Biochemical Markers of Bone Remodeling

Number: 0562

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers measurement of serum or urinary collagen crosslinks or other biochemical markers of bone remodeling experimental and investigational for the screening, diagnosis, or management of osteoporosis because the clinical value of these markers has not been established.

Aetna considers measurement of collagen crosslinks experimental and investigational for screening, diagnosis, or management of bisphosphonate-induced jaw osteonecrosis, chronic kidney disease, osteogenesis imperfecta, or other indications because its clinical value has not been established.

Aetna considers measurements of plasma homocysteine for evaluating fracture risk experimental and investigational because its clinical value for this indication has not been established.

Aetna considers measurement of biochemical markers of bone remodeling for diagnosis and monitoring of aseptic loosening and/or osteolysis related to wear or corrosion in total joint...

Policy History

Last Review 06/08/2017
Effective: 09/25/2001
Next Review: 06/07/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

State Information
arthroplasty experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers measurement of serum tumor necrosis factor-alpha and interleukin-6 for evaluating disease activity in persons with Charcot osteoarthropathy experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers the use of serum microRNAs as biomarkers in bone loss disorders (e.g., osteoporosis and osteoporotic fracture) experimental and investigational because their clinical value for this indication has not been established.

Aetna considers measurements of the following bone turnover markers for evaluating fracture risk experimental and investigational because their clinical value for this indication has not been established (not an all-inclusive list):

- Bone sialoprotein
- Cathepsin K
- Cobalamin Dickkopf-related protein 1
- Hydroxyproline
- Insulin-like growth factor-1 (IGF-1)
- Osteocalcin
- Osteoprotegerin
- Pyridinium crosslinks (pyridinoline, deoxypyridinoline)
- Receptor activator of nuclear factor kappa-B ligand (RANKL)
- Sclerostin
- Tartrate-resistant acid phosphatase,
- Telopeptides of type 1 collagen (C-terminal: CTX-1 and CTX-matrix metalloproteinases (MMP), and N-terminal: NTX-1).

**Background**

Bone strength is affected by its mass, microarchitecture, macrogeometry, and rate of turnover. Bone remodeling can be assessed by the measurement of surrogate markers of bone turnover in the blood or urine. Markers of bone formation include bone-specific alkaline phosphatase, osteocalcin (bone Gla-protein), and procollagen I carboxy (PICP) and N-terminal...
(PINP) extension peptides. Markers of bone resorption include urinary levels of pyridinolines (Pyr or Pyralink) and deoxypyridinolines (D-Pyr or Pyrilink-D) and serum and urine levels of type I collagen telopeptides (C-telopeptide products (CTX) and N-telopeptide to helix (NTX)). The level of these markers may identify changes in bone remodeling within a relatively short time interval (several days to months) before changes in bone mineral density can be detected.

Guidelines from the North American Menopause Society (2010) state that "[t]he routine use of biochemical markers of bone turnover in clinical practice is not generally recommended." The guidelines explain that bone turnover markers vary from day to day, are affected by food intake and time of day, and lack assay standardization, limiting their clinical utility. Although some clinicians have found that biochemical markers can encourage adherence to therapy, several trials have found no difference in adherence when marker values are communicated to women.

An National Institutes of Health consensus conference concluded that although these biochemical markers of bone turnover may be useful as a research tool, their clinical utility has not been defined: "[A]ccording to available data, marker levels do not predict bone mass or fracture risk and are only weakly associated with changes in bone mass. Therefore, they are of limited utility in the clinical evaluation of individual patients" (NIH, 2000).

A systemic review of the evidence from the National Osteoporosis Foundation stated that, although biochemical markers of bone remodeling appear promising, these tests vary in sensitivity and specificity and "their appropriate role in patient management is not yet known." A guideline from the National Osteoporosis Foundation (2003) stated that although biochemical markers have been used to assess risk of fracture, assess bone loss, or monitor response to antiresorptive therapy, "biochemical marker tests cannot replace BMD testing." A National Osteoporosis Foundation clinician's guide to the prevention and treatment of osteoporosis (2008) states that "[b]iochemical markers of bone remodeling (resorption and formation) can be measured in the serum and urine in untreated patients to assess risk of fracture,"
and that "they may predict bone loss" and "may be predictive of fracture risk reduction." The clinician's guide indicates that although biochemical markers of bone turnover may be predictive of greater mean bone mineral density (BMD) responses when evaluating large groups of patients in clinical trials, the "precision error" of the specific biochemical marker, along with daily and seasonal variability in bone turnover, must be taken into account when evaluating individuals. Thus, "because of the high degree of biological and analytical variability in measurement of biochemical markers, changes in individuals must be large in order to be clinically meaningful".

An evidence review for the U.S. Preventive Services Task Force osteoporosis screening guidelines (2002) stated that biochemical markers of bone turnover for osteoporosis screening is "under investigation."

An Agency for Healthcare Research and Quality (AHRQ) technology assessment of diagnosis and monitoring of osteoporosis in women (Nelson et al, 2001) concluded that "[n]o single [biochemical] marker or cluster of markers accurately identified individuals who had osteoporosis, as determined by the results of densitometry. It is not surprising that agreement between the two tests was poor. Densitometry measures current bone status, whereas markers measure the process of bone turnover." The AHRQ assessment concluded that the value of biochemical markers in predicting fracture risk has not been established. "No marker was associated with increased fracture risk consistently across all studies. One study provides evidence that using markers in conjunction with densitometry may increase predictability, but this result has not been otherwise confirmed." The AHRQ found that biochemical markers have not been shown to help select patients for treatment. "Studies correlating marker results and bone loss indicated no clear trend. Furthermore, sensitivity and specificity of markers were too low to be useful for the purpose of selecting patients for treatment."

The AHRQ also found that biochemical markers have not been proven to be useful in predicting a patient's response to therapy. "There is a small correlation between response to therapy as measured by densitometry and marker results, but no marker is
accurate enough to reliably identify those individuals who will fail to respond to treatment." In addition, there are no prospective data showing improved clinical management of patients with other disorders affecting bone resorption and formation (e.g., primary hyperparathyroidism, hyperthyroidism, Paget's disease of the bone, rheumatoid arthritis, renal osteodystrophy, hypogonadism, steroid-induced osteoporosis, etc.) by quantification of collagen crosslinks.

