Role of biochemical markers of bone turnover as prognostic indicator of successful osteoporosis therapy

Abstract

Most of the currently available anti-osteoporosis medications promptly and significantly influence the rate of bone turnover. Biochemical markers of bone turnover now provide a high sensitivity to change, allowing the detection of these bone turnover changes within a couple of weeks. Since the anti-fracture efficacy of inhibitors of bone resorption or stimulators of bone formation appears to be largely independent of baseline bone turnover, biochemical markers do not appear to play a significant role in the selection of one particular drug, for an individual patient. However, there are consistent data showing that short-term changes in biochemical markers of bone turnover may be significant predictors of future changes in bone mineral density or fracture reduction, hence suggesting that bone turnover markers play a significant role in the monitoring of anti-osteoporosis therapy.

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Introduction

Clinical trials, conducted since the early nineties, have unequivocally shown the ability of several anti-osteoporosis medications to reduce fracture occurrence at various skeletal sites, including but not exhaustively the spine and hip [1]. Whereas the operational definition of osteoporosis is still based on a low bone mineral density (BMD), because low BMD is known to contribute to increased fracture risk, changes in bone mass and density, in response to anti-resorptive therapy, account for only a small portion of the predicted fracture risk reduction [2], a picture which may, however, be significantly changed with the availability of new therapies stimulating bone formation [3] or uncoupling bone formation from bone resorption [4].

During the last decade, biochemical markers of bone turnover (BTM) have been developed, that are more sensitive than conventional ones for detecting abnormalities or changes of bone turnover rate [5]. Increased levels of bone resorption, and short-term changes in BTM, have been shown to predict the risk of fracture, independently of the level of BMD in untreated individuals [6,7].

Dynamic changes in bone turnover, estimated by measurement of bone biochemical markers, such as breakdown products of type I collagen and proteins secreted by osteoblasts and osteoclasts in blood and urine, can also account for a major portion of anti-fracture efficacy of anti-resorptive or bone-forming agents [8]. Most of the currently marketed anti-osteoporosis medications induce prompt and significant changes in BTM.

Since BTM measurements are non-invasive, fairly inexpensive and can be repeated often, it seems important to provide some guidance about the role BTM can play to identify patients with rapid bone loss, to aid in therapeutic decision-making and to monitor therapeutic efficacy of various treatments.

Baseline BTM as prognosis of future osteoporosis therapy

One of the major applications of BTM in the field of osteoporosis is to detect high bone turnover in postmenopausal women. This could allow identification of individuals who should be preferentially targeted for prevention or curative therapy, as there is strong evidence that the higher the bone turnover, the greater the future bone loss and/or fracture risk [6].

From a theoretical point of view, it is also conceivable that intervention strategies may differ between patients with various degrees of bone turnover, at the time of diagnosis, i.e. a patient presenting with high rates of bone resorption being optimally treated with anti-resorptive agents, whereas an individual with low remodelling rate expecting greater benefit from a bone-forming agent [9].

However, whether the pretreatment (i.e. baseline) BTM concentrations are predictive of a greater response to any of the anti-osteoporotic drugs remains rather controversial.

In a post-hoc analysis of the Fracture Intervention Trial (FIT), the pivotal study based on which alendronate was granted a marketing authorization for the treatment of osteoporosis, alendronate non-spine fracture efficacy was greater among women with high

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pretreatment N-terminal propeptide of type I collagen (P1NP) (Table 1). For osteoporotic women in the lowest tertile of pretreatment P1NP, the alendronate versus placebo relative hazard for non-spine fracture was 0.88 (95% CI 0.65–1.21) compared to a relative hazard of 0.54 (95% CI 0.39–0.74) among those in the highest tertile of P1NP. Similar results were observed among women without osteoporosis at baseline.

