

Medical Policy Manual

Topic: Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover **Date of Origin:** October 11, 1999

Section: Laboratory

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Bone turnover markers are biochemical markers of either bone formation or bone resorption. Tests are commercially available 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 to aid in treatment decisions. Bone turnover markers are also being studied to determine their ability to evaluate treatment effectiveness before changes in BMD can be observed. Treatment-related changes in BMD occur very slowly, and it is estimated that clinically significant changes in BMD could not be reliably detected for at least 2 years. In contrast, changes in bone turnover markers could be anticipated after 3 months of therapy.

After cessation of growth, bone is in a constant state of remodeling (or turnover), with initial absorption (or resorption) 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. The table below summarizes the various bone turnover markers.

Formation Markers	Resorption Markers
Serum osteocalcin (OC)	Serum and urinary hydroxyproline (Hyp)

Formation Markers	Resorption Markers
Serum total alkaline phosphatase (ALP)	Urinary total pyridinoline (Pyr)
Serum bone specific alkaline phosphatase (BSAP, BALP, or B-ALP)	Urinary total deoxypyridinoline (d-Pyr)
Serum procollagen I carboxyterminal propeptide (PICP)	Urinary free pyridinoline [f-Pyr, also known as Ppyrilinks® (Metra Biosystems)]
Serum procollagen type 1 N-terminal propeptide (PINP)	Urinary free deoxypyridinoline (f-dPyr, also known as Ppyrilinks-D®)
Bone sialoprotein	Serum and urinary collagen type I cross-linked N-telopeptide (NTx, also referred to as Osteomark®)
	Serum and urinary collagen type I cross-linked C-terminal telopeptide (CTx, also referred to as CrossLaps®)
	Serum carboxyterminal telopeptide of type I collagen (ITCP)
	Tartrate-resistant acid phosphatase (TRAP or TRACP)
	Urinary hydroxyproline (Hyp) (This is an older test, less specific than the above.)

Bone turnover markers have been extensively researched in diseases associated with markedly high levels of bone turnover, such as Paget's disease, primary hyperparathyroidism, glucocorticoid-induced osteoporosis or renal osteodystrophy. There has been recent interest in the use of bone turnover markers to evaluate age-related osteoporosis, a disease characterized by slow, prolonged bone loss, resulting in an increased risk of fractures at the hip, spine or wrist. Currently, fracture risk is based primarily on measurement of bone mineral density (BMD) in conjunction with other genetic and environmental factors, such as family history of osteoporosis, history of smoking, and weight. It is thought that the level of bone turnover markers may also predict fracture risk, possibly through a different mechanism than that associated with BMD. However, it must be emphasized that the presence of bone turnover markers in the serum or urine is not necessarily related to bone loss. For example, even if bone turnover is high, if resorption is balanced with formation, there will be no net bone loss. Bone loss will only occur if resorption exceeds formation. Therefore, bone turnover markers have been primarily studied as an adjunct, not an alternative, to measurements of bone mineral density (BMD), to estimate the fracture risk and document the need for preventive or therapeutic strategies for osteoporosis.

Collagen cross links are generally reliable markers of bone resorption because they are stable in serum and urine. Collagen cross links bind three molecules of collagen in the bone and are released from the bone matrix after resorption, either free or bound to the N- or C- telopeptide of collagen. Collagen cross links may be detected using either HPLC (Pyr and D-Pyr) or immunoassays (Pyr, D-Pyr, CTx, NTx). In addition to collagen cross-links, alkaline phosphatase (ALP) is a commonly used marker due to its ease of measurement; however, it lacks sensitivity and specificity for detecting osteoporosis since only about half of the ALP activity is derived from bone. Bone-specific alkaline phosphatase (B-ALP) is a better marker of bone formation than

ALP. Serum osteocalcin is a small noncollagenous protein that is a product of osteoblasts and thus increased levels reflect bone formation. Tartrate-resistant acid phosphatase (TRAP) is produced by osteoclasts; it is thought to be active in bone matrix degradation.

