

# Collagen Crosslinks and Biochemical Markers of Bone Turnover

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Related Policies
None

## 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.

## 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 guideline 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 and Guidelines 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, 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

Crandall et al. (2018) performed a prospective case-control study that included 800 participants (400 cases with hip fracture and 400 matched controls) to determine the associations of serum C-terminal telopeptide of type one collagen (CTX) and serum procollagen type I aminoterminal propetptide (PINP) with hip fracture risk. This study was nested in the Women's Health Initiative (WHI) Observational Study, which enrolled participants across 40 US clinical centers. Ages for participants were 50-79 years with an absence of serious medical conditions. Information for the participants with hip fractures was collected by annual self questionnaires, but confirmed by medical record review. Participants in the control case group provided 12 hour fasting morning serum samples for CTX and PINP. The author analysis identified the serum CTX and PINP was not significantly associated with risk of hip fracture. Limitations of the study included the inability to adjust for bone mineral density since this study was part of the larger WHI study and no sample stability data regarding the stored serum samples. However the study had several strengths including prospective design, long- term follow up, medical record follow for fracture information and fasting serum samples. In summary, the authors concluded the results did not support the utility of serum CTX level or PINP level to predict hip fracture risk in women in this age group.

Jørgensen et al. (2017) investigated the associations between bone turnover markers, bone mineral density (BMD), and prevalent fragility fracture in a cohort of kidney transplantation candidates. Volumetric BMD of spine and hip was measured by quantitative computed tomography. Parathyroid hormone (PTH), bone-specific alkaline phosphatase, procollagen type-1 N-terminal propeptide, tartrate resistant alkaline phosphatase, and C- and N-terminal telopeptides of type 1 collagen were analyzed from fasting morning blood samples. Fragility fractures included prevalent vertebral fractures and previous low-trauma clinical fractures. The fracture prevalence was 18% in 157 adult kidney transplant candidates. Fractured patients had reduced BMD and Z-score at both spine and hip. Levels of bone turnover markers were significantly higher in patients on maintenance dialysis than in pre-dialysis patients; but did not differ between patients with and without fracture. There were strong, positive correlations between PTH and all bone turnover markers. PTH was negatively associated with Z-score at lumbar spine and total hip; in contrast, bone turnover markers were only negatively associated with total hip Z-score. The results showed that bone turnover markers were negatively associated with bone density, but not associated with prevalent fracture in kidney transplantation candidates. The role of bone turnover markers in assessing bone fragility in CKD requires further investigation.

In a systematic review, Greenblatt et al. (2017) evaluated BTMs in the diagnosis and monitoring of metabolic bone disease (most notably osteoporosis). Testing using BTMs has to take into account the large number of preanalytic factors and comorbid clinical conditions influencing BTM levels. BTMs respond rapidly to changes in bone physiology, therefore, they have utility in determining patient response to and compliance with therapies for osteoporosis. However, they concluded that although BTMs are a useful adjunct for the diagnosis and therapeutic monitoring of bone metabolic disorders, their use has to be tempered by the known limitations in their clinical utility and preanalytic variables complicating interpretation. Glendenning et al. (2018) drew similar conclusions regarding the clinical usage of BTMs, noting that data is inconsistent.

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.

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).

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

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.

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.

A position statement from the National Bone Health Alliance Working Group (2014) support the continued use of bone mineral density (BMD) testing and FRAX for diagnosis of osteoporosis; there is no recommendation for biochemical marker use.

The National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases National Resource Center (2015) does not address bone remodeling, or biomarkers in relation to screening for osteoporosis and fracture risk.

The U.S. Preventive Services Task Force (USPSTF) 2018 final recommendation on screening for osteoporosis to prevent fractures 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.

The North American Menopause Society (NAMS) position statement on the management of osteoporosis in postmenopausal women (2010) states that bone turnover markers cannot diagnose osteoporosis and have varying ability to predict fracture risk when studied in groups of patients in clinical trials.

The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) evaluated the clinical potential of bone turnover markers (BTMs) in the prediction of fracture risk and for monitoring treatment. They found the research evidence suggestive 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. 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. The 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).

The IOF and the National Osteoporosis Foundation (NOF) 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 of both genders suffering from osteoporosis, bone turnover markers (BTMs) alone cannot provide a substantial contribution to the diagnosis of the disease. In addition, 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. Finally, 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 (Cavalier et al., 2016).

Collagen crosslinks and bone turnover biomarkers are tests that are considered controversial, but emerging in management of osteoporosis. While they may help add to the prediction of a risk for fracture, these tests lack standardization. There is insufficient clinical evidence to consider them useful therefore additional studies and clinical trials are needed to demonstrate their efficacy.

## Professional Societies

### *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).

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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. For additional information see: <https://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118551.htm> (Accessed January 30, 2019).

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## Guideline History/Revision Information

Date	Summary of Changes
01/01/2021	<b>Template Update</b> <ul style="list-style-type: none"><li>Reformatted policy; transferred content to new template</li></ul>
05/01/2020	<b>Coverage Rationale</b> <ul style="list-style-type: none"><li>Replaced language indicating “serum or urine collagen crosslinks or biochemical markers are unproven and not medically necessary <i>for any indication due to insufficient evidence of efficacy</i>” with “serum or urine collagen crosslinks or biochemical markers are unproven and not medically necessary <i>to assess risk of fracture, predict bone loss, or assess response to antiresorptive therapy</i>”</li></ul> <b>Supporting Information</b> <ul style="list-style-type: none"><li>Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current information</li><li>Archived previous policy version MMG023.H</li></ul>

## Instructions for Use

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare 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 guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member’s benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.