However, the relationship between tertile of bone-specific alkaline phosphatase (BALP) or C-terminal cross-linked telopeptide of type I collagen (sCTX) and the risk of non-spine fracture did not reach statistical significance. There was no relationship between pretreatment P1NP, BALP or sCTX and alendronate efficacy or incident spine fracture among osteoporotic women [10]. Based on the assumption that alendronate may reduce incident non-vertebral fracture to a greater degree in non-osteoporotic women, with high compared to low bone turnover, a recent pharmacoeconomic study (Markov model) concluded that measurement of BTM has the potential to identify a subset of postmenopausal women (top BTM quartile), without osteoporosis by BMD criteria, for whom alendronate therapy to prevent fracture is cost-effective (costs per QALY gained at 34,000 USD and 50,000 USD for women age 70 with high bone turnover and femoral neck BMD T-score of −2.0 and −1.5 respectively) [11].

A similar analysis of the risedronate phase III clinical programmes used the excretion of urinary deoxypyridinoline (DPD) as an index of pretreatment bone resorption rates. During the first year of treatment, women with high DDP (above premenopausal normative median) gained lumbar spine BMD at a faster rate than patients with low DDP. The risedronate-mediated reduction in the incidence of vertebral fractures was independent of baseline DDP. However, the number needed-to-treat (NNT) to avoid one vertebral fracture at 12 months was 15 in the group of patients with high DDP and 25 in patients with low DDP, an observation which is not unexpected, based on the influence of the prevalent absolute risk on NNT calculation [12]. The authors concluded that although the reduction in overall fracture risk seems to occur independent of baseline bone turnover, patient stratification by pretreatment bone resorption rate seems to make some sense from a pharmacoeconomic point of view [9,12].

Little is known about how the baseline levels of BTM relate to the densitometric response or the anti-fracture efficacy of anabolic therapy in postmenopausal women. A post-hoc analysis of the Fracture Prevention Trial (FPT), the study which demonstrated vertebral and non-vertebral fracture reduction with the recombinant human parathyroid hormone rhPTH (1–34) (teriparatide), assessed the correlation between BTM and BMD responses. Bone turnover status at baseline correlated significantly with subsequent BMD responses. The highest correlation was found with the changes in lumbar BMD observed after 18 months for teriparatide treatment. All correlations with BMD were significant and positive and from largest to smallest, with P1NP, urinary N-terminal telopeptide of type I collagen (uNTX), serum carboxy-terminal extension peptide of procollagen type I (P1CP), BALP and DPD. For femoral neck BMD changes, the coefficients of correlation were of a much lower magnitude and remained significant only for uNTX and DPD [13]. In another study assessing the relationship between levels of baseline turnover before PTH (1–84) and the subsequent changes in area and volumetric BMD, higher baseline P1NP levels were associated with greater increase in areal BMD. Each standard deviation (SD) increase in baseline P1NP was associated with an additional 1.7% increase (95% CI 0.5–3.0) in spine BMD (assessed by dual-energy X-ray absorptiometry [DXA]) and a 1.2% increase (95% CI 0.4–2.0) in hip DXA BMD, after 12 months of PTH. Higher baseline BALP or sCTX levels were also associated with greater 1-year increases in hip and spine DXA BMD respectively. Neither baseline P1NP nor BALP were significantly associated with 1-year changes in volumetric BMD (by quantitative computerised tomography [QCT]). Higher baseline sCTX levels were associated with greater 1-year increases in trabecular spine and cortical hip BMD QCT [14]. The association between pretreatment BTM concentration and the absolute and relative risks of vertebral and non-vertebral fractures (FPT of teriparatide) was evaluated after adjusting for baseline femoral neck BMD, number of prevalent fractures and age. Higher pretreatment concentrations of BALP, P1NP, NTX and DPD were associated with a greater risk of fracture. Teriparatide significantly reduced the risk, regardless of pretreatment bone turnover. For each BTM, the absolute risk of an osteoporotic fracture was greatest in the highest tertile, while the relative risk was not associated with baseline bone turnover. Hence, the NNT to prevent a new osteoporotic fracture decreased as the BTM concentration increased (from 10 to 7 for low to high P1NP tertile) [15]. The authors concluded that teriparatide-mediated relative fracture risk reduction was independent of pretreatment bone turnover, which is supported by the absence of correlation between baseline P1CP, DPD or uNTX and changes in structural and dynamic bone parameters analysed from transiliac biopsy specimens obtained during the same FPT [16].

