

# Collagen Crosslinks and Biochemical Markers of Bone Turnover

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[Instructions for Use](#)

Table of Contents	Page
<a href="#">Coverage Rationale</a> .....	1
<a href="#">Applicable Codes</a> .....	1
<a href="#">Description of Services</a> .....	1
<a href="#">Clinical Evidence</a> .....	2
<a href="#">U.S. Food and Drug Administration</a> .....	8
<a href="#">References</a> .....	8
<a href="#">Policy History/Revision Information</a> .....	10
<a href="#">Instructions for Use</a> .....	10

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 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 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.

Even after growth is completed, bones are 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 serum and urine samples, making them a potentially attractive method for determining risk of fracture and for the management of osteoporosis. 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. While these are frequently used in research studies, the use of biochemical markers in clinical practice is 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

The utility of collagen crosslinks and bone turnover biomarkers tests is disputed, but their use is emerging for the 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 in clinical practice and proven to improve patient care; therefore, additional studies and clinical trials are needed to demonstrate their efficacy.

Orford et al. (2024) conducted a randomized control trial to measure the effects of antiresorptive agents on bone turnover markers (BTMs) in critically ill women aged fifty years or greater. BTMs and bone mineral density (BMD) were monitored for 1 year. Out of 253 patients, 18 patients (9 were randomized to denosumab, 7 to placebo, and 2 to zoledronic acid) were enrolled over 35 months before stopping the study due to the COVID-19 pandemic. Of the 18 participants, 10 (56%) completed 1-year follow-up. The authors findings identified antiresorptive medications decreased the BTM type 1 cross-linked c-telopeptide (CTX) from day 0 to 28 by 43%, compared to an increase of 26% observed with placebo. Mixed linear modelling revealed differences in the month after trial drug administration between the groups in serum CTX, alkaline phosphatase, parathyroid hormone, and phosphate. Change in BMD between antiresorptive and placebo groups was not statistically analyzed due to small sample size. No serious adverse events were reported. The authors concluded, in critically ill women aged 50-years and over, antiresorptive agents suppressed bone resorption markers without serious adverse events. Larger clinical trials in the critical illness setting should be conducted to define the efficacy and safety of antiresorptive agents and effect on bone mineral density and fracture over at least 1-year of follow-up. The limitations in the study included the small sample size, the limiting statistical analysis, and the interpretation of the results.

Yoo et al. (2023) conducted a study to investigate real-world data of C-terminal telopeptide (CTX), propeptide of type I collagen (P1NP), and osteocalcin through a multicenter clinical study, and retrospectively analyzed the usefulness of bone turnover markers (BTMs) in Koreans. The selection criteria included pre- and post-menopausal patients with osteoporosis. Patient classifications included demographic characteristics and BTM (CTX, P1NP, and osteocalcin) concentrations. The authors findings among women with no history of fractures, the levels of P1NP (n = 2,100) were  $43.544 \pm 36.902$ , CTX (n = 1,855) were  $0.373 \pm 0.927$ , and osteocalcin (n = 219) were  $10.81 \pm 20.631$ . Among men with no history of fractures, the levels of P1NP (n = 221) were  $48.498 \pm 52.892$ , CTX (n = 201) were  $0.370 \pm 0.351$ , and osteocalcin (n = 15) were  $7.868 \pm 10.674$ . Osteoporosis patients treated with teriparatide had an increase in P1NP levels after 3 months in both men and women, and a 50% increase was observed in women. Similarly, osteoporosis patients treated with denosumab decreased the CTX levels after 3 months in both men and women, with a reduction of 50% observed in women. The authors concluded results of this study can contribute to the specific evaluation of bone turnover status in the Korean population. In addition, the study provides P1NP levels in the Korean population for future comparative studies with other populations.