Seibel (2003) noted that the clinical use of bone remodeling markers in individual patients poses considerable problems which so far have not been sufficiently addressed. Consequently, no scientific or clinical consensus exists as to the use of bone markers in the follow-up of patients with osteoporosis. Cefalu (2004) stated that although data are beginning to accrue suggesting that changes in bone turnover markers may be an accurate predictor of fracture risk reduction, further research is necessary to elucidate the link between changes in bone turnover markers and bone architecture as a measure of osteoporosis treatment efficacy. In a review on the clinical use of serum and urine bone markers in the management of osteoporosis, Srivastava, et al (2005) stated that several clinical studies have established the potential utility of markers to identify patients with rapid bone loss, to aid in therapeutic decision-making, and to monitor therapeutic effectiveness of various treatments. They also noted that elevated marker levels have been demonstrated to be associated with increased risk of fracture in elderly women, but their utility in predicting fracture is not yet established.

Recent evidence demonstrates that bisphosphonates increases bone mineral density (BMD) in the vast majority of patients, so that routine monitoring after initiation of bisphosphonates is not be warranted. Investigators performed a secondary analysis of data from the Fracture Intervention Trial using a mixed model to evaluate whether alendronate treatment had a fixed effect (i.e., similar for all patients) and, therefore, should not require monitoring, or random effects (i.e., different between individuals) (Bell et al, 2009). After 3 years, hip BMD increased by a mean of 0.030 g/cm2 in the alendronate group and decreased by a mean of a 0.012 g/cm2 in the placebo group. Most women in the
alendronate group (97.5 %) experienced benefit (i.e., BMD increases 0.019 g/cm²). Considerable variation in BMD over time among treated patients existed, but this difference was less than the variation within individual patients; furthermore, absolute variation was small. Baseline BMD, age, body mass index (BMI), or general health did not modify treatment effects. The investigators concluded that "monitoring bone mineral density in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary and may be misleading." A commentary on this study (Biggs, 2009) noted that "these results strongly suggest that monitoring BMD after initiation of bisphosphonates is unnecessary. Ascertaining clinically relevant responses to bisphosphonates is difficult because of variability among patients. In addition, the beneficial effects of bisphosphonates might extend beyond their ability to increase BMD: Patients in the alendronate group whose BMD did not increase still had lower risk for fragility fractures." An editorialist (Compston, 2009) stated that "[t]he final nail in the coffin for monitoring bone mineral density is the observation that only a small proportion of reduction in fractures attributable to treatment is explained by a change in bone mineral density. For example, only 16 % and 4 % of the decrease in the risk of fracture associated with treatment with alendronate or raloxifene, respectively, is attributable to an increase in bone mineral density. Furthermore, some studies have found similar reductions in fracture regardless of whether bone mineral density increased or decreased on treatment." The editorialist also noted that there is no evidence that monitoring improves treatment compliance. "Because adherence with treatment for osteoporosis is poor, it could be argued that monitoring bone mineral density is justified because it should improve adherence and thereby maximise efficacy. We have no evidence to support this, however, and it would be difficult to identify people who do not adhere with this test because of the large measurement variability. Because non-adherence occurs mostly within the first three months of starting treatment, early intervention would probably be more effective, and evidence exists that an interview with a healthcare professional a few months after starting treatment improves adherence. Biochemical markers of bone turnover could potentially be used for monitoring because they
change rapidly in response to treatment and are more predictive of fracture reduction. However, at present within person variability and measurement variability are too great for these markers to be useful in clinical practice." The editorialist concluded: "If true non-responders to antiresorptive treatment do exist they are rare, and most cases of non-response are caused by failure to persist with treatment. This is best tackled by carefully explaining the treatment to patients before they start and follow-up after about three months to discuss problems related to treatment. Routine monitoring of bone mineral density during the first few years of antiresorptive treatment cannot be justified because it may mislead patients, lead to inappropriate management decisions, and waste scarce healthcare resources."

A number of additional evidence-based guidelines and technology assessments have concluded that the clinical utility of measurement of biochemical markers of bone remodeling have not been established. Guidelines on osteoporosis prevention and treatment from the University of Michigan Health System (2011) make no recommendation for the use of biochemical markers in osteoporosis. The guidelines state: “Biochemical markers of bone resorption are used in research and may be used clinically to assess the effectiveness of antiresorptive therapy. In the latter setting, a decrease in these markers to premenopausal levels usually occurs after two to three months of therapy. Some data suggest that elevated levels of bone resorption makers in older women are an independent risk factor for fractures. However, bone markers are not a reliable predictor of BMD, and are not a substitute for DXA in women at risk. Generally, their use in the diagnosis of osteoporosis is not recommended.”

An assessment of diagnosis and treatment of osteoporosis by the Swedish Council on Technology Assessment in Health Care (SBU, 2003) concluded that “[b]iochemical markers are currently a research instrument, and are not used in routine health services.”

Guidelines from the Scientific Advisory Council of the Osteoporosis Society of Canada (Brown et al, 2002) concluded: "Bone turnover markers should not yet be used for routine
clinical management. Additional studies are needed to confirm their use in individual patients."

Guidelines on osteoporosis from the Scottish Intercollegiate Guidelines Network (2007) stated that “[b]iochemical markers of bone turnover should have no role in the diagnosis of osteoporosis or in the selection of patients for BMD measurement.” Guidelines from the Royal College of Physicians (2002) on glucocorticoid-induced osteoporosis stated that the role of monitoring the effects of bone-sparing agents in glucocorticoid-induced osteoporosis using biochemical markers of bone turnover "has not been established." The guidelines state that "[r]eported changes in specific resorption markers in response to glucocorticoids have been inconsistent." The guidelines also note that bone resorption markers may be affected by changes in inflammatory activity and hence a decrease following initiation of glucocorticoid therapy may reflect suppression of disease activity rather than reduced bone resorption.