Table 1
Summary of biochemical markers used in studies having assessed their role as predictor of response to anti-osteoporotic drug

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Biochemical marker studied</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Alendronate [10,17,18,19,20,21]</td>
<td>Formation: BALP, PINP, PICP, OC Resorption: sCTX, uNTX, DPD</td>
<td>Fracture, BMD</td>
</tr>
<tr>
<td>Risedronate [12,22]</td>
<td>Resorption: uDPD, uCTX, uNTX, sCTX</td>
<td>Fracture, BMD</td>
</tr>
<tr>
<td>Teriparatide [13,14,15,33]</td>
<td>Formation: BALP, PICP, PINP Resorption: uDPD, uNTX, sCTX</td>
<td>Fracture, BMD</td>
</tr>
<tr>
<td>Raloxifene [30,31,32]</td>
<td>Formation: BALP, PINP, OC Resorption: uCTX</td>
<td>Fracture</td>
</tr>
</tbody>
</table>
Early changes in BTM to monitor anti-osteoporosis therapy

Similar to most chronic diseases, monitoring the efficacy of treatment of osteoporosis is a challenge. In contrast to BMD, which typically changes in response to therapy less than 2–5% per year, or a maximum of 3% in 3–6 months, most of osteoporosis therapies act by reducing or increasing individual BTM levels or their ratios by 30–200% within 3–6 months. Even though BMD measurement is much more precise than BTM, it is still easier to detect a 50% change with a BTM than a 3% change in BMD with a DXA, after 3–6 months of therapy [8]. Generally, the ratio of signal to noise during the first year of treatment is better for BTM than it is for BMD.

In early postmenopausal women receiving alendronate in the prevention of osteoporosis (Early Postmenopausal Intervention Cohort — EPIC study), change from baseline at month 6 in uNTX or osteocalcin (OC) correlated with change from baseline at month 24 in spine, hip and total body BMD. This corresponded to a 4- to 5-fold greater increase at month 24 in BMD in the tertile with the greatest decrease at month 6 in NTX or OC compared to the tertile with the least decrease in the BTM. In this study, a patient with a decrease of 40% for NTX or 20% for OC at month 6 had a 92% probability of a 2-year positive response in spine BMD. In contrast, the poor specificity and negative predictive value of these percentual cut-offs of BTM changes implied that a change in NTX or OC above the cut-point was a poor predictor of bone loss during alendronate treatment [17]. In a smaller cohort of French osteoporotic women, the authors claimed, from observation of changes in BALP, OC, P1CP, P1NP, sCTX, uNTX, total and free DPD after 4 months of alendronate, that sCTX, and to a lesser extend, uNTX, were the best predictors of a significant gain in spine BMD after 1 year of therapy [18]. Early changes of uNTX (3 months) were also shown to be good predictors of 12-month lumbar spine BMD response to alendronate in Korean post-menopausal women with osteoporosis [19]. Similar features were reported for 6-month decreases in uNTX and DPD, as surrogate for 2.5-year increases in hip, trochanter, spine and total BMD in elderly US women [20]. The data from the FIT were used to assess the relationship between changes in bone turnover after 1 year of alendronate and subsequent hip, non-spine and spine fracture risk. Each 1SD reduction in 1-year change in BALP was associated with fewer spine (relative hazard [RH] 0.74, 95% CI 0.63–0.87), non-spine (RH 0.89, 95% CI 0.78–1.00) and hip fracture (RH 0.61, 95% CI 0.46–0.78). Alendronate-treated women with at least a 30% reduction in BALP had a lower risk of non-spine (RH 0.72, 95% CI 0.55–0.92) and hip fracture (RH 0.26, 95% CI 0.08–0.83) relative to those with reduction <30%. The authors concluded that the association between early reduction in bone turnover and long-term fracture reduction during alendronate treatment was at least as strong as that observed with 1-year changes in BMD [21].