Voulgaridou et al. (2023) performed a review of randomized controlled trials (RCTs) to investigate the effects of vitamin D and calcium supplementation separately and in combination, on bone density and circulating serum and blood plasma vitamin D, calcium (Ca), parathyroid hormone (PTH) levels, markers of bone metabolism concentrations, and clinical outcomes, such as falls and osteoporotic fractures (OF). Out of 259 studies, 26 studies met the inclusion criteria. The authors results identified that circulating 25(OH)D levels increased after vitamin D supplementation alone or in combination with calcium. Additionally, calcium with vitamin D supplementation, but not vitamin D alone, leads to an increase in bone mineral density, while no significant differences were documented for the reduction in the risk of total fractures. No significant changes were identified in circulating levels of plasma bone metabolism markers, nor in the incidence of falls. In the groups receiving vitamin D and/or Ca supplementation there was a decrease in blood serum PTH levels. The authors concluded that Vitamin D supplementation, alone or in combination with Ca, is considered as being fundamental to enhancing the positive effects of any therapy in patients, who are more fragile and at higher risk of vertebral and non-vertebral fragility fractures due to disorders related to bone metabolism (e.g., osteoporosis or vitamin D deficiency). However, further studies are needed to determine appropriate dosing regimens for the treatment of osteoporosis and the role of bone metabolism markers. Limitations identified were the short duration studies, small sample sizes, no placebo comparator during the study period, gender bias, ethnic-related differences and vitamin-D drug interactions.

Jia and Cheng (2022) conducted a study to investigate the correlation between risk factors of postmenopausal osteoporotic (PMOP) fracture, BMD, and BTMs, lipid metabolism and body mass index (BMI). Data from 128 patients with postmenopausal osteoporotic fractures was collected. The Cox proportional hazard model was used to conduct univariate and multivariate analysis to screen the risk factors related to postmenopausal osteoporotic fractures. Blood samples were

collected, which included blood lipids (TC, TG, HDL-C, LDL-C), and immunodetection of biochemical markers of bone turnover: serum cathepsin K (CatheK), type II procollagen amino-terminal propeptide (PINP),  $\beta$ -collagen degradation products ( $\beta$ -crosslaps), osteocalcin and tartrate-resistant acid phosphatase (TRAP). BMI of the survey subjects was measured, BMD was detected, and its correlation with lipid metabolism was analyzed. The authors results identified the correlation study with lipid metabolism found that the smaller the BMI value and TG, the greater the BMD loss, exhibiting a downward trend. No significant correlation was observed between HDL-C and LDL-C content ( $p > 0.05$ ). Femoral neck and lumbar spine BMD were negatively correlated with CatheK, serum osteocalcin, PINP,  $\beta$ -crosslaps and TRAP. The authors concluded biochemical markers of bone turnover are highly expressed in postmenopausal women and increase with the decrease of bone density. Additionally, BMD severity, years since menopause, history of hysterectomy or ovariectomy, age, and number of deliveries, are important risk factors for osteoporotic fractures. Further studies should be conducted due to limitations of small sample size and patients' age.

Borgen et al. (2022) completed a prospective cohort study to explore: (i) cut-off values of procollagen type 1 N-terminal propeptide (P1NP) and C-terminal cross-linking telopeptide of type 1 collagen (CTX) that discriminate best patients' adherence to antiresorptive drugs (ARD); (ii) cut-off values of P1NP and CTX that best predict treatment effects in terms of BMD change; (iii) whether P1NP and CTX predict fracture risk during follow-up of patients using and not using ARD; and (iv) variation in BTMs by daytime in patients using or not using ARD. A total of 228 patients (82.2% women) were evaluated for ARD indication after a fragility fracture and were followed for a mean of 4.6 years (SD 0.5 years). BTM was measured at 1-year and 2-year follow-up. At baseline, 18 patients (9%) were already on ARD, and an additional 140 started ARD [alendronate ( $n = 121$ ), denosumab ( $n = 15$ ), and zoledronic acid ( $n = 22$ )]; hence, 158 patients (69%) had prescribed ARD after baseline assessment, whereas 70 patients had no ARD prescribed because they did not have treatment indication (T-score  $> -1.5$  or FRAX-score for MOF  $< 20\%$ ). After 2-year follow-up, 145 of 158 patients were still on ARD [alendronate ( $n = 113$ ), denosumab ( $n = 15$ ), and zoledronic acid ( $n = 18$ )]. Nine patients died during the total observation time of 4.6 years, but no one died during the first 2 years of follow-up. The authors concluded that (i) P1NP and CTX levels below 30 and 0.25  $\mu\text{g/L}$  yield the best discrimination between patients using or not using ARD; (ii) P1NP and CTX levels below 30 and 0.25  $\mu\text{g/L}$  yielded the best prediction for BMD gains after 2 years of ARD treatment; (iii) P1NP can predict fractures in patients on ARD; and (iv) assessment of BTM can be extended to the whole day in patients on ARD. Thus, BTM constitute a valuable supplement to DXA assessment of effects of osteoporosis treatment and might replace DXA in some instances. However, DXA is still needed for decisions with respect to diagnosis, assessment of treatment goals, and treatment pauses. There are several limitations to this study. Patients in the group not using ARD were healthier and younger and had no indication for ARD. Fasting status was not ensured in the patients, and the BTM were not measured at the same year of follow-up in all patients. The authors did not measure BTM in the same patients at different time points of the day, and P1NP and CTX were measured using only the automated electrochemiluminescence immunoassays by Roche. Although the results are promising, the small sample size and lack of a comparison group limit the generalizability of the findings. Further research with randomized controlled trials is needed.

