Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated With High Bone Turnover

Description

Bone turnover markers are biochemical markers of either bone formation or bone resorption. Commercially available tests are used to assess some of these markers in urine and/or serum by high performance liquid chromatography (HPLC) or immunoassay. Assessment of bone turnover markers is proposed to supplement bone mineral density (BMD) measurement in the diagnosis of osteoporosis and aid in treatment decisions. Bone turnover markers could also potentially be used to evaluate treatment effectiveness before changes in BMD can be observed.

Background

After cessation of growth, bone is in a constant state of remodeling (or turnover), with initial absorption of bone by osteoclasts followed by deposition of new bone matrix by osteoblasts. This constant bone turnover is critical to the overall health of the bone, by repairing microfractures and remodeling the bony architecture in response to stress. Normally, the action of osteoblasts and osteoclasts is balanced, but bone loss occurs if the two processes become uncoupled. Bone-turnover markers (BTMs) can be categorized as bone-formation markers or bone-resorption markers, and can be identified in serum and/or urine. Table 1 summarizes the various bone-turnover markers.

Table 1

<table>
<thead>
<tr>
<th>Formation Markers</th>
<th>Resorption Markers</th>
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<tbody>
<tr>
<td>Serum osteocalcin (OC)</td>
<td>Serum and urinary hydroxyproline (Hyp)</td>
</tr>
<tr>
<td>Serum total alkaline phosphatase (ALP)</td>
<td>Urinary total pyridinoline (Pyr)</td>
</tr>
<tr>
<td>Serum bone specific alkaline phosphatase (B-ALP)</td>
<td>Urinary total deoxypyridinoline (dPyr)</td>
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<tr>
<td>Serum procollagen I carboxyterminal propeptide (PICP)</td>
<td>Urinary-free pyridinoline (f-Pyr, also known as Pyrilinks®)</td>
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<tr>
<td>Serum procollagen type 1 N-terminal propeptide (PINP)</td>
<td>Urinary-free deoxypyridinoline (f-dPyr, also known as Pyrilinks-D®)</td>
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</table>
Bone sialoprotein
Serum and urinary collagen type I cross-linked N-telopeptide (NTx, also referred to as Osteomark)

Collagen Cross-Links Tests
1995: Pyrilinks test (Metra Biosystems, Santa Clara, CA) measures collagen type 1 cross-link, pyridinium
1996: Osteomark test (Ostex International, Seattle, WA) measures cross-linked N-telopeptides of type 1 collagen (NTx)
1999: Serum Crosslaps One-step ELISA test measures hydroxyproline
2000: Ostase (Beckman Coulter) measures bone-specific alkaline phosphatase (B-ALP)
2001: N-MID Osteocalcin One-Step ELISA (Osteometer Bio Tech) measures osteocalcin (OC)
Measurement of bone turnover markers is considered **not medically necessary** in the diagnosis and management of age-related osteoporosis.

Measurement of bone turnover markers is considered **not medically necessary** in the management of patients with conditions associated with high rates of bone turnover, including but not limited to Paget disease, primary hyperparathyroidism and renal osteodystrophy.

**Rationale**

In general, to be considered clinically useful, studies need to demonstrate that tests for bone turnover markers are accurate and reliable and that their use can result in improved health outcomes. For example, to evaluate their utility for diagnosing osteoporosis as an adjunct to BMD measurements with dual energy x-ray absorptiometry (DXA), studies would moreover need to show that bone turnover markers independently predict fracture risk beyond BMD and that the additional information provided by information on bone turnover has the potential to influence treatment decisions and clinical outcomes. Similarly, to be considered useful for monitoring osteoporosis treatment beyond follow-up BMD measurements, bone turnover test results would need to impact the decision to continue or change treatment in a way that leads to improved patient outcomes.

Following is a summary of key literature on bone turnover markers published to date:

**Diagnosis and management of osteoporosis**

*Do bone turnover markers independently predict fracture risk beyond BMD measurements?*

Few studies have directly addressed the question of whether any bone turnover markers are independent predictors of fracture risk. One study conducted in men and one conducted in women are described next.