Regulatory Status

Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process:

Collagen Cross-links Tests:

- 1995 Pylrilinks test (Metra Biosystems) measures collagen type 1 cross-link, pyridinium
- 1996 Osteomark test (Ostex International) measures cross-linked N-telopeptides of type 1 collagen (NTx)
- 1999 Serum Crosslaps One-step ELISA test measures hydroxyproline

Other Bone Turnover Tests:

- 2000 Ostase® (Beckman Coulter) measures bone-specific alkaline phosphatase (B-ALP)
- 2001 N-MID Osteocalcin One-Step ELISA (Osteometer Bio Tech) measures osteocalcin (OC)

MEDICAL POLICY CRITERIA

Measurement of bone turnover is considered **investigational** for all indications, including but not limited to the following:

- A. In the diagnosis and management of osteoporosis
- B. In the management of patients with conditions associated with high rates of bone turnover, including but not limited to Paget's disease, primary hyperparathyroidism, and renal osteodystrophy

SCIENTIFIC EVIDENCE

In general, to be considered clinically useful, evidence must demonstrate that tests for bone turnover markers (BTMs) are accurate and reliable (technical and diagnostic performance) and that their use can result in improved health outcomes (clinical utility).

To determine their utility for diagnosing osteoporosis as an adjunct to bone mineral density (BMD) measurements with dual energy x-ray absorptiometry (DXA), evidence needs to demonstrate the following:

- That bone turnover markers independently predict fracture risk beyond BMD measurements.
- The additional information provided by measurement of bone turnover has the potential to influence treatment decisions and improve clinical outcomes.

Similarly, to be considered useful for monitoring osteoporosis treatment beyond follow-up BMD measurements, bone turnover test results need to impact the decision to continue or change treatment in a way that leads to improved patient outcomes.

Literature Appraisal

When this policy was first created, there were studies showing that bone turnover markers predicted subsequent risk of osteoporosis-related fractures in postmenopausal women. However, it was not clear at that time how therapy should be adjusted according to the level of fracture risk or whether the use of bone turnover markers could predict response to therapy. Moreover, studies reported an inconsistent relationship between the change in bone turnover markers in response to therapy and the magnitude of subsequent change in BMD.^[1] In addition, there was marked diurnal variation in bone turnover markers in individual patients, and results of markers measured in the urine had to be correlated to the serum creatinine, all of which complicated the interpretation of serial studies.^[2]

The following discussion summarizes a representative sample of current systematic reviews and randomized controlled trials.

Bone Turnover Markers as Independent Predictors of Fracture Risk

Systematic Reviews

Three systematic reviews were published in 2011 and 2012 by a single research group:

- Biver and colleagues reviewed the literature on bone turnover markers for diagnosing osteoporosis and predicting fracture risk.^[3] To be included in the review, studies needed to report at least one bone turnover marker and report either BMD or fracture assessment. The investigators did not limit their review to particular types of study design; they identified 105 reports on women and 18 reports on men. In postmenopausal women, the markers that had been studied the most and also had the strongest negative correlations with BMD were ALP, osteocalcin (OC), CTx, and NTx. The investigators addressed the issue of the potential association between bone turnover markers and prevalent asymptomatic vertebral fractures. A pooled analysis was conducted only for the marker osteocalcin (OC). When findings from three studies were pooled, there was no statistically significant mean difference in OC levels in patients with and without vertebral fractures (1.61 ng/mL, 95% confidence interval [CI]: -0.59 to 3.81). The authors also reported that bone turnover markers were not able to reliably distinguish primary osteoporosis from secondary causes. There was a high degree of heterogeneity among the published studies included in this review. According to these data, the clinical usefulness of bone turnover markers for diagnosing osteoporosis was reported as low due to patient variability and other factors that can influence bone turnover marker levels.
- A separate report evaluated the literature on the association between bone turnover markers and subsequent risk of fracture in post-menopausal women.^[4] The authors did not conduct any pooled analyses of study findings. Based on their review of observational data, they concluded that bone turnover markers had a modest positive correlation with fractures and could be considered independent risk factors for future fracture risk in this patient population. However, the authors also noted that there was a large degree of variability in the literature. In addition, there was a lack of standardized measures and optimal cutoffs for bone turnover markers, and as a result, it was difficult to use bone turnover markers to make practical treatment decisions in clinical care.
- The final systematic review by this group included 48 studies to evaluate the use of BTMs to 1) aid in treatment choice; 2) monitor short-term changes and clinical response; 3) effect persistence to therapy; 4) predict fracture risk after withdrawal of therapy; and 5) predict serious adverse effects.^[5] The authors reported a correlation between short-term changes in BTMs with bone mineral density variation. However, the authors recommended against the use of pretreatment values for therapy selection. They also noted the lack of evidence for BTM measurement to predict fracture or adverse effects.

