MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Biochemical Markers of Bone Turnover**
Policy Number	**2.02.18**
Category	**Technology Assessment**
Original Effective Date	**02/20/03**
Committee Approval Date	**12/18/03, 12/16/04, 10/20/05, 08/17/06, 08/16/07, 08/21/08, 08/20/09, 08/19/10, 08/18/11, 08/16/12, 08/15/13, 08/21/14, 07/16/15, 07/21/16, 07/20/17, 07/19/18, 07/18/19**
Current Effective Date	**07/18/24**
Archived Date	**07/16/20**
Archive Review Date	**07/15/21, 07/21/22, 07/20/23, 07/18/24**
Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and the lack of peer-reviewed literature, serum and urinary markers of bone turnover have not been proven to improve patient outcomes and, therefore, are considered **investigational** for indications that include, but are not limited to the following:
   A. Monitoring treatment for osteoporosis or other conditions associated with increased bone turnover; or
   B. Identification or diagnosis of osteoporosis or other conditions associated with increased bone turnover.

Refer to Corporate Medical Policy #6.01.05 Bone Densitometry/Bone Density Studies

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

DESCRIPTION

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 to the skeletal structure. Normally, the action of osteoblasts and osteoclasts is balanced, but bone loss can occur if the two processes become uncoupled. It has been proposed that bone remodeling can be assessed by the measurement of surrogate markers of bone turnover in the blood or urine.

Biochemical markers of bone turnover can be categorized as either bone formation markers or bone resorption markers (see list below). Collagen cross links may be the best available markers of bone resorption. They bind three molecules of collagen in the bone and are released from the bone matrix after resorption. They may be detected using Pyr and dPyr or immunoassays (Pyr, D-Pyr, CTx, NTx).

I. Formation Markers
   A. Serum osteocalcin (OC);
   B. Serum total alkaline phosphatase (ALP);
   C. Serum bone specific alkaline phosphatase (BALP);
   D. Serum procollagen I carboxyterminal propeptide (PICP);
   E. Serum procollagen type I N-terminal propeptide (PINP); and
   F. Bone sialoprotein.

II. Resorption Markers
   A. Serum and urinary hydroxyproline (Hyp);
   B. Urinary total pyridinoline (Pyr);
   C. Urinary total deoxypridinoline (dPyr);
   D. Urinary-free pyridinoline (f-Pyr or Pyrilinks);
   E. Urinary-free deoxypyridinolin (f-dPyr or Pyrilinks-D);
   F. Urinary or serum collagen type I cross-linked N-terminal telopeptide A (NTx or Osteomark's NTx test);
   G. Urinary or serum collagen type I cross-linked C-terminal telopeptide (CTxI or Cross Laps);
   H. Serum carboxy-terminal telopeptide or I collagen (ICTP); and
   I. Tartrate-resistant acid phosphatase (TRAP).

Biochemical markers of bone turnover have been 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 is interest in the use of these markers to evaluate age-related osteoporosis. Currently fracture risk is based primarily on measurements of bone mineral density (BMD) in conjunction with other genetic and environmental factors, such as family history of osteoporosis, history of smoking, and weight.

Some researchers believe that the level of biochemical markers of bone turnover may also predict fracture risk. However, the presence of these markers in serum or urine is not necessarily related to bone loss. 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, these markers have been primarily studied as an adjunct, not an alternative, to measurements of bone mineral density, to estimate the fracture risk and document the need for preventive or therapeutic strategies for osteoporosis.

RATIONALE

The following clinical applications of bone-turnover markers have been investigated:

I. In conjunction with measurements of bone mineral densitometry, as a technique to identify those patients at highest risk of osteoporosis-related fractures. Bone-turnover markers may reflect fracture risk through a different mechanism than that associated with BMD. Therefore, markers had been investigated as an adjunct to BMD to increase the prediction assessment for fracture risk compared to the use of BMD alone. It is not clear at this 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.

II. To provide a more immediate assessment of treatment response and predict change in BMD in response to treatment. Treatment-related changes in BMD occur very slowly. This fact, coupled with the precision of BMD technologies, suggest that clinically significant changes in BMD cannot be reliably detected for at least two years. In contrast, changes in bone-turnover markers could be anticipated after three months of therapy. Although bone-turnover markers might be assessed at diagnosis to provide a baseline, followed by repeat assay at three months to determine the response to therapy, studies report an inconsistent relationship between the change in bone-turnover markers in response to therapy and the magnitude of subsequent change in BMD. In addition, there is 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.