A 2013 analysis of population-based data in Japan included postmenopausal women and adjusted for BMD. (1) The study involved baseline surveys, bone turnover marker assessment and BMD measurements, and 3 follow-ups over 10 years. At baseline, 851 women who participated were aged 50 years or older and were eligible for vertebral fracture assessment. Of these, 730 women had BMD measurements taken at the initial examination and at 1 or more follow-ups. Women with early
menopause (ie, <40 years old), with a history or illness or medication known to affect bone metabolism and with incomplete data were excluded. After exclusions, 522 women included in the analysis.

Over a median follow-up period of 10 years, 81 of 522 women (15.5%) were found on imaging to have an incident vertebral fracture. Seventy-eight of the 81 women with radiographically detected vertebral fractures were more than 5 years from menopause at baseline. Risk of incident vertebral fractures adjusted for BMD T-scores was significantly associated with several bone turnover markers, specifically ALP, urinary total deoxypyridinoline (tDPD) and urinary free deoxypyridinoline (IPPD). For example, in a multivariate model adjusting for a variety of covariates including femoral neck BMD, the risk of developing a fracture per SD of change in ALP was increased by 33% (risk ratio, 1.33; 95% CI, 1.06 to 1.66). Risk of incident vertebral fracture was not significantly associated with other bone turnover markers including osteocalcin (OC) and crosslinked C-telopeptide (CTx). It is not clear how generalizable findings from this study are; that is, the association between subsequent fracture risk and certain bone turnover markers, and the lack of association between fracture risk and other bone turnover markers. This study is also limited by the large number of women excluded from analysis due to incomplete data.

In men, a subanalysis of prospectively-collected data from the Osteoporotic Fractures in Men (MrOS) study also included adjustment of BMD. (2) Baseline levels of bone turnover markers were compared in 384 men, age 65 years or older, who had nonspine fractures over an average follow-up of 5 years with 885 men without nonspine fracture. A second analysis compared 72 hip-fracture cases and 993 controls without hip fracture. After adjusting for age and recruitment site, the association between nonspine fracture and quartile of the bone turnover marker procollagen type 1 N-terminal propeptide (PINP) was statistically significant (for each analysis, p<0.05 was used). The associations between nonspine fracture and quartiles of the 2 other bone turnover markers, beta C-terminal cross-linked telopeptide of type 1 collagen (b-CTx) and tartrate-resistant acid phosphatase 5b (TRACP5b) were not statistically significant. Moreover, in the analysis adjusting only for age and recruitment site, when the highest quartile of bone turnover markers was compared with the lower 3 quartiles, the risk of nonspine and hip fractures was significantly increased for PINP and c-CTx but not TRACP5b. After additional adjustment for baseline BMD, or baseline BMD and other potential confounders, there were no statistically significant relationships between any bone turnover marker and fracture risk. The authors concluded that their results do not support the routine use of bone turnover markers to assess fracture risk in older men when there is the option of measuring hip BMD.

Systematic reviews have examined the association between bone turnover markers and fracture risk, but have not included analyses on the additional predictive value beyond BMD. For example, a 2014 meta-analysis by Johansson et al focused on the markers PINP and CTx and examined their ability to predict future fracture risk. (3) The review included 10 prospective cohort studies in which bone turnover markers were measured at baseline and incident fractures were recorded. Pooled analyses were performed on a subset of these studies. A meta-analysis of 3 studies found a statistically significant association between baseline PINP and subsequent fracture risk (hazard ratio [HR]=95% confidence interval [CI], 1.09 to 1.39). Similarly, a meta-analysis of 6 studies found an association between CTx and fracture risk (HR=1.18, 95%, 1.09 to 1.29). None of the individual studies adjusted
for BMD, and consequently the pooled analyses do not reflect the ability of bone turnover markers to predict fracture risk beyond BMD.