Changes in the level of biochemical markers of bone resorption with risedronate treatment for osteoporosis were also examined as a surrogate for the decrease in fracture risk, in osteoporotic patients from the risedronate vertebral fracture trial. The reduction in urinary sCTX (median, 60%) and uNTX (51%) at 3–6 months with risedronate therapy were significantly associated (p<0.05) with the reduction in vertebral fracture risk (75% over 1 year and 50% over 3 years). The changes in both sCTX and uNTX accounted for approximately one-half (sCTX, 55%; uNTX, 49%) of the first year and approximately two-thirds (sCTX, 67%; uNTX, 66%) over 3 years compared with placebo. The changes in sCTX and uNTX accounted for 77% and 54%, respectively, of risedronate effect in reducing the risk of non-vertebral fractures over 3 years compared with placebo. The relationships between vertebral fracture risk and changes from baseline in sCTX and uNTX were not linear (p<0.05). In the original publication [22] below a decrease of 55–60% for sCTX and 35–40% for uNTX, the authors concluded that the decrease in bone resorption in patients taking risedronate accounts for a large proportion of the reduction in fracture risk but that there was little further improvement in anti-fracture efficacy below a decrease of 55–60% for sCTX and 35–40% for uNTX. [22]. The data from this study were recently reanalysed by another team of statisticians. The findings of the reanalysis still support the original conclusion that there is a level of bone resorption below which there is no fracture benefit, but this was only significant for sCTX at a level of 51% decrease [23].

Whereas the relationship between BTM and BMD or fracture reduction, in individual patients, has not yet been published, for oral or intravenous ibandronate, the course of the development of this bisphosphonate strongly support the value of BTM as a surrogate for BMD or fracture assessment in osteoporosis. The earliest studies conducted with ibandronate, using suboptimal doses (1 and 0.5 mg IV given once every 3 months) resulted in marginal decreases in biochemical markers of bone resorption and formation, which eventually translated into small increases in spine BMD and insufficient magnitude of fracture reduction to achieve statistical significance [24]. By contrast, with continuous (2.5 mg daily) or intermittent (20 mg every other days for 12 doses every 3 months) oral doses which were linked to a significant reduction in spinal fractures, similar to that seen with alendronate or risedronate, the rate of bone turnover was reduced by 50–60%, a magnitude also within the range observed with the oral efficacious oral bisphosphonates [25]. For further clinical development of ibandronate, the role of BTM, as predictor of efficacy was even emphasised. Actually, a pharmacokinetic–pharmacodynamic model, accurately describing the dose-dependent predicted urinary excretion of CTX, has surrogate of clinical efficacy, was used to select the appropriate once-monthly dose of ibandronate [26]. Clinical studies, showing the non-inferiority and/or superiority of the 150 mg monthly oral regimen, on BMD, as compared to the daily 2.5 dose, the dose which previously demonstrated anti-fracture efficacy [27] confirmed, a posteriori, the interest of a pharmacostatistical model based on BTM changes to predict the effect of a particular dosage of ibandronate on hard end-points [28].

Data from randomized clinical studies of ibandronate, given orally or intravenously, at different doses and for variable time intervals to women with osteoporosis were examined to explore the relationship between intermittent bisphosphonate therapy, changes in bone resorption and fracture risk. The magnitude of the reduction of the rate of bone resorption at the end of the
drug-free interval rather than its fluctuation pattern after bisphosphonate administration determines anti-fracture efficacy, provided that these fluctuations occur within the premenopausal range [29]. From these results, the authors concluded that prolongation of the drug-free interval should be compensated by a dose higher than the cumulative daily dose [29].

