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Bone turnover markers to monitor oral bisphosphonate therapy

ABSTRACT

Bisphosphonates are widely used as first-line therapy to slow bone loss and decrease fracture risk in postmenopausal women with osteoporosis. Nonadherence to oral bisphosphonates diminishes the benefit of reduced bone loss and fracture risk of these medications. Strategies to enhance osteoporosis monitoring and adherence to therapy are crucial to improve outcomes. Dual-energy x-ray absorptiometry (DXA) is the gold standard for monitoring bone mineral density but is slow to detect change after initiation of oral bisphosphonate therapy. Bone turnover markers (BTMs) are by-products released during bone remodeling and are measurable in blood and urine. We review how the rapid change in BTMs can be a useful short-term tool to monitor the effectiveness of oral bisphosphonate therapy, which may ultimately improve adherence to therapy and outcomes.

KEY POINTS

- Oral bisphosphonates slow bone loss and reduce the risk of fracture in postmenopausal women with osteoporosis.
- Nonadherence to bisphosphonate therapy diminishes the benefits of these medications.
- BTMs are a simple, low-risk, and convenient way to monitor effectiveness and adherence to oral bisphosphonate therapy in addition to DXA.
- Bisphosophonates induce a rapid dose-dependent decrease in bone resorption markers, making them an excellent tool to ascertain adherence to and efficacy of oral antiresorptive therapy.

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Primary osteoporosis and its precursor, low bone mass, affect more than 53 million Americans, the majority of whom are postmenopausal women.[1,2] The prevalence of osteoporosis in adults over age 50 is 12.6%, while prevalence of low bone mass is as high as 43.1% in the same age group.[1] Lifestyle and pharmacologic intervention can halt osteoporosis at any point, stabilize or improve bone density, and greatly reduce fracture risk.

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Oral bisphosphonates (eg, alendronate, risedronate, and ibandronate) are the most prescribed treatment for postmenopausal women with osteoporosis and individuals with low bone mass and high fracture risk. Alendronate and risedronate have broad-spectrum efficacy to reduce hip, spine, and nonvertebral fractures. Their long-established safety and efficacy profile, generic availability, and affordability make them excellent first choices for patients at high fracture risk.[3–5] Ibandronate is also an appropriate initial therapy in patients needing treatment for spine-specific bone loss.[6] Although a number of randomized controlled trials show a reduction in the number of osteoporosis-related fractures and an increase in bone mineral density (BMD) with oral bisphosphonate therapy, adherence to these medications may be as low as 43%.[7–9] A recent systematic review of 89 publications confirmed that early treatment discontinuation is a global problem.[10] In this study, about 35% to 70% of individuals remained on oral

bisphosphonate therapy at 6 months and only 18% to 75% had continued use 1 year after initiation.[10]

Low adherence to oral bisphosphonate therapy significantly hinders its effectiveness in reducing fractures. However, capturing the efficacy of treatment (or lack thereof) using current surrogate markers is a challenge. Current guidelines vary widely regarding repeat dual x-ray absorptiometry (DXA) for treatment monitoring, with most indicating every 1 to 3 years because it takes time for a significant bone density change.[11,12] Moreover, there is no numeric cutoff to indicate a clinically effective treatment response or a practical way to assess adherence based on the change in bone density.

We propose that clinicians consider using bone turnover markers (BTMs) to assess the effect of and adherence to oral bisphosphonate therapy. BTMs decrease with oral bisphosphonate therapy, and changes in BTMs are more rapidly detected than bone density is with BMD testing.[3] Furthermore, many studies have found a positive association between BTMs and fracture reduction.[13–15]

BONE TURNOVER MARKERS: CLINICAL OVERVIEW

BTMs are collagenous and noncollagenous components released in the bloodstream during the process of bone remodeling. They reflect a kinetic measurement of bone formation and resorption. BTMs are elevated during childhood, growth, and fracture healing. In these scenarios, elevations in bone resorption and bone formation markers are balanced. In other words, markers of both formation and resorption increase proportionately, thus maintaining a state of equilibrium. Measuring BTMs in these states is of no diagnostic value.