Slaven et al. (2022) conducted a case-control study to analyze changes in serum markers of bone turnover across multiple decades in osteoporotic women compared with non-osteoporotic controls, to determine their utility as potential predictors for osteoporosis. The study consisted of a convenience sample of 20 osteoporotic patients and 20 control patients, matched by age and BMI. Serum samples were obtained from 20 women given the diagnosis of osteoporosis after age 46 years and 20 age-matched women with normal bone mineral density from 4 time points in their life (ages 25–31, 32–38, 39–45, and 46–60 years). Serum levels of bone turnover markers (propeptide of type I collagen, parathyroid hormone, bone-specific alkaline phosphatase, osteocalcin, C-terminal telopeptide of type I collagen, sclerostin, osteoprotegerin, osteopontin, and 25-OH vitamin D) were measured using commercially available arrays and kits. Logistic regression was used to assess these individual serum markers as potential predictors of osteoporosis, and mixed-effects modeling to assess the change in bone turnover markers between osteoporotic and control groups over time, then performed fivefold cross-validation to assess the classification ability of the models. Markers of bone turnover, bone-specific alkaline phosphatase, C-terminal telopeptide of type I collagen, sclerostin, and osteocalcin were all independent predictors at multiple time points; osteopontin was an independent predictor in the 39- to 45-year age group. Receiver operating characteristic analyses demonstrated moderately strong classification ability at all time points. Sclerostin levels among groups diverged over time and were higher in the control group than the osteoporotic group, with differences observed at time points 3 and 4. The authors concluded that serum biomarker testing has the potential to serve as a screening tool that detects biochemical evidence of increased bone turnover at an age young enough to intervene meaningfully and prevent critical loss of bone mass. Although prospective validation is necessary before recommending widespread clinical use, this information may be used to identify patients at risk for developing low bone mineral density long before traditional screening would take place. This study was designed to test the early diagnostic capability of these biomarker profiles as they relate to osteoporosis; subsequent investigations must be performed with a larger number of subjects, and they should go through a validation process before clinical use. A small sample size ( $n = 20$ ) makes it difficult to decide whether these conclusions can be generalized to a larger population. Further investigation is needed before clinical usefulness of this procedure is proven.

A randomized controlled trial was performed by Stewart et al. (2022) to determine whether 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 include 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.