Royal College of Nursing (2005) guidelines on osteoporosis and menopause stated: "Biochemical markers of bone turnover measured by a urine test are currently being researched and in the future could provide primary care settings with a practical means of monitoring response to treatment." Royal College of Nursing (2005) guidelines on osteoporosis and breast cancer stated that "biochemical markers of bone turnover detectable in a urine test are currently being investigated."

British Society of Gastroenterology guidelines on osteoporosis in inflammatory bowel disease and celiac disease stated that biochemical markers of bone remodelling "may prove useful in practice to assess the efficacy of treatment and the need to change to another agent" (Lewis and Scott, 2007). British Society of Gastroenterology guidelines on osteoporosis associated with chronic liver disease stated that "serum bone markers may prove useful in assessing response to treatment in the future in individuals without chronic liver disease" (Collier et al, 2002). The guidelines stated, however, "as the levels are affected by the extent of hepatic fibrosis and none of these markers has been
studied in patients with chronic liver disease, they cannot yet be recommended as a means of assessing bone loss and the risk of fracture in cirrhotic patients."

An assessment by the Australian Medical Services Advisory Committee (MSAC, 2003) of the Ostase test for the mass measurement of serum bone alkaline phosphatase concluded that there is insufficient evidence of the effectiveness and cost-effectiveness of Ostase in the diagnosis and monitoring of osteoporosis. Guidelines from the Royal Australian College of General Practitioners (O'Neill et al, 2004) stated that biochemical markers of bone remodeling are "rarely needed" in primary care practice.

Guidelines from the Institute for Clinical Systems Improvement (2011) stated that “[a]t this time there is no consensus about the routine use of serum and/or urine markers of bone turnover in the evaluation of patients with osteoporosis.”

Guidelines on osteoporosis from the Kaiser Permanente Care Management Institute (2008) stated: "There is no recommendation for or against routine bone turnover testing with biochemical markers for monitoring women and men taking antiresorptive therapy for osteoporosis." This conclusion was based upon an "I" grade of evidence, based upon a finding that the evidence that this intervention is effective "is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be determined."

A synthesis of guidelines on screening and risk assessment for osteoporosis in post-menopausal women by the National Guideline Clearinghouse (2011) stated: "There is overall agreement that [biochemical markers of bone formation and resorption] do not predict BMD nor reliably estimate fracture risk and that their routine use in clinical practice is not recommended."

Regarding biochemical markers of bone remodeling, guidelines on osteoporosis from the American College of Obstetricians and Gynecologists (2008) stated that "the value of such markers in
routine clinical practice has not been established.” Guidelines on menopause and osteoporosis from the Society for Obstetricians and Gynaecologists of Canada (2009) made no recommendation for the use of biochemical markers of bone turnover in the management of osteoporosis.

Guidelines from the American Association of Clinical Endocrinologists (2003) stated that biochemical markers may have a role in fracture risk assessment and monitoring of therapy. They stated, however, that the role of biochemical markers in clinical management has not been established: "Currently, the precise role of biochemical markers in the clinical management of osteoporosis has not been established. Several confounding issues must be resolved before a clear role for these measurements can be determined. Age, gender, menopausal status, meals, diurnal variation, and certain medications all influence resorption marker levels and can cause extreme variability. Moreover, a relationship has not been demonstrated between changes in bone marker levels after treatment and reduced fracture risk. In addition, the relationship between changes in bone marker levels and bone balance is unclear."

Guidelines from the World Health Organization (WHO, 2003) stated that changes in biochemical markers at menopause "are insufficiently discriminatory, however, to provide a diagnostic test for osteoporosis", and their use in monitoring individuals "requires further study because of their precision errors and biological variation." The guidelines concluded that "[b]iochemical indices for skeletal turnover may be useful in risk assessment, but further research is needed to determine their value in clinical practice to monitor treatment." The guidelines recommended that further research should be carried out on the evaluation of biochemical markers of bone turnover in clinical practice.

American College of Preventive Medicine guidelines on osteoporosis screening (Lim et al, 2009) concluded that biochemical markers "cannot replace BMD testing" and are "not useful for population-based screening". The guidelines explained that "[t]hese biochemical markers of bone turnover are often
used in the research setting but have limited clinical utility." The guidelines noted that they may be useful in monitoring response to therapy, but that "[t]hey do not predict bone mass or reliably estimate fracture risk."

Guidelines on the use of bisphosphonates in multiple myeloma from the American Society for Clinical Oncology (2007) concluded: "The use of biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care because of a lack of prospective studies validating such an approach."

A UK National Health Service (NHS Oxfordshire, 2008) statement found insufficient evidence that biochemical monitoring improves compliance or reduces fracture risk. The statement noted that P1NP is one of a number of biochemical markers of bone turnover that could be measured to monitor compliance and response to drug therapy. The statement indicated that there are no trials looking at the role of serum P1NP measurement in the management of any group or sub-group of patients on long-term drug treatment for osteoporosis. The report described a randomized controlled trial comparing urinary marker measurement with no measurement in post-menopausal women on drug treatment which showed that women who had positive marker results were more likely to persist with treatment than women who did not have marker measurement. However, women who had negative marker results were more likely to give up treatment than those who had no marker measurement. The report also cited a small randomized trial on post-menopausal women on drug treatment compared "nurse monitoring" with "urinary marker measurement and nurse monitoring" and "no monitoring". Patients in the "nurse monitoring" and "marker and nurse monitoring" groups were more likely to persist with treatment than those with "no monitoring". However, both monitored groups were equally likely to persist, and marker measurement made no difference to compliance. The statement indicated that there are no trials looking at the role of monitoring by any marker test in specific groups such as patients considering "drug holidays" from long-term treatment or patients on teriparatide treatment. The statement reported: "There is no trial
evidence showing any impact of treatment monitoring (by any method) on fracture rates." The statement noted the need for appropriately designed studies of the role of monitoring in improving compliance and reducing fracture risk.

The ASCO executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer (Van Poznak et al, 2011) stated that the use of biochemical markers to monitor bone-modifying agents use is not recommended.


Guidelines on osteoporosis from the British Columbia Medical Services Commission (2011) state, regarding bone turnover markers: "[a]t present no single or combined assay is recommended except in specific circumstances. Assays have a proven use in research studies involving large samples but they are complex and variation is too great to be useful at the individual level."