Randomized Controlled Trials (RCTs)

A 2009 study evaluated the association between bone turnover markers and fracture risk in men.^[6] This was a sub-analysis of prospectively-collected data from the randomized Osteoporotic Fractures in Men (MrOS) study. Baseline levels of bone turnover markers were compared in 384 men, age 65 or older, who had non-spine fractures over an average follow-up of 5 years to 885 men without non-spine 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 non-spine fracture and quartile of the bone turnover marker procollagen type 1 N-terminal propeptide (PINP) was statistically significant (for each analysis, p less than 0.05 was used). The associations between non-spine 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, the associations between risk of hip fracture and quartiles of bone turnover markers were not statistically significant. However, in the analysis adjusting only for age and recruitment site, when the highest quartile of bone turnover markers was compared to the lower 3 quartiles, the risk of non-spine and hip fractures was significantly increased for PINP and b-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.

Bone Turnover Markers as Independent Predictors of Response to Osteoporosis Treatment

Systematic Reviews

The 2011 systematic review by Funk-Brentano and colleagues addressed the issue of whether early changes in serum biochemical bone turnover markers predict the efficacy of osteoporosis therapy.^[5] 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, described above) 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.

Randomized Controlled Trials (RCTs)

A subanalysis of the randomized Fracture Intervention Trial (n=6,184) found that pretreatment levels of the bone turnover marker PINP significantly predicted the anti-fracture efficacy of alendronate.^[7] 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 (less than 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.^[8] Another small randomized trial from Japan measured levels of osteocalcin in response to osteoporosis treatment in 109 postmenopausal women.^[9] The authors found that undercarboxylated osteocalcin (uc-OC) levels in serum was 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.

Clinical Utility of Bone Turnover Markers in Osteoporosis Management

Predicting risk or prognosis does not, by itself, directly improve health outcomes. To complete the causal chain, there must be evidence from prospective, comparative studies that patient management decisions based on measurement of bone turnover markers result in improved health outcomes. In order to establish clinical utility, bone turnover markers would need to provide information which improves treatment decisions and health outcomes beyond that of BMD measurements.

Systematic Reviews

A 2014 systematic review by Burch et al. found no RCTs that evaluated the effectiveness of bone turnover marker monitoring on treatment management.^[10] Most studies that assessed test accuracy only reported correlations between changes in bone turnover and BMD. Only 4 studies reported on intra- or interpatient reliability and reproducibility in treated patients. Overall, study results were reported to be inconsistent and inconclusive primarily due to clinical heterogeneity between studies and small sample sizes. The authors concluded that the clinical effectiveness of monitoring of bone turnover markers could not be established.

Randomized Controlled Trials (RCTs)

Two RCTs were found that studied whether feedback to patients' on their BTM would improve their adherence to oral osteoporosis medication regimen.