Li et al. (2021) conducted a cross-sectional study to identify the levels of serum periostin in Chinese postmenopausal women with different bone mass, and the correlations between the periostin levels and the classical BTMs, and BMDs at different sites. A total of 331 Chinese postmenopausal women in Shanghai were enrolled in this study; their clinical features were collected; their levels of serum periostin and traditional BTMs were measured by ELISA or the fully automated immunoassay analyzer; their BMDs at different sites were measured by dual-energy X-ray absorptiometry (DEXA). According to the T-value of BMD, these postmenopausal women were divided into three groups: normal group ( $n = 84$ ), osteopenia group ( $n = 126$ ) and osteoporosis group ( $n = 121$ ). There was no difference noted in the serum periostin levels among the above three groups of subjects. Spearman correlation analysis revealed no correlation observed between the value of serum periostin and those of traditional BTMs, and BMDs at different sites, respectively. The values of traditional BTMs were negatively correlated with those of BMDs at all measured sites. Furthermore, the receiver-operating characteristic (ROC) curves analysis indicated that among the periostin and traditional BTMs mentioned above, the best predictors for postmenopausal osteoporosis in Shanghai Chinese postmenopausal women were osteocalcin (OC) and procollagen type 1 N-terminal propeptide (P1NP) [the areas under the ROC curve (AUC) = 0.746 and 0.761, respectively]. The authors concluded that serum periostin may not be used as a marker of systemic bone metabolism in Shanghai Chinese postmenopausal women without prior fracture. In addition, serum P1NP and OC levels may be the predictors of osteoporosis occurrence in Chinese postmenopausal women. Limitations to this study include a small and unequal number of postmenopausal women among the three groups. In addition, there is no follow-up to observe the changes in serum periostin, traditional BTMs and BMD in postmenopausal women over time. Long-term evaluations of the results and prospective randomized studies are still needed.

Ma et al. (2021) conducted a prospective RCT to investigate the clinical value of perioperative BTM monitoring to guide the treatment of osteoporosis in postmenopausal females after total knee arthroplasty (TKA) from April 2017 to December 2018. The study included a total of 64 patients, divided into two groups: monitoring group ( $n = 32$ ) and a control group ( $n = 32$ ). The patients were given oral medication (alendronate, calcitriol, and calcium), and followed for one year. In the monitoring group, serum BTMs [C-telopeptide of type I collagen (CTX-I), N-terminal propeptide of type I procollagen (PINP), and 25(OH)D] were assessed preoperatively and repeated postoperatively; alendronate was withdrawn when CTX-I and PINP reached the reference interval; and calcitriol and calcium were withdrawn when 25(OH)D reached the reference interval. In the control group, oral medication was implemented for a uniform duration of 3 months. During the 1-year follow-up, the mean maximum total point motion (MTPM) of the tibial component, BMD, visual analog scale (VAS) score, range of motion, and Oxford Knee Score (OKS) score were obtained. In the monitoring group, BTM monitoring prolonged the medication duration, but did not cause more adverse reactions than in the control group. The mean MTPM values at 6 m and 12 m in the monitoring group were lower than those in the control group, and the BMD at 12 m in the monitoring group was significantly higher than that in the control group. Patients in the monitoring group had lower VAS scores at 6 m and higher OKS scores at 6 m and 12 m than those in the control group. The authors concluded that the application of BTM monitoring to guide the treatment of osteoporosis can enhance bone density, maintain prosthesis stability, and improve surgical outcome in postmenopausal females with osteoporosis undergoing primary TKA. Limitations include small sample size and short-term follow-up which did not allow for assessment of long-term outcomes. In addition, several patients in the study were non-compliant with follow-up and/or refusal to provide blood samples post-operatively. Further research is needed to determine the clinical relevance of these findings.