Medicare's coverage of biochemical markers for osteoporosis is not the result of a systematic evidence review, or a determination by the Agency for Healthcare Research and Quality about the clinical utility of these tests.

The labeling for Food and Drug Administration (FDA)-approved
osteoporosis treatments made no recommendation for the use of biochemical markers in the diagnosis of osteoporosis, or in the selection, dosing, or administration of these drugs.

Lee and Suzuki (2010) examined if serum CTX could pre-operatively predict the risk of developing osteonecrosis of the jaws (ONJ) from oral bisphosphonates (BPs). These researchers hypothesized that there is no clinical correlation between the observed pre-operative serum CTX values and the risk of developing ONJ. The authors examined the scientific basis (validity) of the morning fasting serum CTX test in 163 consecutive patients who underwent various oral surgery procedures in the office. The authors also reviewed the laboratory test results and the recommended protocol based on the test values. A total of 163 patients (mean age of 75.9 years) were divided into 2 groups: (i) group I was the control group that consisted of 109 patients taking oral BPs who did not take the CTX test pre-operatively, and (ii) group 2 consisted of 54 patients taking BPs and who elected to have the CTX test performed to assess their level of risk of developing ONJ, pre-operatively. Both groups of patients were observed for a period of 8 weeks for signs and symptoms of BP-associated ONJ after surgery. The clinical data at 8 weeks and beyond revealed that there was no evidence of BP-associated ONJ in all participants. The authors concluded that the serum CTX is not a valid pre-operative test to accurately assess the level of risk of developing ONJ and is not indicated in the oral surgery patient.

Tolouian et al (2010) evaluated urinary NTX as a marker of bone turnover in chronic kidney disease (CKD). These investigators studied the relationship between bone-specific alkaline phosphatase (BSAP), parathyroid hormone (PTH) and urine NTX/creatinine (Cr) in 37 CKD out-patients. In a multi-variate model, PTH had a positive correlation with BSAP (r = 0.44, p < 0.19) and U-NTX/Cr (r = 0.55, p < 0.30), after adjusting for age, gender, estimated glomerular filtration rate (GFR), serum phosphorus, corrected calcium, and race. However, the strongest correlation was found between the 2 direct markers of bone resorption and formation (U-NTX versus BSAP; r = 0.80; p < 0.0001), suggesting a tight coupling of bone resorption and
Homocysteine (Hcy) is a sulfur amino acid. Recent studies suggest that Hcy may affect bone metabolism, bone quality as well as fracture risk in humans; and circulating Hcy may be used as a risk indicator for osteoporosis. Gjesdal et al (2006) reported that plasma total Hcy has been associated with hip fracture, but not directly with BMD. On the other hand, Morris et al (2005) stated that Hcy and vitamin B12 status indicators are associated with BMD in older Americans. Whether this association reflects a causal relation remains unclear and merits further study in light of age-related declines in B12 status and BMD, and the need for low-risk, easily implemented strategies for osteoporosis prevention.

There is currently insufficient evidence to support measurements of plasma Hcy for evaluating the risk of fracture. In fact, Ravaglia et al (2005) reported that low serum folate is responsible for the association between Hcy and risk of osteoporotic fracture in elderly individuals. Hermann and colleagues (2005) stated that initial findings indicate that Hcy is not only a risk indicator, but also a player in bone metabolism. Moreover, existing data open speculation that folate, vitamin B6 and vitamin B12 act not only via Hcy-dependent pathways, but also via Hcy-independent pathways. However, these investigators stated that more studies are needed to clarify the mechanistic role of Hcy, folate, vitamin B6 and vitamin B12 in bone metabolism. Current evidence-based guidelines make no recommendation for Hcy measurement for diagnosis, monitoring, or risk assessment in osteoporosis.

Gjesdal et al (2006) examined the association of hip BMD with levels of plasma total Hcy (tHcy), folate, and vitamin B12 and the
methylene tetrahydrofolate reductase (MTHFR) 677C→T and 1298A→C polymorphisms. Bone mineral density was measured between 1997 and 2000 in 2,268 men and 3,070 women, aged 47 to 50 and 71 to 75 years, from the Hordaland Homocysteine Study cohort. Low BMD was defined as BMD in the lowest quintile for each sex and age group. Linear, logistic, and generalized additive regression models were used. Plasma levels of tHcy were inversely related to BMD among middle-aged and elderly women (p < 0.001) but not among men. The multiple adjusted odds ratio for low BMD among subjects with high greater than or equal to 15 uM/L [greater than or equal to 2.02 mg/L] compared with low (less than 9 uM/L [less than 1.22 mg/L]) tHcy level was 1.96 (95% confidence interval [CI]: 1.40 to 2.75) for women and was not significant for men. Additional adjustments for plasma folate level or intake of calcium and vitamin D did not substantially alter the results. Plasma folate level was associated with BMD in women only. The authors observed no association between BMD and vitamin B12 level or the MTHFR polymorphisms; and they concluded that elevated tHcy and low folate levels were associated with reduced BMD in women but not in men. These findings suggest that tHcy may be a potential modifiable risk factor for osteoporosis in women.

Selhub (2006) stated that data from several studies suggest that mild elevation of plasma Hcy is a risk factor for occlusive vascular disease. In the Framingham studies it was shown that plasma tHcy concentration is inversely related to the intake and plasma levels of folate and vitamin B-6 as well as vitamin B-12 plasma levels. Almost 2/3 of the prevalence of high Hcy is attributable to low vitamin status or intake. Elevated plasma Hcy concentration is a risk factor for prevalence of extra-cranial carotid artery stenosis of at least 25% in both men and women. Prospectively elevated plasma Hcy is associated with increased total and cardiovascular diseases mortality, increased incidence of stroke, increased incidence of dementia and Alzheimer's disease, increased incidence of bone fracture, and higher prevalence of chronic heart failure. This multitude of relationships between elevated plasma tHcy and diseases that afflict the elderly points to the existence of a common denominator that may be responsible for these diseases. Whether this denominator is Hcy
itself or whether Hcy is merely a marker remains to be determined. This is in agreement with the editorial of van Meurs and Uitterlinden (2005) who stated that "despite the potential limitations of the study by Sato et al (2005), the results show that at least in patients following stroke, folate and vitamin B12 supplementation is effective in preventing hip fracture. Whether a similar effect can also be obtained in other (high fracture risk) patients can only be answered by other interventional studies. After the initial observation of association between circulating homocysteine levels and fracture risk less than 1 year ago, these results now support a causal link. However, final proof of causality will have to come from elucidation of the biological mechanism underlying this relationship".