A previous systematic review, published in 2012 by Biver et al, did not find a statistically significant association between another bone turnover marker, OC and fracture risk. (4) When findings from 3 studies were pooled, the mean difference in OC levels in patients with and without vertebral fractures was 1.61 ng/mL (95% CI, -0.59 to 3.81). Both systematic reviews noted a high degree of heterogeneity among the published studies identified.

Section Summary: Prediction of Fracture Risk

Some studies have found statistically significant associations between bone turnover markers and fracture risk, but there is insufficient literature on any specific marker. For example, an analysis of MrOS data found a significant association between PINP and risk of nonspine fracture in men, and the JPOS study from Japan found a significant association between ALP, tDPD and fDPD and risk of incident vertebral fracture in women. Moreover, there is insufficient evidence that any bone turnover marker is an independent predictor of fracture risk, beyond BMD.

Do bone turnover markers independently predict response to osteoporosis treatment?

Studies have also examined the ability of bone turnover markers to evaluate response to osteoporosis treatment. For example, a subanalysis of the randomized Fracture Intervention Trial (n=6184) by Bauer et al found that pretreatment levels of the bone turnover marker PINP significantly predicted the anti-fracture efficacy of alendronate. (5) Over a mean follow-up of 3.2 years, there were 492 non-spine and 294 vertebral fractures. Compared to those in the placebo group, the efficacy of alendronate for reducing non-spine fractures was significantly greater in women who were in the highest tercile of PINP (>56.8 ng/mL) than those in the lowest tercile (<41.6 ng/mL). Baseline bone turnover rates were not associated with alendronate efficacy in reducing vertebral fractures. The authors indicated that this result needed confirmation in additional studies, and, even if verified, the impact on treatment recommendations is not clear. A small randomized trial of an osteoporosis treatment (n=43) found that urinary cross-linked N-terminal telopeptides provided a more sensitive measure of treatment response than serum levels. (6) Another small randomized trial from Japan measured levels of OC in response to osteoporosis treatment in 109 postmenopausal women. (7) The authors found that undercarboxylated osteocalcin (uc-OC) levels in serum were significantly lower at 1 month in the group receiving active treatment for osteoporosis compared to the control intervention; the implication for fracture prevention was not studied.

A 2011 systematic review by Funck-Brentano et al addressed the issue of whether early changes in serum biochemical bone turnover markers predict the efficacy of osteoporosis therapy. (8) Their review included 24 studies that presented correlations between bone turnover markers and the outcomes of fracture risk reduction or change in BMD. Five studies (including the Bauer study, previously described) reported on fracture risk and 20 studies reported on BMD changes. The review authors discussed study findings qualitatively but did not pool study results. The evidence did not
support a correlation between short-term changes in bone turnover markers and fracture risk reduction. In addition, few studies were available on this topic, leading to the conclusion that bone turnover markers “have shown limited value” as a technique to monitor osteoporosis therapy. An additional study on this topic was published by Baxter et al in 2013. (9) This was a retrospective review of data on 200 patients commencing treatment with bisphosphonates for osteoporosis or osteopenia requiring treatment. The investigators found statistically significant inverse correlation between change in urine NTx at 4 months and change in spine BMD at 18 months (Pearson product-moment correlation coefficient r=0.33, p<0.001). There was not a significant association between change in urine NTx and hip BMD.

Section Summary: Response to Treatment

The available evidence on the association between any specific bone turnover marker and response to osteoporosis treatment is limited in quantity and quality. While some individual studies have reported positive correlations for markers, such as PINP in the Fracture Intervention Trial, a body of evidence in support of any specific marker is lacking. As a result, the evidence is insufficient to conclude whether bone turnover markers are an independent predictor of treatment response.

Does information provided by bone turnover markers improve treatment decisions and/or improve health outcomes?