A sub-analysis of a randomized controlled trial was performed by Curtis et al. (2021) to evaluate markers of maternal bone resorption, urinary C-terminal telopeptide of type I collagen (CTX), influence of gestational vitamin D supplementation, and associations between CTX and maternal postnatal bone indices across pregnancy. MAVIDOS (the Maternal Vitamin D Osteoporosis Study) is a randomized, double-blind, placebo-controlled trial of 1000 IU cholecalciferol/d compared with placebo from 14 weeks of gestation to birth. Maternal second-void urinary  $\alpha$ - and  $\beta$ -CTX were measured (ELISA) at 14 and 34 weeks of gestation; DXA was performed within 2 weeks postpartum. The Mann–Whitney Rank Sum test, Spearman’s rank correlation, and linear regression were used to compare median CTX values within and between groups from early to late pregnancy, and associations with maternal bone outcomes. In total, 372 women had CTX and 25-hydroxyvitamin D [25(OH)D] measured in early and late pregnancy. CTX at 14 and 34 weeks of gestation were correlated in both placebo ( $r = 0.31$ ) and cholecalciferol ( $r = 0.45$ ) groups ( $p < 0.0001$ ). Median CTX increased from 14 to 34 weeks of gestation in both groups ( $n = 372$  total) [placebo ( $n = 188$ ): from 223.6 to 449.7  $\mu\text{g}/\text{mmol}$  creatinine; cholecalciferol ( $n = 184$ ): from 222.3 to 419.3  $\mu\text{g}/\text{mmol}$  creatinine;  $p = 0.03$  for placebo compared with cholecalciferol difference in CTX at 34 weeks of gestation]. The conditional mean  $\pm$ SD increase in CTX [z-score (SD)] from early to late pregnancy was greater in the placebo group ( $n = 188$ ) than in the cholecalciferol group ( $n = 184$ ) (placebo:  $0.16 \pm 0.92$ ; cholecalciferol:  $-0.16 \pm 1.06$ ; P-difference  $< 0.01$ ). Higher CTX at 34 weeks of gestation was associated, similarly in both groups, with lower maternal total hip and lumbar spine bone mineral content and bone mineral density (BMD) (e.g., lumbar spine BMD:  $\beta = -0.02 \text{ g} \cdot \text{cm}^{-2} \text{ SD}^{-1}$  increase in CTX; 95% CI:  $-0.027, -0.002 \text{ g} \cdot \text{cm}^{-2} \text{ SD}^{-1}$ ;  $p = 0.02$ ,  $n = 283$ ). The authors concluded that bone resorption marker, maternal urinary CTX, rises through pregnancy, although to a lesser degree with gestational cholecalciferol supplementation, and is inversely associated with maternal bone mass postpartum. Limitations include the possibility that some participants were taking vitamin D in addition to the study drug. In addition, the use of CTX as a marker of bone resorption should also be recognized including its circadian rhythm and relation with food intake (although early-morning, second-void urine was used to minimize this variation), although the differences in CTX between groups and associations with bone indices are biologically plausible and consistent with existing medical literature, they should be recognized as post hoc and require replication.

Migliorini et al. (2021a) performed a systematic review of randomized controlled trials (RCTs) to investigate the use of biochemical markers of bone turnover (BMTs) in predicting clinical outcomes in post-menopausal osteoporosis. A total of 35 RCTs and 36,706 patients were included. Data concerning bone alkaline phosphatase (bALP), procollagen type I N propeptide (PINP), serum cross-linked C-telopeptides of type I collagen (bCTX), and urinary cross-linked N-telopeptides of type I collagen (NTx) were extracted at baseline and last follow-up. The outcomes of interest were to assess the association between biomarkers and patient characteristics, bone mass density, and adverse events at the last follow-up. No time constraints were set for the database search. Study generalities (author, year, journal, duration of the follow-up, daily calcium and vitamin D supplementation, treatment) and patient baseline demographic information were collected: number of samples, mean age, BMI, mean BMD (overall, spine, hip, femur neck), t score (spine, hip, femur), and number of previous vertebral and non-vertebral fragility fractures. Data concerning the following endpoints were collected at the last follow-up: mean BMD (overall, spine, hip, femur neck), rate of vertebral, non-vertebral, femoral, hip fragility fractures, and body height. Data concerning the following adverse events at the last follow-up were collected: overall adverse events, serious adverse events and those leading to study discontinuation, gastrointestinal events, musculoskeletal events, rate of osteonecrosis, and mortality. Results revealed values of NTx at baseline were associated with a greater rate of adverse events at the last follow-up ( $p = 0.02$ ). Greater values of CTx at baseline were associated with a greater rate of adverse events leading to discontinuation ( $p = 0.04$ ), gastrointestinal adverse events ( $p = 0.0001$ ), musculoskeletal adverse events ( $p = 0.04$ ), and mortality ( $p = 0.04$ ). Greater values of PINP at baseline were associated with greater rates of gastrointestinal adverse events ( $p = 0.02$ ) at the last follow-up. The authors concluded that their systematic review supports the adoption of BMTs during pharmacological therapy in patients with post-menopausal osteoporosis, however, further studies are needed to validate the use of BMTs in clinical practice. Limitations include a high risk for bias due to data based on a large population. The available literature does not include data regarding the therapeutic role of these BMTs, nor did the studies evaluate BMTs as primary outcomes. In addition, future studies are needed to standardize measurement methods of BMTs.

