

COLLAGEN CROSSLINKS AND BIOCHEMICAL MARKERS OF BONE TURNOVER

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[Instructions for Use](#) ⓘ

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Related Policies

None

APPLICABLE LINES OF BUSINESS/PRODUCTS

This policy applies to Oxford Commercial plan membership.

NON-COVERAGE RATIONALE

Serum or urine collagen crosslinks or biochemical markers are unproven and not medically necessary to assess risk of fracture, predict bone loss or assess response to antiresorptive therapy.

There is insufficient evidence in the clinical literature that current methods for measuring 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 or improves health outcomes such as reducing fracture rates.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
82523	Collagen cross links, any method

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DESCRIPTION OF SERVICES

Bone turnover markers are biochemical markers of either bone formation or bone resorption. Commercially marketed tests are available to assess some of these markers in urine and/or serum by high performance liquid chromatography (HPLC) or immunoassay.

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.

Biochemical markers of bone turnover in the serum or urine are sometimes used to assess risk of fracture, predict bone loss or assess response to antiresorptive therapy. Biochemical markers such as pyridinoline and telopeptides and

urinary cross linked N-telopeptide of type I collagen (NTx) (which measure bone resorption) and osteocalcin and bone alkaline phosphatase (which measure bone formation) are obtained through minimally invasive tests involving serum and urine, making biochemical markers an attractive method for determining risk of fracture and for osteoporosis management. Specifically, the information obtained could potentially be used to measure the rate of bone loss, assist in determining osteoporosis management, monitor changes in bone metabolism and density resulting from therapy, and manage osteoporosis therapy as needed for the individual patient. Biochemical markers are controversial because of the complexity of interpreting the values for individual patients related to the intricacies inherent in bone metabolism, and the lack of standardization, which has led to unacceptable levels of variation between processing laboratories.

CLINICAL EVIDENCE

A systematic review published in 2012 by Biver and colleagues reviewed the literature on bone turnover markers for diagnosing osteoporosis and predicting fracture risk. To be included in the review, studies needed to report at least one bone turnover marker and report either BMD or fracture assessment. In post-menopausal women, the markers that have been studied the most and also have the strongest negative correlations with BMD are alkaline phosphatase (ALP), osteocalcin (OC), type 1 cross-linked C-telopeptide (CTx), and type 1 cross-linked N-telopeptide (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 3 studies were pooled, there was not a statistically significant mean difference in OC levels in patients with and without vertebral fractures. 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 is low due to patient variability and other factors that can influence bone turnover marker levels.

In a review of current methodologies for osteoporosis prevention, screening, and treatment, Kling et al. (2014) noted that biochemical markers can be used to identify the balance of bone formation and resorption; these are useful for aiding in osteoporosis diagnosis and monitoring treatment response. High bone turnover, reflected by elevated marker levels, might predict fracture development. The authors concluded that given limitations such as biologic variability and difference in assays, these markers are not yet included in algorithms that calculate fracture risk, but they are being used to monitor osteoporosis treatment.

Parviainen et al. (1999) studied the clinical usefulness of urinary bone resorption markers in postmenopausal women with symptomatic osteoporosis in a randomized double-blind placebo controlled study in which patients were daily treated for 24 months either with a hormone analogue plus 800 mg calcium (n = 14), or with placebo plus 800 mg calcium (n = 19). All resorption markers decreased for both groups during the 2 years the study was conducted. After 2 years there was, however, a significant increase in bone density both in the spine and in the femoral neck in the women with hormone treatment. In the control group a significant increase (P = 0.0012) in the spine, whereas a non-significant decrease in the femoral neck was observed. The investigators concluded that measurement of urinary cross-linked peptides derived from Type I collagen (NTx and DPD) might be a useful biochemical method of observing the positive clinical effect (i.e., reduction in bone resorption) following hormone replacement therapy in postmenopausal fracture patients.

Marcus et al. (1999) assessed the associations of eight bone turnover markers (BTMs) with baseline and 1-year percentage changes in lumbar spine and hip bone mineral density (BMD) of 293 postmenopausal women undergoing treatment with hormone replacement therapy (HRT) (n=293) or placebo (n=54). In 239 women assigned to treatment with estrogen alone or with estrogen plus progestins (active treatment), mean percentage changes for all markers decreased significantly and remained below baseline values through 3 years of study, whereas mean percentage changes for 54 women assigned to the placebo group showed no significant change from baseline in any marker. The investigators concluded that BTMs are not a surrogate for BMD to identify women with low bone mass and that they offer little useful information for predicting BMD changes for individual untreated or HRT-treated postmenopausal women.

