MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Biochemical Markers of Bone Turnover**
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Category	**Technology Assessment**
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Product Disclaimer	• *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

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:

I. Monitoring treatment for osteoporosis or other conditions associated with increased bone turnover; or

II. 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.

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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.

Updated guidelines from the National Osteoporosis Foundation (2013) indicate that biochemical marker changes in individuals must exceed the least significant change in order to be clinically meaningful. The least significant change is specific to the biomarker being utilized, which is calculated by multiplying the "precision error" of the specific biochemical marker (laboratory provided) by 2.77 (95% confidence level). Biological variability can be reduced by obtaining samples in the early morning after an overnight fast. Serial measurements should be made at the same time of day. In order to have any clinical validity, sequential testing must be performed at the same laboratory.

In 2010, the North American Menopause Society issued an updated position statement on management of osteoporosis in postmenopausal women, asserting that, "the routine use of biochemical markers of bone turnover in clinical practice is not generally recommended." The guidelines explain that bone turnover markers vary from day to day, are affected by food intake and time of day, and lack assay standardization, limiting their clinical utility. Although some clinicians have found that biochemical markers can encourage adherence to therapy, several trials have found no difference in adherence when marker values are communicated to women.

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)

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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)

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

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*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 08/04/23.