To provide clinical utility, bone turnover markers would need to provide information beyond that offered by BMD measurements that has an impact on treatment decisions and/or leads to improved health outcomes. Bone turnover markers can be measured more frequently than BMD and thus could potentially provide information with clinical utility. For example, the 2013 guideline from the National Osteoporosis Foundation states that biochemical markers of bone turnover can be used to predict the extent of fracture risk reduction when measured 3-6 months after starting FDA-approved osteoporosis treatments. (10)

Several randomized controlled trials (RCTs) have addressed the issue of whether measurement of bone turnover markers can improve adherence to oral bisphosphonate treatment. A 2014 systematic review identified 5 RCTs and did not find significant differences in compliance rates between groups that did and did not receive feedback on bone turnover marker test results. (11) Study data were not pooled. The authors noted a high baseline compliance rate that limited the studies’ ability to detect an impact of feedback. As an example, a 2011 industry-sponsored study by Roux et al from France randomized physicians to manage patients on oral monthly ibandronate with a collagen crosslinks test (CTX) or usual care. (12) In the CTX group, bone marker assessment was done at baseline and week 5 for the week 6 visit, a standardized message was delivered to patients regarding change in CTX since baseline. If the decrease in CTX was more than 30% of the baseline value, they were told that the treatment effect was optimal. If not, they were told that the treatment effect was suboptimal, and they were given additional advice. Patients told they had a suboptimal response were retested with CTX at week 13 for the week 14 visit.
The primary outcome was the proportion of patients who were adherent at 1 year. After 1 year, rates of adherence to ibandronate were 74.8% in the CTx group and 75.1% in the usual care group; the difference between groups was not statistically significant (p=0.93). There was also not a statistically significant difference in the proportion of patients having taken at least 10 out of 12 pills; 82.4% in the CTx group and 80.0% in the usual care group. In this study, monitoring bone markers and providing this information to patients did not improve adherence to oral osteoporosis medication.

Section Summary: Impact on Treatment Decisions and Health Outcomes

There is a limited amount of evidence on the impact of bone turnover markers on management of osteoporosis. Individual RCTs and a meta-analysis of these RCTs have not found that feedback on bone turnover marker results improves adherence rates. No studies were identified that evaluate whether the use of bone turnover markers lead to management changes that are expected to improve outcomes.

Management of other conditions associated with high rates of bone turnover

There is little published literature on use of bone turnover markers in the management of conditions associated with high rates of bone turnover, such as Paget disease, primary hyperparathyroidism, and renal osteodystrophy, and many of the available studies were published 10 or more years ago.

Hyperparathyroidism

One study, published in 2012 by Rianon et al, reported on 198 patients with primary hyperparathyroidism who underwent parathyroidectomy. (13) The authors found a statistically significant association (p<0.05) between preoperative serum OC levels and persistent postoperative elevation of parathyroid hormone 6 months after the surgery.

Paget Disease

A 2015 systematic review and meta-analysis by Al Nofal et al reviewed the literature on bone turnover markers in Paget disease. (14) The authors focused on the correlation between bone markers and disease activity before and after treatment with bisphosphonates. All study designs were included in the review and bone scintigraphy was used as the reference standard. The authors identified a total of 18 studies. Seven studies assessed bone markers in patients with Paget disease before treatment, 6 considered both the pre- and posttreatment associations and 5 included only the posttreatment period. Only 1 of the studies was an RCT and the rest were prospective cohort studies. There was a moderate to strong correlation between several bone turnover markers (bone ALP, total ALP, PINP, and NTx) and pretreatment disease activity. In a pooled analysis of available data, there was a statistically significant correlation between levels of bone turnover marker and disease activity after treatment with bisphosphonates (p=0.019). The systematic review did not address the potential impact on bone turnover measurement on patient management or health outcomes.
Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in July 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements

In 2014, the National Osteoporosis Foundation updated their guideline for prevention and treatment of osteoporosis. (10) Regarding biochemical markers of bone turnover, the guideline states:

Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density
- Predict extent of fracture risk reduction when repeated after 3-6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Predict rapidity of bone loss.
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy.
- Help determine duration of 'drug holiday' and when and if medication should be restarted (Data are quite limited to support this use, but studies are underway).