Trento et al. (2009) investigated the clinical role of the bone turnover markers type I collagen C telopeptide (CTX), osteocalcin (OC) and bone-specific alkaline phosphatase (BAP) in the assessment of bone status in 200 women with postmenopausal osteoporosis. Serum bone turnover markers were measured at the initial visit and correlated with spine and femur bone mineral density (BMD), determined on dual-energy X-ray absorptiometry. No correlation was found between serum levels of OC and BAP and vertebral or femur BMD when analyzed against biochemical markers of bone turnover and age, age at menopause, body mass index (BMI) and BMD. S-CTX levels were higher in women with osteoporosis than in women with normal or moderately low (osteopenic) values of BMD. The sensitivity and specificity versus spine BMD were 73.9% and 41.6% for s-CTX, 40.4% and 80.6% for BAP, and 68.3% and 39% for OC, respectively. The sensitivity and specificity versus femur BMD were 76.9% and 40.4% for s-CTX, 23.8% and

88.3% for BAP, and 80.4% and 53.3% for OC, respectively. The authors concluded that determination of s-CTX, BAP and OC is of limited clinical value in the initial evaluation of bone status in menopausal women.

Lukaszkiwicz et al. (2008) evaluated the correlation between bone resorption and bone formation markers to assess bone turnover rate and qualify an individual postmenopausal woman as a possible elevated bone turnover (EBT) subject. A total of 320 postmenopausal women were enrolled at seven clinical sites in this cross-sectional observational study. The group was a random sample of the population. BMD measurements of the lumbar spine, total hip, trochanter, and femoral neck regions were performed. Bone resorption and formation rates were evaluated by serum levels of C-terminal telopeptide of type I collagen (CTX) and osteocalcin (OC), respectively. Using logistic regression to correlate the concentrations of CTX and OC it was possible not only to distinguish the EBT subgroup, but also to construct a simple nomogram for easy classification of individual patients as possible EBT subjects. EBT patients showed generally decreased BMD values and increased bone formation and resorption rates. The investigators concluded that evaluation of both CTX and OC levels enables a more proper indication for EBT.

An observational study that included 432 Japanese elderly women who were not receiving any drug treatment for osteoporosis were followed for 5.2 ± 3.3 years. Vertebral fractures and bone mineral density were assessed at baseline and then at 1- to 2-year intervals or at indication of any symptom. Two types of collagen metabolites were measured at baseline: urinary N-terminal telopeptide of type I collagen (NTX), a marker of pyridinium cross-link, and urinary pentosidine, a nonenzymatic collagen cross-link produced by AGEs. A total of 97 incident vertebral fractures on 72 subjects were observed. Simple regression analysis using Cox's hazards model showed that log-transformed urinary NTX and pentosidine are significant risk factors for time-dependent incidence of vertebral fractures, in addition to the traditional risk factors (age, lumbar bone mineral density, and number of prevalent vertebral fractures). However, urinary excretion of pentosidine was a significant predictor of incident vertebral fracture after adjustment for other traditional risk factors. The present data suggest that AGE-related collagen cross-link is a novel risk for vertebral fracture. (Shiraki et al., 2008).

Perier and colleagues (2007) noted that Homocysteine (Hcy) has recently been described as an independent risk factor for osteoporotic fractures in the elderly. These investigators prospectively followed women belonging to the OFELY study during a mean follow-up of 10 years. Homocysteine was measured at baseline in 671 post-menopausal women from the OFELY cohort (mean age of 62.2 ± 9 years). Incident clinical fractures were recorded during annual follow-up and vertebral fractures were evaluated with radiographs every 4 years. A Cox proportional hazards model based on time to first fracture was used to calculate hazard ratios for quartiles of Hcy values. Mean Hcy was 10.6 ± 3.4 $\mu\text{mol/L}$, increasing with age. After adjustment for age, Hcy was significantly associated with physical activity, calcium intake, serum albumin and serum creatinine; but not with bone turnover markers and bone mineral density (BMD). During a mean follow-up of 10 years, 183 fractures occurred among 134 women. After adjustment for age, the overall relative risk of fracture for each one SD increment of Hcy was 1.03 (95% CI 0.87 - 1.31). Fracture risk was higher in women with Hcy in the highest quartile without adjustment but no longer after adjustment for age. The authors concluded that Hcy is not an independent risk factor of osteoporotic fractures in healthy post-menopausal women from the OFELY cohort with a broad age range.