Perier and colleagues (2007) noted that 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 mumol/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 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 1 SD increment of Hcy was 1.03 (95 % CI: 0.87 to 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 +/- SD was higher (p < 0.001) in women with SLE (9.88 +/- 3.8 micromol/L) than in women without SLE (7.98 +/- 2.6 micromol/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 4 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.

Zhu et al (2009) examined the effects of Hcy and MTHFR genotype on hip bone loss (as indexed by BMD) and fracture risk over 5 years in a cohort of 1,213 community-dwelling women aged 70 to 85 years. Nutritional intake and prevalent fracture status were assessed at baseline, plasma Hcy was measured at year 1, and hip dual-energy X-ray absorptiometry (DXA) BMD was measured at years 1 and 5. Clinical incident osteoporotic fractures confirmed by radiographical report were collected throughout the study and the MTHFR gene C677T and A1298C polymorphisms genotyped. Data were analyzed using analysis of co-variance and Cox proportional hazard regression. The highest tertile of Hcy was associated with a greater hip BMD loss over 4 years (-2.8 %) compared to the middle (-1.6 %) and lowest tertiles (-1.2 %) (p < 0.001). This effect remained after adjustment for co-
Variates. There was no effect of Hcy on fracture prevalence or incidence. Gene variation in MTHFR was only weakly related to one of the bone outcome measures. The authors concluded that in this study population, high Hcy is associated with greater hip bone loss but not fracture risk.

Vasikaran and associates (2011) determined the clinical potential of bone turnover markers (BTMs) in the prediction of fracture risk and for monitoring the treatment of osteoporosis. Evidence from prospective studies was gathered through literature review of the PUBMED database between the years 2000 and 2010 and the systematic review of the Agency for Healthcare Research and Quality up to 2001. High levels of BTMs may predict fracture risk independently from BMD in post-menopausal women. They have been used for this purpose in clinical practice for many years, but there is still a need for stronger evidence on which to base practice. Bone turnover markers provide pharmacodynamic information on the response to osteoporosis treatment, and as a result, they are widely used for monitoring treatment in the individual. However, their clinical value for monitoring is limited by inadequate appreciation of the sources of variability, by limited data for comparison of treatments using the same BTMs and by inadequate quality control. The International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine recommend one bone formation marker (serum procollagen type I N propeptide [PINP]) and one bone resorption marker (serum CTX) to be used as reference markers and measured by standardized assays in observational and intervention studies in order to compare the performance of alternatives and to enlarge the international experience of the application of markers to clinical medicine. The authors concluded that BTMs hold promise in fracture risk prediction and for monitoring treatment. Uncertainties over their clinical use can be in part resolved by adopting international reference standards.

Funck-Brentano et al (2011) stated that serum BTMs (sBTMs) are used in clinical practice for patients undergoing post-menopausal osteoporosis therapy. These researchers analyzed the literature on the ability of sBTMs to monitor therapy, focusing on the
following 5 objectives: (i) pre-treatment values and treatment choice; (ii) short-term changes and clinical response; (iii) sBTMs effect on persistence to therapy; (iv) sBTMs ability to predict fracture risk after withdrawal of therapy; and (v) the prediction of serious adverse effects. A systematic search on Medline completed manually was performed until November 2010 and was limited to post-menopausal osteoporosis and marketed therapies. Following the PRISMA statement for systematic reviews, a total of 48 studies were selected. Baseline sBTMs levels were not able to predict fracture risk reduction with either treatment. There was more evidence for the prediction of fracture risk reduction with bone formation sBTMs including PINP than with serum CTX. Most of the studies found correlations between sBTMs and BMD changes under anti-resorptive therapies, although inconsistently. The only published study on the impact of sBTMs on persistence to therapy showed negative results. There was no evidence that sBTMs allow the prediction of adverse effects, especially osteonecrosis of the jaw. The authors concluded that sBTMs reflect the skeletal effects of anti-osteoporotic treatments. Pre-treatment values are not recommended for selecting therapy. Short-term changes are significantly correlated with BMD variation, but there is no published evidence that they predict benefit on fracture risk at the individual level.

Biver and colleagues (2012) noted that osteoporosis diagnosis is based on BMD but bone remodeling is also a crucial issue. It can be assessed by BTMs. Their interest for the positive and etiological diagnosis of osteoporosis at baseline, and their predictive value for past asymptomatic vertebral fractures, were evaluated by a systematic review of the literature. Medline database was searched to identify all published reports analyzing BTMs and BMD or fractures. These investigators conducted meta-analyses on BTMs levels according to osteoporotic status using random effects models. Moderate and negative correlations were found, mainly in post-menopausal women, between BTMs and BMD, especially with bone alkaline phosphatase (bone ALP), osteocalcin, serum C-terminal and urine N-terminal cross-linking telopeptides of type I collagen (serum CTX and urine NTX). Bone ALP and serum CTX levels are higher in
osteoporotic patients compared to controls. High levels of bone ALP in primary hyper-parathyroidism and low levels of osteocalcin in endogenous hypercorticism are the most relevant data reported in endocrine diseases associated with osteoporosis.

High levels of BTMs, especially osteocalcin, bone ALP or serum CTX, may be associated with prevalent vertebral fractures. The authors concluded that the diagnostic value of BTMs at baseline in osteoporosis is very low. The interest of BTMs for the etiological diagnosis of secondary osteoporosis has not been demonstrated. Furthermore, they stated that data are lacking to address the interest of BTMs assessment to screen for vertebral fractures in asymptomatic patients with high-risk factors of fractures.