III. As an alternative to an additional central measurement. If a patient has been initially diagnosed with osteoporosis using a peripheral BMD measurement, some physicians may recommend an additional BMD of the more clinically

relevant central sites, i.e., the hip and spine, to serve as a baseline for future serial measurements of BMD. This strategy, thus requires two BMD measurements in patients with osteoporosis. In this setting, bone-turnover markers have been proposed as an alternative to an additional central measurement.

IV. Use in other diseases associated with high bone-turnover rates, such as glucocorticoid-induced osteoporosis, hyperparathyroidism, or renal osteodystrophy. Similar to the discussion above regarding age-related osteoporosis, it is unclear how levels of collagen cross-link as a marker of bone turnover might be used in the management of the patient.

In 2022, the Bone Health and Osteoporosis Foundation (formerly the National Osteoporosis Foundation) published updated guidelines on the prevention and treatment of osteoporosis to prevent fractures. Regarding biochemical markers of bone turnover, the guidelines stated: "Biochemical bone turnover markers can play a role in assessing fracture risk in appropriate individuals."

Furthermore, biochemical markers of bone turnover may:

- Predict rapidity of bone loss in untreated postmenoupausal women
- Predict extent of fracture risk reduction when repeated after 3-6 months of treatment with FDA [Food and Drug Administration]-approved therapies
- Predict magnitude of BMD [bone mineral density] increases with FDA-approved therapies
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy using a serum CTX for an antiresorptive medication and P1NP for an anabolic therapy (least significant change [LSC] is approximately a 40% reduction in CTX)
- 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 2021, the North American Menopause Society issued an updated position statement on management of osteoporosis in postmenopausal women, asserting that, “bone turnover markers are serum tests that reflect either bone resorption by osteoclasts (fasting serum C-telopeptide of type I collagen) or bone formation by osteoblasts (bone specific alkaline phosphatase or serum procollagen type I N-terminal propeptide). Bone turnover markers cannot diagnose osteoporosis and have varying ability to predict fracture risk in clinical trials. Bone turnover markers have been used primarily in clinical trials to demonstrate group responses to treatment. Although used by some osteoporosis specialists, the routine use of bone turnover markers in the evaluation of patients with osteoporosis is not recommended”.

The International Osteoporosis Foundation and the European Calcified Tissue Society convened a meeting in 2017 to propose a screening strategy to detect a lack of adherence to oral bisphosphonates. The recommendations were based on results from the TRIO study which was a single-center, randomized, controlled trial of three oral bisphosphonates (alendronate, ibandronate, and risedronate) at their licensed doses to study their effect on bone turnover markers (serum CTX and PINP) and bone mineral density in postmenopausal osteoporosis. The Working Group recommended measuring PINP and CTX at baseline and at three months after starting therapy, to check for a decrease above the least significant change of more than 38 percent for PINP and 56 percent for CTX. If a significant decrease were observed, the treatment would continue, but if no decrease were to occur, the clinician should reassess to identify problems with the treatment, mainly low adherence. The TRIO study was a small study and only included postmenopausal women from a single center. The results cannot be translated to men and premenopausal women.

According to conclusions reached by the National Institutes of Health and the Agency for Healthcare Research and Quality, the sensitivity and specificity of bone turnover markers are too low to be useful in identifying patients for treatment of osteoporosis and no marker is accurate enough to reliably identify individuals who fail to respond to therapy. There are a number of variables that can influence the results of bone marker tests, drugs (corticosteroids, anticonvulsants, and certain types of diuretics), the circadian cycle, the need for separate reference ranges based on age, sex and menopause and type of test. It is because of these factors and limitations that biochemical markers of bone turnover are of limited utility in the diagnosis and management of individuals with osteoporosis or other conditions associated with increased bone turnover.