Rhew et al. (2008) examined the relationship of baseline Hcy levels with BMD and incidence of fractures over 2 years in women with and without systemic lupus erythematosus (SLE). Women with SLE ($n = 100$) and without SLE ($n = 100$) were matched according to age (± 5 years), race, and menopausal status. Data were collected from 1997 to 2004, including hip, lumbar spine (L-spine), and distal forearm BMD, serum Hcy levels, and a self-administered questionnaire on osteoporosis risk factors, medications and symptomatic fractures at baseline and 2-year follow-up. Analyses were performed to compare Hcy levels, BMD, and incident fractures and to evaluate the relationship of Hcy with BMD and incident fractures in both groups. Mean Hcy \pm SD was higher ($p < 0.001$) in women with SLE (9.88 ± 3.8 $\mu\text{mol/L}$) than in women without SLE (7.98 ± 2.6 $\mu\text{mol/L}$). Women with SLE had significantly lower L-spine BMD Z-scores, while hip BMD Z-scores and distal forearm BMD T-scores were non-significantly lower than in women without SLE. No significant correlations were observed between Hcy and BMD in either group. A total of 13 women with SLE experienced new fractures, while four women without SLE had new fractures over 2 years ($p = 0.035$); however, there was no association between Hcy levels and incident fractures in either group. The authors concluded that women with SLE had significantly greater baseline Hcy, lower L-spine BMD, and more new fractures over 2 years, compared with women without SLE. However, Hcy levels were not significantly associated with BMD and did not predict new fractures in women with or without SLE over 2 years.

Several nonrandomized controlled trials also discussed the potential value of bone turnover markers (Meier, 2005; Worsfold, 2004; Garner, 2000; Iki, 2006). However, no outcomes studies were found in which patient management was changed by the results of bone turnover markers.

Bergmann et al. (2009) published evidence-based guidelines for the Belgian Bone Club on the use of biochemical markers for osteoporosis. The guidelines state that although the correlation between bone mineral density (BMD) and bone turnover markers (BTM is statistically significant), BTM cannot be used as predictive markers of BMD in an

individual patient. Both are independent predictors of fracture risk, but BTM can only be used as an additional risk factor in the decision to treat. Current data do not support the use of BTM to select the optimal treatment. However, they can be used to monitor treatment efficacy.

The National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases National Resource Center does not address bone remodeling, or biomarkers in relation to screening for osteoporosis and fracture risk.

The U.S. Preventive Services Task Force (USPSTF) 2011 recommendation on screening for osteoporosis does not include biochemical marker assessment of bone turnover as a diagnostic tool.

The National Institute for Health and Care Excellence (NICE) (2017) does not include biochemical markers in their recommendation for osteoporosis and assessing the risk of fragility fracture.

Professional Societies

The American Academy of Family Physicians (AAFP)

The AAFP 2015 guideline on diagnosis and management of osteoporosis does not address biochemical markers for the diagnosis and management of osteoporosis. (Jeremiah et al. 2015).

American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE)

In their 2016 clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis, the AACE and ACE (Camacho et al., 2016) remark that bone turnover markers (BTMs) can provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Although they alone cannot be used to diagnose osteoporosis, elevated BTM levels can predict more rapid rates of bone loss and are associated with increased fracture risk independent of bone marrow density (grade B; best evidence level 1, downgraded based on expert consensus). Their use in clinical practice, however, is limited by high in vivo and assay variability (e.g., urinary resorption markers), poor predictive ability in individual patients, and lack of evidence-based thresholds for clinical decision-making. Consider using BTMs for assessing patient compliance and therapy efficacy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction; significant increases indicate good response to anabolic therapy (grade B; best evidence level 1; downgraded based on expert consensus).

American College of Obstetricians and Gynecologists (ACOG)

An ACOG practice bulletin addresses the use of biochemical markers to predict bone turnover in osteoporosis. The guideline states that bone turnover markers cannot be used to diagnose osteoporosis, and the usefulness of markers as an incentive for adherence has been questioned. (ACOG, 2012; reaffirmed 2016).