An UpToDate review on “Use of biochemical markers of bone turnover in osteoporosis” (Rosen, 2013) states that “The use of biochemical bone turnover markers (BTMs) in clinical trials has been helpful in understanding the mechanism of action of therapeutic agents. However, their role in the care of individual patients is not well established. Biologic and laboratory variability in BTM values have confounded their widespread use in clinical practice .... There is no consensus on a role for BTMs in the diagnosis of osteoporosis or the selection of candidates for therapy. There is currently insufficient data to support the use of BTMs for deciding when to restart bisphosphonate therapy after a drug holiday or for the assessment of risk (osteonecrosis of the jaw) in bisphosphonate-treated patients undergoing invasive dental procedures”.

Garnero et al (2013) stated that sclerostin, an osteocyte soluble factor, is a key regulator of bone formation. Circulating sclerostin levels were reported to increase with age and to be modestly associated with BMD and bone turnover, but there are no data on the association with fracture risk. In a population of 572 post-menopausal women (mean age of 67 years) followed prospectively for a median of 6 years, there was no significant association between baseline levels of serum sclerostin and incidence of all fractures that occurred in 64 subjects. These researchers investigated 572 post-menopausal women (mean age of 67 ± 8.5 years) from the OFELY population-based cohort. The
associations of serum sclerostin measured with a new 2-site ELISA and spine and hip BMD by DXA, serum β-isomerized CTX, intact N-terminal PINP, intact PTH, 25-hydroxyvitamin D [25(OH)D], estradiol, testosterone, and fracture risk were analyzed. At the time of sclerostin measurements, 98 post-menopausal women had prevalent fractures. After a median of 6 years (interquartile range, 5 to 7 years) follow-up, 64 post-menopausal sustained an incident fracture. Serum sclerostin correlated positively with spine (r = 0.35, p < 0.0001) and total hip (r = 0.25, p < 0.0001) BMD. Conversely, serum sclerostin was weakly negatively associated with the bone markers PINP (r = -0.10, p = 0.014) and CTX (r = -0.13, p = 0.0026) and with intact PTH (r = -0.13, p = 0.0064). There was no significant association of serum sclerostin with 25(OH)D, estradiol, free estradiol index, or testosterone. Serum sclerostin considered as a continuous variable or in quartiles was not significantly associated with the risk of prevalent or incident fracture. The authors concluded that serum sclerostin is weakly correlated with BMD, bone turnover, and PTH in post-menopausal women. It was not significantly associated with the risk of all fractures, although the number of incident fractures recorded may not allow detecting a modest association.

In a prospective cohort study, Amrein et al (2014) evaluated the association between levels of circulating sclerostin and laboratory parameters of bone and mineral metabolism, BMD and quality measured using quantitative ultrasound (QUS), fracture risk, and mortality. Female nursing home residents aged 70 and older (mean 84 ± 6; n = 539) included in this study. Serum sclerostin, bone turnover markers, and BMD and quality were measured at baseline. Participants were followed for clinical fractures and all-cause mortality. Partial correlation analysis adjusted for age, weight, and renal function revealed a significant positive correlation between sclerostin levels and calcaneal stiffness and radial and phalangeal speed of sound (all p < 0.01) and a significant negative correlation between sclerostin levels and osteocalcin, serum CTX, and PTH (p < 0.05). After a mean follow-up of 27 ± 8 months, 139 participants (26 %) had died and 64 had a hip or other non-vertebral fracture (12 %). Sclerostin was not predictive of mortality. In women with a negative fracture history, it was significantly but not linearly associated with
fracture risk. The authors concluded that in institutionalized elderly women, there is a significant relationship between serum sclerostin levels and QUS indices, bone turnover, and PTH, but sclerostin was not strongly associated with important clinical outcomes. Thus, it remains unclear whether sclerostin is a clinically useful predictor of fractures or mortality, at least in this setting.

Lewerin et al (2014) noted that cobalamin deficiency in elderlies may affect bone metabolism. These researchers examined if serum cobalamin or holotranscobalamin (holoTC; the metabolic active cobalamin) predicts incident fractures in old men. Men participating in the Gothenburg part of the population-based Osteoporotic Fractures in Men (MrOS) Sweden cohort and without ongoing vitamin B medication were included in the present study (n = 790; age range of 70 to 81 years). During an average follow-up of 5.9 years, 110 men sustained X-ray-verified fractures including 45 men with clinical vertebral fractures. The risk of fracture (adjusted for age, smoking, BMI, BMD, falls, prevalent fracture, tHcy, cystatin C, 25(OH)D, intake of calcium, and physical activity (fully adjusted)), increased per each standard deviation decrease in cobalamins (hazard ratio (HR), 1.38; 95 % CI: 1.11 to 1.72) and holoTC (HR, 1.26; 95 % CI: 1.03 to 1.54), respectively. Men in the lowest quartile of cobalamins and holoTC (fully adjusted) had an increased risk of all fracture (cobalamins, HR = 1.67 (95 % CI: 1.06 to 2.62); holoTC, HR = 1.74 (95 % CI: 1.12 to 2.69)) compared with quartiles 2 to 4. No associations between folate or tHcy and incident fractures were seen. The authors presented novel data showing that low levels of holoTC and cobalamins predicting incident fracture in elderly men. This association remained after adjustment for BMI, BMD, tHcy, and cystatin C. However, any causal relationship between low cobalamin status and fractures should be explored in a prospective treatment study.

An UpToDate review on “Use of biochemical markers of bone turnover in osteoporosis” (Rosen, 2015) states that “The use of biochemical markers of bone turnover (BTMs) for managing osteoporosis is not a central component of most osteoporosis guidelines. When BTMs are addressed, guideline committees
typically recommend against their routine use, due to the limitations of measuring and interpreting BTMs in individual patients. Most committees agree that a potential role of BTMs is monitoring osteoporosis therapy to identify non-responders. However, prospective trials to define the most optimal approach for incorporating markers into management strategies are needed”.