Stewart et al. (2022) performed a randomized controlled trial (RCT) to determine whether bone turnover markers (BTMs) can be used as early markers of delayed fracture healing, and the effect of vitamin D on BTM response after fracture. A total of 102 participants aged 18 to 50 years (median 28 years (interquartile range 23 to 35)), receiving an intramedullary nail for a tibial or femoral shaft fracture, were enrolled in a randomized controlled trial comparing vitamin D3 supplementation to placebo. Serum C-terminal telopeptide of type I collagen (CTX; bone resorption marker) and N-terminal propeptide of type I procollagen (P1NP; bone formation marker) were measured at baseline, six weeks, and 12 weeks post-injury. Clinical and radiological fracture healing was assessed at three months. Results showed CTX and P1NP concentrations peaked at six weeks in all groups. Elevated six-week CTX and P1NP were associated with radiological healing at 12 weeks post-injury (odds ratio (OR) 10.5; 95% confidence interval 2.71 to 53.5, p = 0.002). There was no association between CTX or P1NP and functional healing. Baseline serum 25(OH)D showed a weak inverse relationship with P1NP (p = 0.036) and CTX (p = 0.221) at 12 weeks, however, the authors observed no association between vitamin D supplementation and either BTM. The authors stated that the association between six-week BTM concentrations and three-month radiological fracture healing, CTX and P1NP appeared to be potential surrogate markers of fracture healing and concluded that CTX and P1NP concentrations increase during acute fracture healing. Limitations of the RCT included unfasted blood draws, potentially introducing variability to the CTX measurements, the sample included both tibia and femur fractures potentially introducing variability to the BTM response, and despite numerous contact attempts, attrition in the sample reached 35%. In addition, the short terms follow-up did not allow for assessment of intermediate and long-term outcomes. Further investigation is needed before clinical usefulness of this procedure is proven.

Current literature indicates that alternative measures of bone strength have the potential to assess individual responses to treatment or identify individuals at high risk of future fracture, thereby potentially altering clinical management. However, the methods for measuring markers of bone turnover are not sufficiently sensitive (the least significant change) to reliably determine individual treatment responses, and other types of assays appear to be at an early stage of development. Existing methods of assessing bone turnover have not been shown to improve health outcomes.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
82523 **(E/I)**	Collagen cross links, any method
83937 **(E/I)**	Osteocalcin (bone g1a protein)

HCPCS Codes

Code	Description
No code(s)	

ICD10 Codes

Code	Description
M14.671-M14.679	Charcot's joint, ankle and foot (code range)

Includes Initial Encounter only (7th character of code is A):	
M48.50XA-M48.58XA	Collapsed vertebra (code range)
M80.00XA-M80.8AXA	Age-related or Other Osteoporosis with current pathological fracture (code range)
M81.0-M81.8	Osteoporosis without current pathological fracture (code range)
M84.40XA-M84.48XA	Pathological fracture (code range)
M84.50XA-M84.58XA	Pathological fracture in neoplastic disease (code range)
M84.60XA-M84.68XA	Pathological fracture in other disease (code range)
Q78.0	Osteogenesis imperfecta
Z13.820	Encounter for screening for osteoporosis
Z82.62	Family history of osteoporosis
Z87.310	Personal history of (healed) osteoporosis fracture

REFERENCES

*Agency for Healthcare Research and Quality. Evidence Report/Technology Assessment #28: Osteoporosis in postmenopausal women: diagnosis and monitoring. Publication #01-E032. 2001 Feb.

Bager CL, et al. Low bone turnover levels predict increased risk of cancer. Bone 2019;127(2):75-81.

Bihlet AR, et al. Associations between biomarkers of bone and cartilage turnover, gender, pain categories and radiographic severity in knee osteoarthritis. Arthritis Res Ther 2019 Sep 3;21(1):203.

*Bruyére O, et al. Monitoring of osteoporosis therapy. Best Pract Res Clin Endocrinol Metab 2014 Dec;28(6):835-41.

*Cavalier E, et al. The role of biochemical of bone turnover markers in osteoporosis and metabolic bone disease: a consensus paper of the Belgian Bone Club. Osteoporos Int 2016 Jul;27(7):2181-2195.

*Chopin F, et al. Prognostic interest of bone turnover markers in the management of postmenopausal osteoporosis. Joint Bone Spine 2012 Jan;79(1):26-31.

*Farahmand P, et al. Early changes in biochemical markers of bone formation during teriparatide therapy correlate with improvements in vertebral strength in men with glucocorticoid-induced osteoporosis. Osteoporos Int 2013 Dec;24(12):2971-81.

