BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.15 Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated With High Bone Turnover

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2023

Policy Review/Revision Date: New Policy

Related Policies:

6.01.01 - Bone Mineral Density Studies
6.01.44 - Vertebral Fracture Assessment with Densitometry

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

Description

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

OBJECTIVE

The objective of this review is to assess whether the measurement of bone turnover markers to manage individuals with osteoporosis or other diseases associated with high bone turnover improves the net health outcome.

POLICY STATEMENT

Measurement of bone turnover markers is considered **not medically necessary** to determine fracture risk in individuals with osteoporosis or with age-related risk factors for osteoporosis.

Measurement of bone turnover markers is considered **not medically necessary** to determine response to therapy in individuals who are being treated for osteoporosis.

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Several tests for bone turnover markers have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Examples are listed in Table 1. FDA product codes: NEO, JMM, CIN.

Table 1. FDA-Cleared Tests for Bone Turnover Markers

Test	Manufacturer	Year	Indication
Pyrilinks	Metra Biosystems	1995	Collagen type 1 cross-link, pyridinium
Osteomark	Ostex International	1996	Cross-linked N-telopeptides of type 1 collagen
Serum CrossLaps ELISA	Immunodiagnostic Systems	1999	Hydroxyproline
Ostase	Beckman Coulter	2000	Bone-specific alkaline phosphatase
N-MID Osteocalcin One-Step ELISA	Osteometer BioTech	2001	Osteocalcin
Elecsys N-MID Osteocalcin	Roche Diagnostics	2005	Osteocalcin
IDS-iSYS Ostase BAP	Immunodiagnostic Systems	2020	Bone-specific alkaline phosphatase

ELISA: enzyme-linked immunosorbent assay; FDA: U.S. Food and Drug Administration.

RATIONALE

Summary of Evidence

For individuals with osteoporosis or risk factors for age-related osteoporosis who receive a measurement of bone turnover markers to determine fracture risk, the evidence includes observational studies on the association between markers and osteoporosis and fracture risk, and systematic reviews of those studies. Relevant outcomes are test validity and morbid events. Few studies have directly addressed whether any bone turnover markers beyond bone mineral density (BMD) measurements are independent predictors of fracture risk. One meta-analysis investigated the independent role of bone turnover markers in fracture risk prediction and found a statistically significant but modest association between bone turnover markers (specifically, procollagen type 1 N-terminal propeptide and cross-linked C-telopeptide) and future fracture risk after adjusting for BMD and clinical risk factors. Other studies have suggested that bone turnover marker levels may be independently associated with osteoporosis and fracture risk in some groups, but there is insufficient evidence reporting on an association with any specific marker. Questions remain whether bone turnover markers are sufficiently sensitive to determine reliably individual treatment responses. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being treated for osteoporosis who receive a measurement of bone turnover markers to determine response to therapy, the evidence includes an observational study, randomized controlled trials (RCTs), and a systematic review of these RCTs. Relevant outcomes are test validity and morbid events. There is limited evidence on the impact of bone turnover markers on the management of osteoporosis. Individual RCTs and a systematic review of these RCTs have not found that feedback on bone turnover marker improves treatment adherence rates. No studies were identified that evaluated whether the use of bone turnover markers leads to management changes that are expected to improve outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with conditions associated with high rates of bone turnover other than age-related osteoporosis (eg, primary hyperparathyroidism, Paget disease, renal osteodystrophy) who receive a measurement of bone turnover markers, the evidence includes observational studies on the association between markers and disease activity and a systematic review of those studies. Relevant outcomes are 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 the measurement of bone turnover markers can change patient management or improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

The North American Menopause Society

In 2021, the North American Menopause Society (NAMS) issued a position statement on the management of osteoporosis in postmenopausal women.[19,] Per the NAMS:

- "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."
- "Although changes in bone turnover markers are used by some specialists to assess adherence and effectiveness of therapy, routine use of bone markers is not recommended."

