Bone Turnover Markers Testing

<table>
<thead>
<tr>
<th>Policy Number: APEA-G2051 – Bone Turnover Markers Testing</th>
<th>Initial Presentation Date: 7/01/2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Revision Date: 7/01/2020</td>
</tr>
</tbody>
</table>

Policy Description

Bone metabolism involves a continual, dynamic equilibrium between bone growth and resorption. Bone turnover markers (BTMs) are biochemical markers for assessment of bone formation or bone resorption. These markers may be useful in determining risk of fracture and bone loss (Rosen, 2018).

Related Policies

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Policy Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>APEA-G2005</td>
<td>Vitamin D Testing</td>
</tr>
<tr>
<td>APEA-G2164</td>
<td>Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing</td>
</tr>
</tbody>
</table>

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

1. Measurement of bone turnover markers (Note 1) DOES NOT MEET COVERAGE CRITERIA in the diagnosis and management of osteoporosis.

2. Measurement of bone turnover markers (Note 1) DOES NOT MEET COVERAGE CRITERIA in the management of patients with conditions associated with high rates of bone turnover, including but not limited to Paget's disease, primary hyperparathyroidism and renal osteodystrophy.

Note 1: Bone turnover markers include (Rosen, 2018; Talwar, 2017):

1. Bone formation markers
   a. Serum bone–specific alkaline phosphatase (BALP)
   b. Serum osteocalcin (OC)
c. Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP

2. Bone resorption markers
   a. Urinary hydroxyproline (HYP)
   b. Urinary total pyridinoline (PYD)
   c. Urinary free deoxypyridinoline (DPD)
   d. Urinary or serum collagen type 1 cross-linked N-telopeptide (NTX)
   e. Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)
   f. Bone sialoprotein (BSP)
   g. Serum Tartrate-resistant acid phosphatase 5b (TRACP5b)
   h. Cathepsin K

**Scientific Background**

The resorption and reformation of bone are normally tightly regulated and coupled so that bone mass does not change. Bone disease occurs when these processes are uncoupled (Rosen, 2018). Biomarkers involved in the processes of resorption or formation have been proposed as measures for prediction of future bone loss, fracture risk, and more. Resorption markers include pyridinium crosslinks (PYD, DPD), C- and N-telopeptides (CTX, ICTP, NTX), tartrate-resistant acid phosphatase (TRACP) 5b, and cathepsin K, while formation markers include procollagen type I propeptides (PICP, PINP), osteocalcin, and bone isoform of alkaline phosphatase (BALP) (Rosen, 2018).

Formation markers are characteristic of bone formation rate. PICP and PINP are carboxy- and amino-sides of the tropocollagen peptide, which is a precursor to type I collagen in bone. The serum concentration of these peptides reflects synthesis of new collagen. Osteocalcin is a component of osteoid, and BALP is the alkaline phosphatase specific to osteoblasts. These biomarkers reflect the activity of osteoblasts. Of these markers, BALP and PINP are considered the most clinically useful (Rosen, 2017).

Resorption markers are characteristic of bone resorption rate (breakdown of bone). Pyridinium crosslinks are components of bone collagen, C- and N-telopeptides are crosslinks between bone collagen molecules, TRACP is anchored to the osteoclasts that initiate bone resorption, and cathepsin K is involved in digestion of the organic matrix (Manolagas, 2018; Rosen, 2017). Of these markers, urinary NTX and serum CTX are considered the most clinically useful (Rosen, 2017).

The measurement and use of these biomarkers remain complicated. Biologic variability between and within patients is significant, as factors such as age, gender, body mass index, circadian rhythms, menstruation, smoking, time of food consumption, exercise, and more may influence the levels of BTMs (Rosen, 2017, 2018). Moreover, assays used to measure these biomarkers vary considerably, as both urinary and serum samples have been used. Lack of standardization has limited the use of BTMs in the clinical setting (Rosen, 2017).