Summer et al (2014) stated that identification of biomarkers associated with wear and tribocorrosion in joint arthroplasty would be helpful to enhance early detection of aseptic loosening and/or osteolysis and to improve understanding of disease progression. There have been several new reports since the last systematic review (which covered research through mid-2008) justifying a new assessment. These researchers sought to determine which biomarkers have the most promise for early diagnosis and monitoring of aseptic loosening and/or osteolysis related to wear or corrosion in total joint arthroplasty. They performed a systematic review using MEDLINE and EMBASE databases, covering the period through December 2013, and identified 1,050 articles. They restricted the definition of biomarker to biomolecules and imaging parameters useful for diagnosis and monitoring of disease progression, only including articles in English. These investigators chose 65 articles for full review, including 44 from the original search and 21 from subsequent hand searches. They used the 22 articles in which patients with total joint arthroplasty who had aseptic loosening and/or peri-implant osteolysis unrelated to sepsis had been compared with patients with total joint arthroplasty with stable implants. There were 90 comparisons of these 2 patient populations involving 35 different biomarkers. Diagnostic accuracy was assessed in 9 of the 90 comparisons with the highest accuracy found for tartrate-resistant acid phosphatase 5b (0.96), although a separate comparison for this biomarker found a lower accuracy (0.76). Accuracy of greater than 0.80 was also found for cross-linked n-telopeptide of type I collagen, osteoprotegerin, and deoxypyridinoline. The most studied markers, tumor necrosis factor-α and interleukin-1β, were found to differ in the affected and control groups in less than 30 % of the comparisons. Thirty of the 35 biomarkers were studied in 4
or fewer separate comparisons with nearly 50% of the biomarkers (17) studied in only 1 comparison. Many of the comparisons were not able to eliminate a number of confounding variables, and there was only 1 prospective study. The authors concluded that currently, there are no validated biomarkers for early diagnosis and monitoring of the biological sequelae of wear or tribocorrosion, although there are some promising leads, including markers of bone turnover.

**Bone Turnover Markers in Charcot Osteoarthropathy:**

Petrova et al (2015) evaluated markers of inflammation and bone turnover at presentation and at resolution of Charcot osteoarthropathy. These investigators measured serum inflammatory and bone turnover markers in a cross-sectional study of 35 people with Charcot osteoarthropathy, together with 34 people with diabetes and 12 people without diabetes. In addition, a prospective study of the subjects with Charcot osteoarthropathy was conducted until clinical resolution. At presentation, C-reactive protein (CRP; \( p = 0.007 \)), tumor necrosis factor-alpha (TNF-\( \alpha \); \( p = 0.010 \)) and interleukin-6 (IL-6; \( p = 0.002 \)), but not IL-1\( \beta \), (\( p = 0.254 \)) were significantly higher in people with Charcot osteoarthropathy than in people with and without diabetes. Serum C-terminal telopeptide (\( p = 0.004 \)), bone alkaline phosphatase (\( p = 0.006 \)) and osteoprotegerin (\( p < 0.001 \)), but not tartrate-resistant acid phosphatase (\( p = 0.126 \)) and soluble receptor activator of nuclear factor-\( \kappa \)B ligand (\( p = 0.915 \)), were significantly higher in people with Charcot osteoarthropathy than in people with and without diabetes. At follow-up it was found that TNF-\( \alpha \) (\( p = 0.012 \)) and IL-6 (\( p = 0.003 \)), but not CRP (\( p = 0.101 \)), IL-1\( \beta \) (\( p = 0.457 \)), C-terminal telopeptide (\( p = 0.743 \)), bone alkaline phosphatase (\( p = 0.193 \)), tartrate-resistant acid phosphatase (\( p = 0.856 \)), osteoprotegerin (\( p = 0.372 \)) or soluble receptor activator of nuclear factor-kB ligand (\( p = 0.889 \)), had significantly decreased between presentation and the 3 months of casting therapy time-point, and all analytes remained unchanged from 3 months of casting therapy until resolution. In people with Charcot osteoarthropathy, there was a positive correlation between IL-6 and C-terminal telopeptide (\( p = 0.028 \)) and TNF-\( \alpha \) and C-terminal telopeptide (\( p = 0.013 \)) only at
presentation. The authors concluded that at the onset of acute Charcot foot, serum concentrations of TNF-α and iIL-6 were elevated; however, there was a significant reduction in these markers at resolution. The authors stated that these markers may be useful in the assessment of disease activity.

**Serum MicroRNAs as Biomarkers in Bone Loss Disorders:**

Kagiya (2015) noted that osteolytic bone metastasis frequently occurs in the later stages of breast, lung, and several other cancers. Osteoclasts, the only cells that resorb bone, are hijacked by tumor cells, which break down bone remodeling systems. As a result, osteolysis occurs and may cause patients to suffer bone fractures, pain, and hypercalcemia. It is important to understand the mechanism of bone metastasis to establish new cancer therapies. MicroRNAs are small, non-coding RNAs that are involved in various biological processes, including cellular differentiation, proliferation, apoptosis, and tumorigenesis. The authors stated that microRNAs have significant clinical potential, including their use as new therapeutic targets and disease-specific biomarkers.

Sun and colleagues (2016) stated that microRNAs are involved in many cellular and molecular activities and played important roles in many biological and pathological processes, such as tissue formation, cancer development, diabetes, neurodegenerative diseases, and cardiovascular diseases. Recently, it has been reported that microRNAs can modulate the differentiation and activities of osteoblasts and osteoclasts, the key cells that are involved in bone remodeling process. Meanwhile, the results from the authors and other research groups showed that the expression profiles of microRNAs in the serum and bone tissues are significantly different in post-menopausal women with or without fractures compared to the control. Therefore, it can be postulated that microRNAs might play important roles in bone remodeling and that they are very likely to be involved in the pathological process of post-menopausal osteoporosis. The authors presented the updated research on the regulatory roles of microRNAs in osteoblasts and osteoclasts and the expression profiles of microRNAs in osteoporosis and osteoporotic fracture.
patients. The perspective of serum microRNAs as novel biomarkers in bone loss disorders such as osteoporosis has also been discussed.