The Endocrine Society

In 2019, guidelines from the Endocrine Society recommended that in postmenopausal women with a low BMD and at high-risk of fractures who are being treated for osteoporosis, monitoring should be conducted by dual-energy X-ray absorptiometry (DXA) at the spine and hip every 1 to 3 years.[20,] The Society considers measuring bone turnover markers (serum C-telopeptide [CTX] for antiresorptive therapy or procollagen type 1 N-terminal propeptide [PINP] for bone anabolic therapy) as an alternative way of monitoring for poor response or nonadherence to therapy. The Society notes that there is uncertainty over what constitutes an optimal response to treatment, but some experts suggest that a meaningful change is approximately 40% when compared from before to 3 to 6 months after starting treatment. A guideline update was published in 2020, in which the statements concerning measurement of bone turnover markers remained unchanged.[21,]

The Endocrine Society also published guidelines regarding the management of Paget disease in 2014.[22,] The guideline states:

- "We recommend measurement of serum total alkaline phosphatase or, when warranted, a more specific marker of bone formation or bone resorption to assess the response to treatment or evolution of the disease in untreated patients."
- "In patients with monostotic disease who have a normal serum total alkaline phosphatase, we suggest that a specific marker of bone formation and bone resorption be measured, although these may still be normal. Serial radionuclide bone scans may determine the response to treatment if the markers are normal."
- "In assessing the response to treatment: "For most patients, measurement of total ALP [alkaline phosphatase] or other baseline disease activity markers at 6 to 12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option."

The American Association of Clinical Endocrinologists and the American College of Endocrinology

The 2020 guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) gave a Grade B recommendation to consider using bone turnover markers for assessing patient compliance and therapy efficacy.[23,] AACE/ACE reviewed evidence that markers respond quickly to therapeutic intervention, and changes in markers have been associated with bone response to therapy and fracture risk reduction.

National Osteoporosis Foundation

In 2014, the National Osteoporosis Foundation published its guidelines on the prevention and treatment of osteoporosis to prevent fractures.[24,] Regarding biochemical markers of bone turnover, the guidelines stated:

Biochemical markers of bone turnover can

- "Aid in risk assessment and serve as an additional monitoring tool when treatment is initiated", and
- "Be repeated to determine if treatment is producing expected effect."

"Biochemical markers of bone turnover may

- Predict risk of fracture independently of bone density in untreated patients
- Predict rapidity of bone loss in untreated patients
- 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
- 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 Society for Clinical Densitometry

In 2011, a joint statement by the International Society for Clinical Densitometry (ISCD) and the International Osteoporosis Foundation on the Fracture Risk Assessment Model (FRAX) fracture risk prediction algorithms indicated that the "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."[25,]

In the 2019 ISCD position statement on repeating measurement of BMD when monitoring with DXA, there is a comment on bone turnover markers: "Serial BMD testing in combination with clinical assessment of fracture risk, bone turnover markers, and other factors...can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines."[26,]

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2018) recommended screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older.[27,] The Task Force recommended screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool. The recommendations on osteoporosis screening addressed DXA testing but did not mention bone turnover markers.

Medicare National Coverage

In November 2002, the Centers for Medicare & Medicaid Services issued a national coverage determination on collagen cross-links.[28,] The Centers for Medicare & Medicaid Services identified a set of clinical conditions for which collagen cross-links would be considered eligible for coverage. The decision is limited to urine-based collagen cross-link tests and does not address serum-based collagen cross-link tests.

Previously, the *Federal Register* (2001) noted that Medicare carriers have the discretion to make their own determinations on the medical necessity of serum-based collagen cross-link tests for assessing or monitoring bone loss therapy.[29,] The *Federal Register* also noted that the U.S. Food and Drug Administration approved 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.

Note that the Centers for Medicare & Medicaid Services 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through November 23, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. FEP 2024 Benefit change. New FEP Policy.