**Analytical Validity**

Eastell et al assessed the biological variability between serum and urinary N-telopeptides of type I collagen (NTX). 277 postmenopausal women were included, and urine and serum specimens were included to identify short-term variability. Long-term variability was determined by comparing NTX at baseline and at 2 months. The authors found the median
short-term coefficient of variation (CV) was 13.1% for urinary NTX and 6.3% for serum NTX. Long-term CV% was found to be 15.6% for urinary NTX and 7.5% for serum NTX. The authors also observed that to be 90% confident that a decrease in NTX after antiresorptive therapy was not caused by variability alone, a 31% decrease in urinary NTX and a 14% decrease in serum NTX are needed (R. Eastell et al., 2000).

Seibel et al (2001) described the results of an international proficiency testing program for biochemical bone markers among clinical laboratories. The authors sent out 2 urinary and 2 serum pools (both normal and increased concentrations of markers) to 79 laboratories. The CVs were as follows: "serum bone-specific alkaline phosphatase (n = 47 laboratories), 16–48%; serum osteocalcin (n = 31), 16–42%; urinary free deoxypyridinoline (n = 30), 6.4–12%; urinary total deoxypyridinoline and pyridinoline (n = 29), 27–28%; urinary N-terminal cross-linked telopeptide of type I collagen (n = 10), 39%; serum C-terminal cross-linked telopeptide of type I collagen (ICTP; n = 8), 22–27%; urinary hydroxyproline (n = 13), 12%". The authors concluded that “even with identical assays and methods, results for most biochemical markers of bone turnover differ markedly among laboratories (Seibel et al., 2001).”

Schafer et al (2010) assessed the laboratory reproducibility of urine N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP). The authors obtained serum and urine from five postmenopausal women and sent specimens to six labs over 8 months. They found that “Longitudinal coefficients of variation (CVs) ranged from 5.4% to 37.6% for NTX and from 3.1% to 23.6% for BAP. Within-run CVs ranged from 1.5% to 17.2% for NTX.”

Hlaing et al notes that “although automated platforms have substantially improved the analytical variability of bone turnover markers, reproducibility still varies substantially” (Hlaing & Compston, 2014). The National Bone Health Alliance executed a project to standardize bone turnover marker collection procedures and reduce pre-analytical variability (Bauer et al., 2012). The results of that project and the IOF and IFCC Bone Marker Standards Working Group identification of PINP and CTX-I in blood to be the reference markers of bone turnover for the fracture risk prediction and monitoring of osteoporosis treatment (Vasikaran, Eastell, et al., 2011) have resulted in recommendations for standard sample handling and patient preparation (Szulc, Naylor, Hoyle, Eastell, & Leary, 2017). Standardization and harmonization of clinical assays for bone turnover markers such as CTx and P1NP are ongoing (IFCC, 2018).

Clinical Validity and Utility

Johansson et al (2014) performed a meta-analysis to “examine the performance characteristics of serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) in fracture risk prediction in untreated individuals in prospective cohort studies.” Six studies were included. The authors identified a “significant” association between s-CTX and risk of fracture (gradient of risk [GR] = 1.18). The hazard ratio per standard deviation increase in s-PINP was found to be 1.23 for men and women and unadjusted for bone mineral density. The association between s-CTX and fracture risk was found to be 1.23. The authors concluded that “there is a modest but significant association between BTMs and risk of future fractures”.

