

Zoledronic Acid

In the HORIZON trial, a subset of 1270 and 604, respectively, had serum P1NP and CTX measured at baseline and at 1, 3, 6, 12, and 36 months after baseline. Compared with baseline, P1NP and serum CTX declined a mean 60%, and 17%, respectively, and 17% and 19% had levels below the premenopausal range [38]. There was no significant association between the level of P1NP or CTX achieved by 1 year and fracture reduction benefit from zoledronic acid. However, the association of the change of bone marker levels between any of the follow-up time points and baseline with fracture reduction benefit was not reported. Moreover, the proportion of those who do not suppress their marker of bone resorption activity may be very low. Thus, only criterion 1 is satisfied for monitoring zoledronic acid treatment with any bone marker.

Ibandronate

A post hoc analysis of 323 participants in the MOBILE trial of ibandronate 150 mg once monthly versus placebo has shown that decreases in serum CTX between baseline and 3 months are correlated with increases of BMD at the lumbar spine and hip trochanter [39]. Although the median decrease in serum CTX by 3 months was 66%, a minority did not show significant decreases of serum CTX beyond the LSC (30%). However, at the individual level, the correlation between change of serum CTX and increases of BMD, although significant, were weak. Moreover, it remains unclear as to whether or not those who have less than 30% decrease in serum CTX truly identifies those with a genuine suboptimal response (eg, those who will not experience a reduction in their fracture risk with continued use of the medication). Only criteria 1 and 2 are satisfied for monitoring ibandronate treatment with serum CTX.

Teriparatide

For bisphosphonate-naive patients, brisk increases of bone formation markers are seen within 1 month of starting teriparatide followed within a few months by increases of bone resorption markers. Relative to the imprecision of each bone turnover marker, the change in P1NP appears to be the largest (highest signal-to-noise ratio). Changes in P1NP are associated with subsequent improvements in BMD but the correlation coefficient is only modest (0.41) [40]. By 3 months, virtually all who are on teriparatide have rises in P1NP beyond what is seen in those taking placebo [40], and rises beyond the LSC may occur in over 90% [41]. Brisk responses of P1NP also occur in most treated with 1–84 parathyroid hormone. Among those in the lowest tertile of P1NP change very little mean improvement in hip trabecular BMD measured by quantitative computed tomography is seen, suggesting some potential for P1NP to distinguish adequate responders from suboptimal responders [42].

Those on glucocorticoids treated with teriparatide also show an average brisk increase in bone formation markers [43, 44], but it is unclear what proportion do not show an increase, or if changes in bone turnover markers are associated with fracture reduction efficacy. Changes in bone turnover markers on teriparatide in those previously treated with bisphosphonates are lower compared with bisphosphonate-naive individuals [45]. However, the proportion of those whose bone turnover markers do not rise and whether or not a lack of substantial rise indicates lack of fracture reduction efficacy remain unclear.

Based on three teriparatide trials (one of which enrolled patients switching to teriparatide from bisphosphonate therapy) Eastell et al. [46] estimated that 77% to 79% of individuals on teriparatide will have a greater than 10-ng/mL rise of P1NP level. They suggested those with a greater than 10-ng/mL rise in P1NP levels within a few months of starting teriparatide be given a positive response that they are responding to the drug, and that those who have a less than 10-ng/mL rise in P1NP level be assessed for noncompliance, and medication injection and storage techniques. If no issues are found in these areas, they are given a neutral message that they may be responding to the medication but this cannot be confirmed. However, it should be noted that those with a less than 10-ng/mL rise in P1NP still had a mean significant improvement in lumbar spine BMD (albeit less than those with a larger rise

in P1NP), and thus it remains unclear if those with a low P1NP response are truly suboptimal responders. No data have been published regarding the association of changes in bone formation markers and fracture reduction efficacy. Thus far, only criteria 1 and 2 have been satisfied for monitoring teriparatide with serum P1NP.

Denosumab

Denosumab is a monoclonal antibody against RANK ligand that acts as a powerful antiresorptive agent by inhibiting both osteoclastogenesis and mature osteoclast function. Suppression of serum CTX to a level below the premenopausal range occurs in virtually all postmenopausal women 1 month after receipt of subcutaneous denosumab [47•]. Therefore, by bone marker criteria, it is not clear if there is any suboptimal response and that any clinically actionable information would be obtained by measuring bone marker levels after starting denosumab. The magnitude of bone marker decrease after denosumab has been shown to be weakly to modestly associated with BMD increases attributable to the drug [47•]. No data have been published regarding the association of decreases in bone marker levels and fracture reduction efficacy. Thus, only criterion 1 is satisfied for monitoring denosumab use and response with any bone turnover marker.