BTMs (resorption and formation markers) decrease in response to hormone replacement therapy and oral or parenteral antiresorptive therapy. In contrast, bone formation markers increase within days of starting anabolic therapy with teriparatide and abaloparatide, and bone resorption markers increase months later. Romosozumab, another anabolic agent approved for osteoporosis, increases bone formation markers and decreased bone resorption markers.[16]

SPECIMEN REQUIREMENTS FOR MONITORING

It is important for clinicians to be aware of the unique pharmacokinetic properties associated with the BTM they plan to monitor. Some BTMs such as C-terminal telopeptide of type I collagen (CTX) or urine N-terminal telopeptide of type I collagen (NTX) show variation with circadian rhythm and meals, so blood or urine samples should be drawn after an overnight fast. Discontinuation of multivitamins and supplements containing biotin for 24 hours before CTX or urine NTX measurement is prudent to prevent assay interference. Fasting is not indicated for measurement of N-terminal propeptide of type I procollagen (PINP) and bone-specific alkaline phosphatase (BSAP), and multivitamins and biotin-containing supplements need not be discontinued. Serum-based BTMs tend to show less individual and analytical variability when compared with urine-based markers.[17] Renal and liver dysfunction alters the clearance of the majority of BTMs. Thus, it is important to be aware of the limitations associated with specific markers. **Table 1** provides a summary of common BTMs and their properties.[18–20]

BONE TURNOVER MARKERS AND ORAL BISPHOSPHONATE THERAPY

BTMs are lowered by bisphosphonate therapy. In our clinical practice, we consider at least a 25% decrease in CTX, PINP, or BSAP and at least a 30% decrease in urine NTX at 3 to 6 months from baseline levels (ie, prior to starting therapy) to be an indication of adequate therapeutic response to bisphosphonate therapy. Therapeutic intervention is considered effective when the marker continues to remain suppressed from baseline along with BMD stability at 12 months. The magnitude of change in the markers on antiresorptive therapy correlates to the reduction in fracture risk.[13–15] **Table 2** presents the case of an 82-year-old postmenopausal woman treated with oral alendronate for osteoporosis. The patient tolerated the oral bisphosphonate well, did not report gastrointestinal upset, and no fractures occurred during the treatment period.

When using a BTM for monitoring, it is important to determine the critical difference or least significant change (LSC). The LSC is the smallest difference between a measurement and a previous measurement that is associated with a true change in the patient. The International Osteoporosis Foundation and European Calcified Tissue Society (IOF-ECTS), the Endocrine Society, and the American Association of Clinical Endocrinology, whose contemporary guidelines are followed worldwide, recently proposed using CTX or PINP for monitoring adherence to bisphosphonate treatment.[3,4,21] According to the IOF-ECTS guidelines, if the magnitude of decline in BTMs is greater than the LSC, then treatment should be continued; if the decrease is smaller, clinicians should reassess possible problems with treatment, including adherence.[21,22]