Marques et al “assessed whether circulating bone formation and resorption markers (BTM) were individual predictors for trabecular and cortical bone loss, periosteal expansion, and fracture risk in older adults aged 66 to 93”. 1069 participants were included. Bone formation was assessed by serum procollagen type I N propeptide (PINP) and osteocalcin, and bone resorption was assessed by C-terminal cross-linking telopeptide of type I collagen (CTX). Inter-assay coefficients of variation were <3% for all BTM. A total of 54 men and 182 women sustained a fracture during the median follow-up of 11.7 years. The authors found that “increase in BTM levels was associated with faster cortical and trabecular bone loss at the femoral neck and proximal femur in men and women. Higher BTM levels were positively related with periosteal expansion rate at the femoral neck in men. Markers were not associated with fracture risk (Marques et al., 2016).”
Mederle et al investigated the correlation between bone mass density (BMD) and “serum levels of BTMs (tartrate-resistant acid phosphatase-5b [TRAP-5b]), bone-specific alkaline phosphatase (BSAP), in postmenopausal osteoporotic women as compared to healthy postmenopausal subjects”. 132 postmenopausal women with osteoporosis were included along with 81 healthy postmenopausal women. BSAP was found to have a sensitivity of 76.5% and specificity of 84.3% at a cutoff of 21.27 U/L, and TRAP-5b was found to have a sensitivity of 86.3% and specificity of 90.6% at a cutoff of 3.45 U/L. The authors concluded that “our study showed that BMD correlates negatively with BTMs and TRAP-5b presents a good specificity in identifying patients with postmenopausal osteoporosis (Mederle et al., 2018).”

Tian et al performed a meta-analysis “to explore whether bone turnover biomarkers (BTMs), i.e., C-terminal telopeptide of type I collagen (CTX) and procollagen type I amino-terminal propeptide (PINP), are associated with fracture.” Nine studies were included. PINP had a “significant” positive association with fracture (adjusted gradient risk [GR] = 1.28) after adjusting for confounders. CTX was also seen to associate with fracture (GR = 1.20). The authors concluded, “Our results indicate a statistically significant but modest association between BTMs (s-PINP or s-CTX) and future fracture risk after adjusting for BMD and clinical risk factors. The causal relationship between the two clinical conditions requires future validation with more standardized studies (Tian et al., 2019).”

Guidelines and Recommendations

National Osteoporosis Foundation

In 2014, the National Osteoporosis Foundation updated their guideline for prevention and treatment of osteoporosis (Cosman et al., 2014). Regarding biochemical markers of bone turnover, the guideline states:

Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density.
- 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.
- 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.)

The North American Menopause Society

In 2010, the North American Menopause Society issued an updated position statement (NAMPS, 2010) on the management of osteoporosis in postmenopausal women. It stated, “the routine use of biochemical markers of bone turnover in clinical practice is not generally recommended.”

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

In 2011, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) published a position statement by a joint IOF-IFCC Bone Marker Standards Working Group (Vasikaran, Cooper, et al., 2011). The group’s overall conclusion was, “In summary, the available studies relating to bone turnover marker changes to fracture risk reduction with osteoporosis treatments are promising. Further studies are needed that take care of sample handling, ensure that bone turnover markers are measured in all available patients, and use the appropriate statistical methods, including an assessment of whether the final bone turnover marker level is a guide to fracture risk.”
International Society for Clinical Densitometry and the International Osteoporosis Foundation (IOF)

In 2011, the Joint Official Positions Development Conference of the International Society for Clinical Densitometry and the IOF on the FRAX fracture risk prediction algorithms published the following statement “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 (Hans et al., 2011).”

American Association of Clinical Endocrinologists and American College of Endocrinology

The 2016 AACE/ACE guidelines (Camacho et al., 2016) recommend:

• “Consider using bone turnover markers (BTMs) in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk (Grade B; BEL 1, downgraded based on expert consensus).”

• “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; BEL 1; downgraded based on expert consensus).”

They summarize that BTMs provide a dynamic and useful assessment of skeletal activity and "may be useful in certain situations for fracture risk assessment or determining medication compliance, drug absorption, or therapeutic efficacy.” However, their use in clinical practice is limited by high assay variability, poor individual predictive ability and lack of evidence-based thresholds for clinical decision making.

U.S. Preventative Services Task Force (USPSTF, 2018)

The 2018 USPSTF recommendation on screening to prevent osteoporotic fractures (Viswanathan et al., 2018) address clinical risk assessment and bone density measurement but do not mention bone turnover markers.

Endocrine Society

The Endocrine Society released a guideline titled “Pharmacological Management of Osteoporosis in Postmenopausal Women”, which noted, “Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type 1 N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy (Richard Eastell et al., 2019).”