Raloxifene

In the subset (2622) of participants in the MORE trial of raloxifene versus placebo who had serum and urine markers of bone turnover assessed serially, those in the lowest tertile of change of bone alkaline phosphatase and osteocalcin did not show any significant reduction in vertebral fracture versus placebo [48]. The association between changes in urine CTX and vertebral fracture reduction efficacy was weaker. No studies have examined if switching apparent raloxifene suboptimal responders to a different agent would successfully reduce incident fractures compared with staying on raloxifene. Moreover, as is true of alendronate and risedronate, the cut point of bone marker change that should be employed to define suboptimal response remains unclear. If the cut point defining the boundary between the first and second tertiles of bone marker change is chosen, then by definition one third of those on raloxifene would be considered suboptimal responders. However, given the imprecision of the tests, a significant proportion of “suboptimal responders” and/or “adequate responders” may be misclassified. Additional data analyses examining the association between bone marker decrease and fracture reduction efficacy using different cut points in bone marker change to define suboptimal response would be helpful. Thus, for monitoring raloxifene therapy, criteria 1 through 3 are satisfied, criteria 4 is partially satisfied, and criteria 5 and 6 are not satisfied (Table 1).

Detect and Improve Compliance with Drug Therapy

Even if bone marker turnover studies can identify individuals with suboptimal response to antifracture medication, most nonresponders to fracture prevention medications, a significant proportion of that suboptimal response is likely to be due to medication nonpersistence and noncompliance.

Some have postulated that measurement of bone markers and feeding back to patients these results can not only identify noncompliant individuals but also encourage better compliance.

However, current evidence does not support this. Among 75 women treated with raloxifene, compliance was improved 57% in both a group receiving periodic calls from a study nurse and feedback regarding changes in their bone turnover markers and in another group receiving periodic nurse calls only [49]. In the IMPACT study, persistence and compliance with risedronate was not different among those told their bone marker result changes on therapy compared to those who received no such [50]. Those with a significant reduction of bone resorption marker level had a hazard ratio of 0.71 for nonpersistence compared with the nonintervention group, whereas those with either no change or an increase in their bone resorption, respectively, had hazard ratios of 1.02 and 2.22 for nonpersistence compared with those receiving no bone turnover marker feedback.

Thus, bone marker studies may aid identification of those who are noncompliant with fracture prevention therapy, but it remains unclear that this is superior to simply asking the patient as to whether or not they have been taking their medication. There is no evidence that using bone markers can be used to improve adherence.

Conclusions

The measurement of bone turnover markers has improved over the past decade, and their use in monitoring those taking fracture prevention medications is promising. In the case of zoledronic acid and denosumab, substantial changes in currently available markers of bone turnover may be sufficiently ubiquitous that identification of suboptimal responders (to the extent that they exist) seems implausible. For alendronate, risedronate, raloxifene, and teriparatide, changes in bone turnover markers during the first several months of therapy are heterogenous, and those with low or no change in bone marker level during the first few months of therapy on average experience less fracture reduction benefit compared to those with more robust changes of bone markers. Moreover, at least in the instance of risedronate, the association of little or no change in bone marker level with suboptimal fracture reduction benefit can be seen even in the setting of high medication compliance.

However, before use of bone markers to monitor use of these four agents can be recommended for routine use in clinical practice, bone marker tests with lower within-person variability are required and as pointed out in a recent comprehensive review [16••], better standardization of assays of bone markers are needed. The latest generation of tests for serum P1NP and CTX are promising, but even if these are proven to be sufficiently precise to support monitoring individual patients, the optimal cut points of bone marker change to identify suboptimal responders have to be explicated. Further studies are also needed showing that changes in management of those at high risk of fracture based on monitoring of bone turnover markers would result in further reduction of incident fractures.

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Clinical Trial Acronyms

FIT	Fracture Intervention Trial
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
IMPACT	Improving Measurements of Persistence on Actonel Treatment
MOBILE	Monthly Oral Ibandronate in Ladies
MORE	Multiple Outcomes of Raloxifene Evaluation

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Table 1

Fulfillment of criteria for bone marker utility monitoring fracture prevention therapies

Pharmacologic agent	Alendronate	Risedronate	Ibandronate	Zoledronic acid	Raloxifene	Teriparatide	Denosumab
Bone marker(s)	BSAP, P1NP	CTX, NTX	CTX	P1NP, CTX	BSAP	P1NP	P1NP, CTX
Criterion 1	+	+	+	+	+	+	+
Criterion 2	+	+	+	–	+	+	–
Criterion 3	+	+	–	–	+	–	–
Criterion 4	+/–	+/–	–	–	+/–	–	–
Criterion 5	–	–	–	–	–	–	–
Criterion 6	–	–	–	–	–	–	–

Criterion 1: Significant proportion of those prescribed medication have a change of bone turnover marker level beyond the LSC
Criterion 2: There is significant heterogeneity of changes in bone marker level among individuals who take that medication
Criterion 3: There is a significant association between changes of bone marker level and magnitude of fracture reduction benefit from the medication
Criterion 4: There is a cut point of bone marker change that differentiates two groups with sufficient difference in fracture reduction benefit that can be expected from the medication, such that switching to a different medication for one of the two groups is reasonable
Criterion 5: The precision of the test is sufficiently good such that “suboptimal responders” can be differentiated from “adequate responders” with no more than modest misclassification
Criterion 6: There are data from observational studies or randomized controlled trials that switching those in the group deemed “suboptimal responders” to a different medication reduces fractures compared to staying with the first medication

BSAP bone-specific alkaline phosphatase; *CTX* C-telopeptides; *LSC* least significant change; *NTX* N-telopeptides; *P1NP* procollagen 1N-terminal propeptide

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