TABLE 1
Common bone turnover markers, their properties, and pros and cons

Markers of bone formation	Measured in	Diurnal variation	Renal function variation	Pros	Cons
Bone-specific alkaline phosphatase (BSAP)	Serum	No	No	No postprandial changes Stable sample due to half-life of 1–2 days Widely available	Roughly 20% cross-reaction with other types of alkaline phosphatase
N-terminal propeptide of type I procollagen (PINP)	Serum	Yes	Yes	Well studied in clinical trials Relatively low intra-individual variability PINP measures response to therapy more effectively than BSAP	Hepatic function can affect levels depending on the assay and form of propeptide being measured Increased in patients on hemodialysis
Procollagen type I carboxy-terminal propeptide (PICP)	Serum	Yes	Renal variation unknown		Less studied than other bone formation markers
Osteocalcin	Serum and urine	Yes	Yes	Correlates well with bone turnover	Less stable; must process within hours Production is dependent upon vitamin K and can decrease in response to vitamin K antagonists (eg, warfarin)
Markers of bone resorption	**Measured in**	**Diurnal variation**	**Renal function variation**	**Pros**	**Cons**
C-terminal telopeptide of type I collagen (CTX)	Serum and urine	Yes	Yes	Stable biomarker Rapidly decreases with antiresorptive therapy	Postprandial variability Can be impacted by hepatic function
N-terminal telopeptide of type I collagen (NTX)	Serum and urine (24-hour urine collection or second morning void)	Yes	Yes	Minimal postprandial variability	Fasting measurements recommended Impacted by hepatic function
Pyridinoline and deoxy-pyridinoline	Urine (24-hour urine collection or second morning void with creatinine correction)	Yes	Yes	Can be renally adjusted	Impacted by hepatic function
Tartrate-resistant acid phosphatase 5b	Serum	Yes	No	No change with renal function	Predominately from but not exclusive to bone Unstable at room temperature Increases immediately after exercise

Based on data from references 18–20.

Calculating the least significant change

Calculating the LSC is not straightforward. The calculation relies on intra-individual variability (ie, the amount of normal day-to-day variation in a patient) as well as the impression of the assay (ie, reproducibility of the assay from day to day).[21,23,24] The intra-individual variability of many markers is not well known or established, and the impression of the assay is variable among laboratories. Clinicians should therefore become familiar with the LSC of the individual

TABLE 2
An 82-year-old postmenopausal woman treated with oral alendronate for osteoporosis

Background:
- Left proximal humerus fracture 4 years prior due to a fall from standing height during a syncopal event
- Left femural neck T-score of –2.5 on dual-energy x-ray absorptiometry
- No history of celiac disease, paraproteinemia, or bariatric surgery
- Renal function and vitamin D levels were normal
- Patient concerned about falls and balance; another fall 6 months prior without fracture.

After ruling out secondary causes of osteoporosis, oral alendronate 70 mg once weekly was initiated.

Bone mineral density and bone turnover markers:

	Before treatment	At 3 months	At 1 year
T-scores:			
Lumbar spine	–1.6		–1.7
Left femoral neck	–2.5		–2.4
Right femoral neck	–2.2		–2.1
Bone turnover marker: C-terminal telopeptide of type I collagen	520 pg/mL	177 pg/mL (66% reduction from baseline)	273 pg/mL (48% reduction from baseline)

markers they utilize in clinical practice by consulting with their laboratory counterparts.

Not uncommonly, clinicians evaluate patients after they have already started oral bisphosphonate therapy. In such cases, the IOF-ECTS proposes targeting post-treatment BTMs to be reduced to at least the lower half of the premenopausal reference interval.[21,23,24]

Additionally, many women with osteoporosis and high fracture risk have baseline BTMs that may already be in the lower half of the reference range before they start therapy. In this scenario, it is hard to rely on a change in BTMs because little research has been conducted on the impact of fracture risk reduction when the markers are low before treatment initiation. For these patients, it is prudent to rely on BMD changes to make clinical decisions. A few studies and guidelines have proposed checking an alternative marker at baseline (eg, if the PINP is below the reference level, measure BSAP as an alternative approach).[21,23,24]

BONE TURNOVER MARKERS AND BISPHOSPHONATE 'DRUG HOLIDAY'

Due to concerns about long-term side effects of antiresorptive therapy, such as jaw osteonecrosis and atypical femur fractures, clinicians may recommend that patients with a significant therapeutic response pause therapy and enter a bisphosphonate "drug holiday." The optimal duration of the pause has not been established and needs to be individualized based on clinical circumstances, such as a significant decline in DXA or an increase in BTMs.