The Endocrine Society also released guidelines regarding the management of Paget’s Disease. They recommended “that in patients with increased bone turnover, biochemical follow-up should be used as a more objective indicator of relapse than symptoms” (Singer et al., 2014).

"For most patients, measurement of total alkaline phosphatase or other baseline disease activity markers at 6 to 12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option” (Singer et al., 2014).

National Osteoporosis Guideline Group (NOGG, 2017)

The NOGG notes bone turnover markers as a possible measure to evaluate during investigation of osteoporosis (NOGG, 2017).


KDIGO released guidelines pertaining to bone turnover related to CKD.
• “In patients with CKD [stages] G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover.”

• “In patients with CKD [stages] G3a–G5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline)” (KDIGO, 2017).

Fourth International Workshop on the Management of Asymptomatic PHPT (Primary Hyperparathyroidism, 2014)

This workshop published guidelines regarding management of asymptomatic PHPT. They note bone turnover markers as an optional measurement of asymptomatic PHPT, listing “bone-specific alkaline phosphatase activity, osteocalcin, P1NP [select one]; serum CTX, urinary NTX [select one]” (Bilezikian et al., 2014).

International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (IOF/ESCEO, 2018)

The IOF/ESCEO issued joint guidelines stating the following:

“Bone markers (serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) as markers of bone formation and bone resorption, respectively) have some prognostic significance for fracture in situations where bone mineral density (BMD) is unavailable.”

The joint guidelines also note that if harmonization efforts for other bone turnover markers are successful, these markers may see use for fracture risk. Procollagen I N-terminal peptide (P1NP) and C-telopeptide breakdown products (especially serum CTX) are considered the most informative biochemical markers for monitoring of osteoporosis (Kanis, Cooper, Rizzoli, & Reginster, 2018).

The International Federation of Clinical Chemistry and Laboratory Medicine (2018)

The most recent review of bone turnover markers for the journal of the International Federation of Clinical Chemistry and Laboratory Medicine (Bhattoa, 2018) found that “Although quite sensitive to a multitude of exogenous and endogenous pre-analytical factors, bone markers are best used in monitoring anti-osteoporosis therapy efficacy and compliance. Combination of BMD measurement by DEXA with biochemical markers of bone turnover levels, at least one bone resorption and one bone formation marker, may potentially improve early detection of individuals at increased risk for bone loss and eventually non-traumatic bone fracture. Furthermore, they have widespread clinical utility in osteoporosis, renal osteodystrophy, certain oncological conditions and rheumatic diseases.”

State and Federal Regulations, as applicable

Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process including the collagen cross-links tests; pyrilinks test from Metra Biosystems which measures collagen type 1 cross-link, pyridium, Osteomark test from Ostex International which measures cross-linked N-telopeptides of type 1 collagen (NTx), and Serum Crosslaps One-step ELISA test which measures hydroxyproline. Other bone turnover cleared through the FDA 510(k) process tests include; Ostase from Beckman Coulter which measures bone-specific alkaline phosphatase (B-ALP), N-MID Osteocalcin One-step ELISA from Osteometer Bio Tech which measures osteocalcin (OC), and Elecsys® N-MID Osteocalcin Immunoassay (Roche Diagnostics).
Other tests of bone turnover are considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared these tests; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>82523</td>
<td>Collagen cross links, any method</td>
</tr>
<tr>
<td>83500</td>
<td>Hydroxyproline; free</td>
</tr>
<tr>
<td>83505</td>
<td>Hydroxyproline; total</td>
</tr>
<tr>
<td>83937</td>
<td>Osteocalcin (bone g1a protein)</td>
</tr>
<tr>
<td>84080</td>
<td>Phosphatase, alkaline; isoenzymes</td>
</tr>
</tbody>
</table>


Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

**Evidence-based Scientific References**


sample handling and patient preparation to reduce pre-analytical variability. *Osteoporos Int, 28*(9), 2541-2556. doi:10.1007/s00198-017-4082-4


**Policy Implementation/Update Information**

7/1/20 New Policy

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.