A systematic review and meta-analysis by Migliorini et al. (2021b) were performed to evaluate the role of biochemical markers of bone turnover (BTMs) as therapy monitoring for post-menopausal osteoporotic patients. The authors reviewed randomized clinical trials (RCTs) comparing two or more pharmacological treatments for post-menopausal osteoporosis were accessed. Only studies that reported the value of bALP, PINP, bCTX, and NTx at last follow-up was included. A multivariate analysis was performed to assess associations between these biomarkers and clinical outcomes and rate of adverse events in patients with postmenopausal osteoporosis. A multiple linear model regression analysis through the Pearson product-moment correlation coefficient was used. The study included a total of 16 RCTs (14,446 patients). The median age was 67 years, and the median BMI 25.4  $\text{kg}/\text{m}^2$ . The median vertebral BMD was 0.82, hip BMD 0.79, and femur BMD 0.64  $\text{g}/\text{cm}^2$ . The ANOVA test found optimal within-group variance concerning mean age, body mass index, and BMD. Greater bALP was associated with lower femoral BMD ( $p = 0.01$ ). Greater NTx was associated with a greater number of non-vertebral fractures ( $p = 0.02$ ). Greater NTx was associated with greater rate of therapy discontinuation ( $p =$

0.04). No other statistically significant associations were detected. The authors concluded that their analysis supports the adoption of BTMs in therapy monitoring of osteoporotic patients. Limitations include and enhanced risk of bias due to analyses being performed regardless of drug type and administration. The findings of this study need to be validated by well-designed studies and further investigation is needed before clinical usefulness of this procedure is proven.

Tian et al. (2019) completed a meta-analysis study to investigate whether C-terminal telopeptide of type I collagen (CTX) and procollagen type I aminoterminal propeptide (PINP) BTMs are associated with fracture. Nine prospective-cohort studies including 11,572 patients, from inception to August 22, 2018, and then updated on October 14, 2018, were included in the meta-analysis. The average follow-up time ranged from 2.0 to 7.13 years. The primary outcome of interest was the crude and adjusted associations of BTMs (i.e., s-PINP or s-CTX) with incidence of fracture, expressed by HR for fracture per SD difference (the GR) and 95% confidence interval (CI). The crude and adjusted effect size between PINP and fracture were extracted from two and five studies, respectively. PINP was not associated with fracture incidence without adjusting covariates (crude GR, 1.03; 95% CI, 0.91–1.17). After adjusting for potential confounders, PINP demonstrated a significant positive association with fracture (adjusted GR, 1.28; 95% CI, 1.15–1.42). In the subgroup analysis of studies after adjusting covariates, there were significant associations in women. Both the crude (1.16, 95%CI, 1.04–1.20) and adjusted GR (1.20, 95%CI, 1.05–1.37) shown positive relationships between CTX and fracture, which were extracted from four and six studies, separately. The sensitivity analysis confirmed the stability of the results. In the subgroup analysis of studies after adjusting covariates, there were significant associations in the subgroups of elderly, female, and hip fracture patients. The authors conclude that BTMs hold promise as an independent predictor for fracture. Limitations include varying metrics, false positives related to several fracture endpoints and a variety of settings for adjustment among the studies. The findings of this study need to be validated by well-designed studies. Further investigation is needed before clinical usefulness of this procedure is proven.

A systematic review performed by Lorentzon et al. (2019) to evaluate an algorithm for the use of biochemical markers of bone turnover in the diagnosis, assessment and follow-up of treatment for osteoporosis. The aim of this study is to provide guidance, based on the opinion of the experts of the authors, to clinicians on how to use bone turnover markers in patient evaluation, in fracture risk prediction and in monitoring treatment effect and adherence to oral bisphosphonates in postmenopausal osteoporosis. An international working group was gathered to develop recommendations for the use of bone turnover markers in the diagnosis and treatment of osteoporosis during a 1-day in-person meeting in Geneva on February 5, 2019, hosted by the Scientific Advisory Board of European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO). The IOF and International Federation of Clinical Chemistry and Laboratory Medicine recommend that the bone formation marker PINP and resorption marker  $\beta$ CTX-I be used as reference markers and measured in serum using standardized assays. These markers were chosen based on several criteria, including adequate characterization of the marker, specificity to bone, performance in clinical studies, biological and analytical variability, wide availability, potential for standardization of methods, sample handling, stability and medium of measurement (serum vs. urine). The use of bone turnover markers has been extensive in clinical trials, prospective cohort studies, case-control studies and at many clinics included in standard patient evaluation for many years, their value in clinical practice is not entirely clear. Limitations include challenges relating to large pre-analytical (diurnal variations, feeding, age, gender, menopausal status, etc.) and analytical variations. The use of a multitude of markers in different clinical scenarios have impaired the interpretation of their value and makes recommendations for their use in the individual patient more difficult. The authors concluded that bone turnover markers cannot be used to diagnose osteoporosis but can be of value in patient evaluation and can improve the ability to detect some causes of secondary osteoporosis.