Thus, monitoring for rising BTMs during a pause in bisphosphonate therapy may be useful in determining when to restart therapy. Some experts feel that a rise in the markers to pretreatment levels provides early feedback about the loss of therapeutic effect and signals a need to resume osteoporosis treatment. Of note, adequately powered clinical studies to support this approach are lacking. Additionally, as stated earlier, this approach may not apply to patients with osteoporosis who had low BTMs before treatment was started. With that in mind, when BTMs start to rise to pretreatment levels, our approach has been to re-evaluate the patient for development of new clinical risk factors for fracture and, sometimes, to repeat DXA earlier to initiate discussion about resuming therapy.[3,4]

BONE TURNOVER MARKERS TO MONITOR PATIENT ADHERENCE

Nonadherence to bisphosphonate therapy usually occurs after 6 to 7 months of treatment, well before DXA is repeated for treatment monitoring.[9,10,25] Clowes et al[26] showed that measuring BTMs can help increase adherence to oral bisphosphonate therapy. This association was supported by another study, which found an increase in persistence with oral risedronate when a positive BTM response was shared with patients.[27] However, not all published studies have observed this effect.[28]

TABLE 3
A 63-year-old postmenopausal woman treated with oral alendronate for osteoporosis

Background:
- History of breast cancer treated with lumpectomy, radiation therapy, and 5 years of tamoxifen
- Outside DXA scans showed a progressive decline in her lumbar spine T-score from –3.1 to –3.3
- Femoral neck bone density was stable
- Past medical history was otherwise unremarkable
- No history of lactose intolerance, celiac disease, or chronic glucocorticoid use
- She did not take calcium supplements, but took over-the-counter vitamin D
- No history of antifracture therapy.

The patient was prescribed oral alendronate 70 mg once weekly.

Bone mineral density and bone turnover markers:

	Before treatment	3 months	1 year
T-scores:			
Lumbar spine	NA		–2.6
Left femoral neck	NA		–1.5
Right femoral neck	NA		–1.5
Bone turnover marker: C-terminal telopeptide of type I collagen	653 pg/mL	361 pg/mL (45% reduction from baseline)	188 pg/mL (72% reduction from baseline)

NA = Not available: baseline dual-energy x-ray absorptiometry (DXA) was done at an outside facility and thus was not appropriate for comparison.

Because BTMs respond rapidly to changes in treatment, their utilization is endorsed by contemporary societal guidelines as an effective feedback tool to improve patient adherence.[3,4,21,24] A positive treatment response (suppressed markers) reinforces to patients that treatment is effective and helps promptly identify patients not responding to treatment (unsuppressed markers).

As is often encountered in the real-world setting, a patient's baseline BMD testing may have been done at an outside facility. **Table 3** provides details of a 63-year-old postmenopausal woman referred to our endocrinology clinic with DXA done outside our facility and with a reported T-score of −3.3 at the lumbar spine. Repeat DXA at our facility showed a lumbar spine T-score of −2.6. Since DXA done at different facilities cannot quantify bone density changes without cross-calibration, a BMD change could not be assessed. Given this scenario, we felt that her early and persistent BTM response was particularly valuable in developing confidence that her treatment was effective. No gastrointestinal upset was reported, and no fractures occurred during treatment.

LIMITATIONS OF BONE TURNOVER MARKERS

BTMs should not be used as a screening test for osteoporosis in the general population. Up to 20% of postmenopausal women with osteoporosis taking calcium and vitamin D supplementation may have baseline BTMs below the premenopausal mean reference range and will not be identified appropriately for therapy, highlighting a key problem with this approach.[23]

When interpreting BTMs, one should keep in mind that they fluctuate in response to any process that manipulates the bone remodeling process. Therefore, BTM testing may be unhelpful in patients with recent glucocorticoid use (resorption markers rapidly increase, formation markers decrease), recent fracture (resorption markers double in weeks, formation markers double in roughly 3 months and stay elevated up to 1 year), or autoimmune conditions affecting bones (eg, rheumatoid arthritis), where markers do not correlate with disease progression or treatment effect.[16,29]

DISCLOSURES

Dr. Algeciras-Schimnich has disclosed consulting for Fujirebio and Roche Diagnostics. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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