In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which demonstrated vertebral fracture reduction with raloxifene, changes in OC and BALP, after 6 and 12 months, were significantly related to future risk of vertebral fracture, also after adjusting for baseline vertebral status and BMD. For a decrease of 9.3 µg/l in OC after 1 year raloxifene therapy, the odds ratio (OR) for a new vertebral fracture during 3 years was 0.69 (95% CI, 0.54–0.88). Similarly, for a decrease of 5.91 µg/l in BALP, OR was 0.75 (95% CI, 0.62–0.92) [30]. After adjustment of each significant baseline variable, in logistic regression models using 1-year percent changes in BMD and bone turnover and relevant baseline demographics to predict the risk of vertebral fracture with raloxifene therapy at 3 years, the percent changes in OC was better able to predict the reduction in fracture risk than the percent changes in femoral neck BMD [31]. When logistic regression analysis models were used to evaluate the relationship between the changes at 1 year in P1NP, OC, BALP, and urinary CTX and the risk of new vertebral fractures at 3 years, in the same study, a 1-year decrease in P1NP, BALP or OC but not urinary CTX was again predictive of the 3-year vertebral fracture risk reduction with raloxifene. The decrease in P1NP at 1 year accounted for 28% of the total reduction in vertebral fracture risk [32].

Among all studied BTM in the teriparatide FPT, increases in P1CP at 1 month and P1NP at 3 months correlated best with increases in lumbar spine BMD at 18 months. The relationship between these two BTM and the lumbar spine BMD response, was stronger than the corresponding relationship for the femoral neck BMD response [13]. Greater short-term changes in P1NP during PTH (1–84) treatment were associated with greater 1-year increase in spine and hip BMD among postmenopausal osteoporotic women. Each SD increase in the 3-month change of P1NP was associated with a 21% greater increase in QCT spine trabecular BMD [14]. When evaluating associations between early changes in biochemical markers and structural and dynamic bone parameters during teriparatide treatment, changes in BALP at 1 month correlated with changes at 22 months in two-dimensional wall thickness, trabecular bone volume, marrow star volume and trabecular thickness while changes in P1CP at 1 month correlated with change in wall thickness. Whereas no data are currently available to claim that short-term changes in BTM during teriparatide are predictive of future fracture reduction, the correlation of biochemical markers of bone formation (but not resorption) with improvements of bone structure indirectly support this hypothesis [16]. Based on these results, an algorithm for using P1NP to monitor treatment of patients with teriparatide was further developed [33]. Patients with P1NP increases >10 µg/l after 1–3 months, were considered as responders while it was recommended that patients with P1NP increases <10 µg/l should be assessed for adherence, teriparatide administration and storage technique and for the presence of medical conditions that might limit their therapeutic response to teriparatide [33].

Conclusion

In conclusion, most of the currently available pharmacological treatments for osteoporosis promptly and significantly impact on the rate of bone turnover. BTM do not appear to be a significant determinant in the selection of a particular anti-osteoporosis drug. With the exception of a single and equivocal study with alendronate, the anti-fracture efficacy of anti-osteoporosis agents appears to be largely independent of baseline bone turnover. However, short-term changes in BTM reflecting bone resorption (raloxifene, bisphosphonates) or bone formation (raloxifene, teriparatide, (1–84) parathyroid hormone) have been consistently shown to predict future BMD changes (teriparatide, parathyroid hormone) or long-term fracture reduction (alendronate, risedronate, raloxifene), strongly suggesting that BTM could play a significant role in the monitoring of anti-osteoporosis therapy. Further research should be stimulated to assess the relevance of these findings to the care of individual patients, i.e. how to define a response to a specific treatment based on the short-term changes observed in BTM.

References

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