An ECRI (2018) Health Technology Assessment was conducted on biochemical markers of bone turnover in age-related osteoporosis. The assessment included one systematic review, one randomized controlled trial (RCT), and six case series. ECRI concluded that there was insufficient evidence to determine whether BTMs are useful in diagnosing osteoporosis or monitoring response to osteoporosis treatment because the studies reported mixed results and are at risk of bias. The evidence was also insufficient to determine whether BTMs can determine fracture risk. Additional research is needed to determine whether BTMs are appropriate for monitoring osteoporosis treatment response.

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 propeptide (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 and case groups 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, 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.

## **Clinical Practice Guidelines**

### ***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 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 A; best evidence level 1). 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, adjusted down due to limited evidence) (Camacho et al., 2016). An updated review of literature performed by Camacho et al. (2020) reaffirmed that there is no new evidence that conflicts with the previous recommendations published in the original version of the guideline.

### ***Endocrine Society (ES)***

The 2020 Clinical Practice Guideline update on Pharmacological Management of Osteoporosis in Postmenopausal Women states the following:

- In postmenopausal women with a low bone mineral density and at high risk of fractures who are being treated for osteoporosis, we suggest monitoring the bone mineral density by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment.  
Technical remark: Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy. (Eastell et al., 2019; updated Shoback, et al., 2020)

The 2012 Clinical Practice Guideline on Osteoporosis in Men recommends the following:

- Clinicians consider measuring a bone turnover marker (BTM) at 3–6 months after initiation of treatment using a bone resorption marker [such as serum C-telopeptide of type I collagen (CTX) or serum or urine N-telopeptide of type I collagen (NTX)] for antiresorptive therapy and a bone formation marker [such as serum procollagen I N-propeptide (PINP)] for anabolic therapy. (Watts et al., 2012)

### ***International Society for Clinical Densitometry (ISCD)***

The 2023 ISCD position on serial BMD measurements recommends the following:

- Serial BMD testing, in combination with clinical assessment of fracture risk, bone turnover markers, and other factors including height loss and trabecular bone score (TBS), can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines. (Kendler et al., 2019; updated Shepherd, 2023)

## ***International Society for Clinical Densitometry (ISCD)/International Osteoporosis Foundation (ISCD/IOF)***

The 2023 ISCD/IOF position for FRAX clinical regarding biochemical markers states the following:

- 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. (McCloskey et al., 2011; updated Shepherd 2023)

## ***North American Menopause Society (NAMS)***

A 2021 NAMS position statement on the management of osteoporosis in postmenopausal women states bone turnover markers cannot diagnose osteoporosis and have varying ability to predict fracture risk in clinical trials. The routine use of biochemical markers of bone turnover in clinical practice is not recommended.

## ***Osteoporosis Society of Canada (OSC)***

A 2002 OSC clinical practice guideline for the diagnosis and management of osteoporosis in Canada states bone turnover markers should not yet be used for routine clinical management. Additional studies are needed to confirm their use in individual patients. (Brown & Josse, 2002)

## **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 refer to: <https://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118551.htm>. (Accessed September 11, 2024)

## **References**

- 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. [2024T0419W]
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## Policy History/Revision Information

Date	Summary of Changes
02/01/2025	<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 RADIOLOGY 006.33</li></ul>

## 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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual<sup>®</sup> criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies 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.