In 2010, the North American Menopause Society issued an updated position statement on management of osteoporosis in postmenopausal women. The statement included the recommendation, “routine use of biochemical markers of bone turnover in clinical practice is not generally recommended.” (15)

In 2011, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) published a position statement by a joint IOF–IFCC Bone Marker Standards Working Group. (16) The aim of the group was to evaluate evidence on using bone turnover markers for fracture risk assessment and monitoring of treatment. The group’s overall conclusion was, “In summary, the available studies relating bone turnover marker changes to fracture risk reduction with osteoporosis treatments are promising. Further studies are needed that take care of sample handling, ensure that bone turnover markers are measured in all available patients, and use the appropriate statistical methods, including an assessment of whether the final bone turnover marker “level is a guide to fracture risk.

In 2011, the Joint Official Positions Development Conference of the International Society for Clinical Densitometry and the IOF on the FRAX® fracture risk prediction algorithms published the following statement (17): “Evidence that bone turnover markers predict fracture risk independent of BMD is inconclusive. Therefore, bone turnover markers are not included as risk factors in FRAX.”
U.S. Preventive Service Task Force Recommendations

The U.S. Preventive Services Task Force 2011 recommendations on osteoporosis screening address DXA testing but do not mention bone turnover markers. (18)

Summary of Evidence

The evidence on bone turnover markers for diagnosis and management of osteoporosis includes a number of observational studies on the association between markers and osteoporosis and fracture risk. Relevant outcomes are test accuracy, test validity, and morbid events. Studies suggest that bone turnover marker levels may be independently associated with osteoporosis and fracture risk in some groups, but there is insufficient evidence reporting an association for any specific marker. Questions remain about whether bone turnover markers are sufficiently sensitive to reliably determine individual treatment responses. In addition, there is insufficient evidence from controlled studies that bone turnover marker measurement improves adherence to treatment, impacts management decisions, and/or improves health outcomes such as reducing fracture rates. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence on bone turnover markers for management of patients with conditions associated with high rates of bone turnover, including but not limited to, Paget disease, primary hyperparathyroidism, and renal osteodystrophy includes a number of observational studies on the association between markers and disease activity. Relevant outcomes are test accuracy, test validity, and morbid events. The largest amount of evidence has been published on Paget disease; a systematic review found correlations between several bone turnover markers and disease activity prior to and/or after bisphosphonate treatment. There is a lack of evidence on how measurement of bone turnover markers can change patient management or improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Medicare National Coverage

On November 25, 2002, the Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) on collagen cross-links. (19) The CMS NCD identifies a set of clinical conditions for which collagen cross-links would be considered eligible for coverage. The CMS NCD is limited to urine-based collagen cross-link tests and does not address serum-based collagen cross-link tests.

The Federal Register (20) notes that Medicare carriers have discretion to make their own determinations on the medical necessity of serum-based collagen cross-link tests for assessing or monitoring bone loss therapy. The Federal Register also notes that the FDA approved the serum-based collagen cross-link tests under 510(k) review, as substantially equivalent to the urine-based collagen cross-link test. It should be noted that the serum-based collagen cross-link tests are more commonly performed than urine collagen cross-link tests.
The Medicare NCD analysis focused on the technical feasibility of collagen cross-links and anticipated outcomes. The discussion above focused on the impact on health outcomes as documented in controlled studies.

References


March 2016 Update Policy Policy updated with literature review through August 5, 2015; reference 14 added. Second policy statement changed to not medically necessary. The BCBS FEP contract stipulates that certain FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may not only be assessed based on medical necessity.

Keywords

Bone Turnover Markers
Collagen Cross links, Osteoporosis
Osteoporosis, Bone Turnover Markers
Pyridinoline
Deosypyridinoline
Pyrilinks
Pyrilinks-D
N-telopeptide
NTx
Osteomark
C-telopeptide
CTx
Cross Laps
Telopeptide
Popeptide

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 18, 2016 and is effective April 15, 2016.

Signature on file
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