*Garnero P, et al. Long-term variability of markers of bone turnover in postmenopausal women and implications for their clinical use: the OFELY study. J Bone Miner Res 2003 Oct;18(10):1789-94.

*Huang Q, et al. Biochemical-markers for the diagnosis of bone metastasis: A review of clinical. Cancer Epidemiol 2012 Feb;36(1):94-8.

*Krege JH, et al. PINP as a biological response marker during teriparatide treatment for osteoporosis. Osteoporos Int 2014 Sep;25(9):2159-71.

Massera D, et al. Biochemical markers of bone turnover and risk of incident hip fracture in older women: the Cardiovascular Health Study. Osteoporos Int 2019 Sep;30(9):1755-1765.

*McCloskey EV, et al. Official positions for FRAX clinical regarding biochemical markers from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX. J Clin Densitom 2011 Jul-Sep;14(3):220-2.

National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases National Resource Center. Osteoporosis overview. October 2019. [https://www.bones.nih.gov/health-info/bone/osteoporosis/overview] accessed 06/04/24.

*North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement. Menopause. J N Amer Menopause Society 2010;17(1):23-56.

*Prestwood KM, et al. Ultralow-dose micronized 17beta-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 2003 Aug 27;290(8):1042-8.

*Romero Barco CM, et al. Biochemical markers in osteoporosis: usefulness in clinical practice. Rheumatol Clin 2012 May-Jun;8(3):149-52.

*Saad F, et al. Biochemical marker of bone turnover and clinical outcomes in men with prostate cancer. Urol Oncol 2012 July;30(4):369-378.

*Sculz P. The role of bone turnover markers in monitoring treatment in postmenopausal osteoporosis. Clin Biochem 2012 Aug;45(12):907-19.

Sivapalan P, et al. Bone turnover biomarkers in COPD patients randomized to either a regular or shortened course of corticosteroids: a substudy of the randomized controlled CORTICO-COP trial. Respiratory Research 2020;21:263.

Solling AS, et al. The predictive value of bone turnover markers during discontinuation of alendronate: the PROSA study. Osteoporos Int 2021 Aug;32(8):1557-1566.

Stewart CC, et al. Bone turnover markers as surrogates of fracture healing after intramedullary fixation of tibia and femur fractures. Bone Joint Res 2022 Apr;11(4):239-250.

*Terreni A, et al. Biochemical markers in the follow-up of the osteoporotic patients. Clin Cases Miner Bone Metab 2012 May;9(2):80-4.

*U.S. Preventive Services Task Force (USPSTF). Osteoporosis to Prevent Fractures: Screening. June 2018 [https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/osteoporosis-screening#fullrecommendationstart] accessed 06/04/24.

*Valimaki MJ, et al. Effects of risedronate 5 mg/d on bone mineral density and bone turnover markers in late-postmenopausal women with osteopenia: a multinational, 24-month, randomized, double-blind, placebo-controlled, parallel-group, phase III trial. Clin Ther 2007 Sep;29(9):1937-49.

*Vergnaud P, et al. Is the predictive power of previous fractures for new spine and non-spine fractures associated with biochemical evidence of altered bone remodeling? The EPOS study. European prospective osteoporosis study. Clin Chim Acta 2002 Aug;322(1-2):121-32.

Vlot MC, et al. Gender-affirming hormonal treatment decreases bone turnover in trans women and older trans men. Bone Min Res 2019 Oct;34(10):1862-1872.

Voulgaridou G, et al. Vitamin D and calcium in osteoporosis, and the role of bone turnover markers: a narrative review of recent data from RCTs. Diseases 2023 Feb 8;11(1):29.

*Yoon BH and Yu W. Clinical utility of biochemical marker of bone turnover: fracture risk prediction and bone healing. J Bone Metab 2018 May;25(2):73-78.

*Wheater G, et al. The clinical utility of bone marker measurements in osteoporosis. J Transl Med 2013 Aug 29;11:201.

*Key Article

KEY WORDS

Bone resorption, Collagen cross links, NTx, ITCP.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD#190.19) for Collagen Crosslinks, any method. Please refer to the following NCD website for Medicare Members: [http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=96&ncdver=1&bc=AgAAgAAAAAAA&] accessed 06/04/24.