International Osteoporosis Foundation (IOF)/National Osteoporosis Foundation (NOF)

The IOF and NOF (Cavalier et al., 2016) created a consensus paper on the role of biochemical markers of bone turnover in the management of metabolic bone diseases to address the controversial nature of the topic. They conclude that:

- In patients from both genders, suffering from osteoporosis, bone turnover markers (BTMs) alone cannot provide a substantial contribution to the diagnosis of the disease. However, if measurements of BTMs are properly conducted, in experienced facilities, they can contribute to a better appraisal of the underlying pathophysiological process and, in some cases, to confirm either adherence to treatment or to predict, to some extent, the long-term efficacy of the treatment.
- Particularly in elderly patients, comorbidities or co-prescriptions may significantly influence the level of BTMs, making their interpretation more convoluted. Therefore, their use as diagnostic tools in secondary osteoporosis, particularly in glucocorticoid-induced osteoporosis, remains in the authors' opinion highly equivocal.
- In other specific conditions like pregnant and lactating women, who might be affected by dramatic loss of bone or in intensive care, during which some conditions like severe burn injury may be associated with bone wasting, a condition which might be aggravated by hypo-dynamism, BTMs are considered as a positive tool to screen patients at high risk of bone alterations.
- The practical use of BTMs in clinical practice does not clearly appear. Eventually, with the new anti-osteoporosis chemical entities that are currently developed for the management of osteoporosis, BTMs may be difficult to interpret and to follow, as they may substantially change over time, reflecting the complex mechanism of action of these new therapies. BTMs remain today one of the less invasive approaches to better understand the dynamics of bone remodeling and, in some cases, to monitor the activity of medicines that interfere either with bone formation or bone resorption.

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

The IOF and the IFCC evaluated the clinical potential of bone turnover markers (BTMs) in the prediction of fracture risk and for monitoring treatment. Research evidence suggests that BTMs may provide information on fracture risk

independently from BMD, so that fracture risk prediction might be enhanced by their inclusion in assessment algorithms. The potential use of BTMs to predict the response to treatments for osteoporosis in the individual patient is also of great interest. Treatment-induced changes in specific markers account for a substantial proportion of fracture risk reduction. However, there is still a need for stronger evidence on which to base practice in both situations. IOF/IFCC recommends one bone formation marker (serum procollagen type I N propeptide, s-PINP) and one bone resorption marker (serum C-terminal cross-linking telopeptide of type I collagen, s-CTX) to be used as reference markers and measured by standardized assays in observational and intervention studies in order to enlarge the international experience of the application of markers to clinical medicine and to help resolve uncertainties over their clinical use. (Vasikaran et al., 2011).

National Osteoporosis Foundation (NOF)

In a general guidance statement, the NOF states that biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density 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
- Predict rapidity of bone loss in untreated patients
- 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) (NOF, 2014).

The North American Menopause Society (NAMS)

A NAMS guideline on managing osteoporosis in postmenopausal women states that the routine use of biochemical markers of bone turnover is not generally recommended (NAMS, 2010).

U.S. FOOD AND DRUG ADMINISTRATION

The FDA regulates commercially marketed tests and test systems such as bone markers and categorizes these test systems to one of three Clinical Laboratory Improvement Act (CLIA) of 1988 regulatory categories (i.e., waived, moderate, or high) based on their potential risk to public health. Commercially marketed tests that have received 510(k) marketing clearance can be accessed through the 510(k) database (search by manufacturer or test system name) or through the CLIA database search by manufacturer, test system, or analyte name). Laboratories that use their own tests but do not market the kits to others are subject to the standards of the Clinical Laboratory Improvement Act (CLIA), but not to FDA marketing regulations.

Information was not identified regarding FDA-approved osteoporosis treatments and the use of biochemical markers in the diagnosis of osteoporosis, or in the selection, dosing, or administration of these drugs. In addition, the FDA consumer-focused website publication on osteoporosis does not include biochemical markers in its list of diagnostic tests.

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0419N]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2018	<ul style="list-style-type: none"> • Reorganized policy template: <ul style="list-style-type: none"> ○ Simplified and relocated <i>Instructions for Use</i> ○ Removed <i>Benefit Considerations</i> section • Updated non-coverage rationale; modified language to clarify the listed services are unproven and not medically necessary • Archived previous policy version RADIOLOGY 006.2 T2

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state

mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

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