- A 2011 industry-sponsored study randomized physicians to manage patients on oral monthly ibandronate with a collagen cross-links test (CTX) or usual care.^[11] Eighty-six physicians who recruited at least one patient were included in the CTX group, and 74 were included in the usual care group. Physicians in the CTX group recruited a total of 346 patients, and physicians in the usual care group recruited 250 patients. In the CTX group, bone marker assessment was done at baseline and week 5 and, at 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 sub-optimal and they were given additional advice. Patients told they had a sub-optimal response were re-tested with CTX at week 13 for the week 14 visit. The primary outcome was the proportion of patients' adherent at one year. After one 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. The adherence rates reported in this study were higher than those expected in clinical care, but monitoring bone markers did not improve adherence to oral osteoporosis medication.
- Silverman et al. randomized 240 women with BMD at least 2 SDs below normal and a new prescription for alendronate to one of four groups: 1) BTM results at baseline, 3 and 12 months; 2) monthly educational materials and National Osteoporosis Foundation membership; 3) BTMs and educational information; and 4) control group receiving no information other than usual care.^[12] Overall, 130 (54%) patients adhered to medication through the 12-month follow-up. The authors reported no significant difference among the four groups for persistence to oral bisphosphonate therapy. However, interpretation of these results is difficult due to an unexpected number of patients excluded because they did not begin their prescribed bisphosphonate regimen.

Bone Turnover Markers in Other Conditions Associated with High Bone Turnover

There is little published literature on the use of bone turnover markers in the management of conditions associated with high rates of bone turnover other than osteoporosis, such as Paget's disease, primary

hyperparathyroidism, and renal osteodystrophy. Moreover, very few studies on this topic have been published since 2000. One recent study by Rianon and colleagues reported on 198 patients with primary hyperparathyroidism who underwent parathyroidectomy.^[13] The authors found a statistically significant ($p < 0.05$) association between pre-operative serum osteocalcin levels and persistent postoperative elevation of parathyroid hormone 6 months after the surgery. In addition, several studies were identified that tested bone turnover levels in patients with Paget's disease before and after treatment with bisphosphonates.^[14-16] For example, Alvarez and colleagues found that the mean values of bone markers decreased significantly after bisphosphonate treatment in 31 of 38 patients who completed a 3-month course of oral bisphosphonates. Bone markers measured in the Alvarez study included serum total alkaline phosphatase (ALP), serum bone-specific alkaline phosphatase (B-ALP), and PINP and urinary hydroxyproline (Hyp), CTx, and NTx. No studies were identified that addressed whether bone turnover markers for these conditions associated with high bone turnover resulted in improved patient management decisions or health outcomes.

Clinical Practice Guidelines and Position Statements

National Osteoporosis Foundation (NOF)

The 2014 NOF Clinician's Guide on osteoporosis applies to postmenopausal women and men aged 50 years and older.^[17] This document is a guide, but is not an evidence-based practice guideline; no critical analysis of the evidence is included. Nor are any specific recommendations provided for patient selection or testing protocols. The guide lists the following possible uses of biochemical markers of bone turnover:

- Predict risk of fracture independently of bone density in untreated patient
- Predict rapidity of bone loss in untreated patients
- 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.
- 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)

International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

A 2011 position statement by a joint IOF–IFCC Bone Marker Standards Working Group.^[18] 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.

International Society for Clinical Densitometry (ISCD) and the IOF

In 2011, the Joint Official Positions Development Conference of the ISCD and the IOF on the FRAX® fracture risk prediction algorithms published the following statement:^[19]

"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."

A 2010 updated position statement on the management of osteoporosis in postmenopausal women included the recommendation, “the routine use of biochemical markers of bone turnover in clinical practice is not generally recommended.”^[20]

Summary

The literature suggests that bone turnover marker levels may be independently associated with osteoporosis and fracture risk in a select group of individuals. However, there is insufficient evidence that current methods for measuring bone turnover markers are sensitive enough to reliably determine individual treatment responses. In addition, there is insufficient evidence that bone turnover marker measurement improves adherence to treatment or improves health outcomes such as reducing fracture rates. Thus, bone turnover markers for the diagnosis and management of osteoporosis or other conditions associated with high bone turnover is considered investigational.

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[21]

CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
There are no specific codes for bone-specific alkaline phosphatase (ALK) but several laboratories' Web sites identify CPT 84080 (Phosphatase, alkaline; isoenzymes) as being used for the Ostase test.		
CPT	82523	Collagen cross links, any method
	83937	Osteocalcin (bone gla protein)
	84080	Phosphatase, alkaline; isoenzymes
	84999	Unlisted chemistry procedure
HCPCS	None	