_Bone Turnover Markers (BTMs) for Evaluating Fracture Risk:_

Shetty and colleagues (2016) stated that bone is a dynamic tissue which undergoes constant remodeling throughout the life span. Bone turnover is balanced with coupling of bone formation and resorption at various rates leading to continuous remodeling of bone. A study of BTMs provided an insight of the dynamics of bone turnover in many metabolic bone disorders. An increase in bone turnover seen with aging and pathological states such as osteoporosis leads to deterioration of bone micro-architecture and thus contributes to an increase in the risk of fracture independent of low BMD. These micro-architectural alterations affecting the bone quality can be assessed by BTMs, and thus may serve as a complementary tool to BMD in the assessment of fracture risk. These researchers carried out a systematic search of literature regarding BTMs using the PubMed database for the purpose of this review. Various reliable, rapid, and cost-effective automated assays of BTMs with good sensitivity were available for the management of osteoporosis. However, BTMs were subjected to various pre-analytical and analytical variations necessitating strict sample collection and assays methods along with utilizing ethnicity-based reference standards for different populations. Estimation of fracture risk and monitoring the adherence and response to therapy, which is a challenge in a chronic, asymptomatic disease such as osteoporosis, are the most important applications of measuring BTMs. The authors described the physiology of bone remodeling, various conventional and novel BTMs, and BTM assays and their role in the assessment of fracture risk and monitoring response to treatment with anti-resorptive or anabolic agents. The bone resorption markers are categorized as follows:

1. Collagen Degradation Products:

- Telopeptides of type 1 collagen (C-terminal: CTX-1 and CTX-matrix metalloproteinases [MMP], N-terminal: NTX-1)
• Hydroxyproline
• Pyridinium crosslinks (pyridinoline [PYD], deoxypyridinoline [DPD])

2. Non-Collagenous Proteins:

• Bone sialoprotein

3. Osteoclastic Enzymes:

• Tartrate-resistant acid phosphatase
• Cathepsin K

4. Osteocyte Activity Markers:

• Receptor activator of nuclear factor kappa-B ligand (RANKL)
• Osteoprotegerin (OPG)
• Dickkopf-related protein 1
• Sclerostin

The authors stated that understanding the biological and pre-analytical variations and availability of reliable, rapid, cost-effective and standardized BTMs assays may help in better utilization of BTMS in the management of osteoporosis. Moreover, they noted that limitations of BTMs include the following:

• Pre-analytical and analytical variability
• Inadequate appreciation of sources of variability of each BTMs
• Lack of standardization of the assays for BTMs
• Ethnic variations of BTMs and lack of ethnicity based reference interval for each population
• Non-availability of data on response of various BTMs to different osteoporosis treatment and comparison between them

Starup-Linde and Vestergaard (2016) noted that diabetes mellitus (DM) is associated with an increased risk of fractures, which is not explained by BMD. Other markers as BTMs may be useful. These researchers examined the relationship between BTMs, diabetes,
and fractures. A systematic literature search was conducted in August 2014. The databases searched were Medline at PubMed and Embase. Medline at PubMed was searched using "Diabetes Mellitus" (MESH) and "bone turnover markers" and Embase was searched using the Emtree by "Diabetes Mellitus" and "bone turnover", resulting in 611 studies. The eligibility criteria for the studies were to assess BTM in either type 1 diabetes (T1D) or type 2 diabetes (T2D) patients. Of the 611 eligible studies, removal of duplicates and screening by title and abstract lead to 114 potential studies for full-text review. All these studies were full-text screened for eligibility and 45 studies were included. Two additional studies were added from other sources. Among the 47 studies included there were 1 meta-analysis, 29 cross-sectional studies, 13 randomized controlled trials (RCTs), and 4 longitudinal studies. Both T1D and T2D were studied. Most studies reported fasting BTM and excluded renal disease. The authors concluded that markers of bone resorption and formation appeared to be lower in diabetes patients. The authors concluded that bone specific alkaline phosphatase is normal or increased, which suggested that the matrix becomes hyper-mineralized in diabetes patients. They stated that BTMs (e.g., C-terminal cross-link of collagen, insulin-like growth factor-1, and sclerostin) may potentially predict fractures, but longitudinal trials are needed.

In a systematic review and meta-analysis, Hygum and colleagues (2017) examined the differences in bone turnover between diabetic patients and controls. These researchers performed a literature search using the databases Medline at PubMed and Embase. The free text search terms “diabetes mellitus” and “bone turnover”, “sclerostin”, “RANKL”, “osteoprotegerin”, “tartrate-resistant acid” and “TRAP” were used. Studies were eligible if they investigated bone turnover markers in patients with DM compared with controls. Data were extracted by 2 reviewers. A total of 2,881 papers were identified of which 66 studies were included. Serum levels of the bone resorption marker C-terminal cross-linked telopeptide (-0.10 ng/ml (-0.12, -0.08)) and the bone formation markers osteocalcin (-2.51 ng/ml (-3.01, -2.01)) and procollagen type 1 amino terminal propeptide (-10.80 ng/ml (-12.83, -8.77)) were all lower in patients with DM.
compared with controls. Furthermore, s-tartrate-resistant acid phosphatase was decreased in patients with type 2 DM (-0.31 U/L (-0.56, -0.05)) compared with controls. S-sclerostin was significantly higher in patients with type 2 DM (14.92 pmol/L (3.12, 26.72)) and patients with type 1 DM (3.24 pmol/L (1.52, 4.96)) compared with controls. Also, s-osteoprotegerin was increased among patients with DM compared with controls (2.67 pmol/L (0.21, 5.14)). The authors concluded that markers of both bone formation and bone resorption are decreased in patients with DM; suggesting that DM is a state of low bone turnover, which in turn may lead to more fragile bone. They stated that altered levels of sclerostin and osteoprotegerin may be responsible for this.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
</tr>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
</tbody>
</table>

**Measurement of serum tumor necrosis factor-alpha and interleukin-6 and measurement of serum microRNAs - no specific code:**

- 82523 Collagen cross links, any method
- 82607 Cyanocobalamin (Vitamin B-12)
- 82608 Cyanocobalamin (Vitamin B-12); unsaturated binding capacity
- 83090 Homocysteine
- 83937 Osteocalcin (bone g1a protein)

**Other CPT codes related to the CPB:**

- 76977 Ultrasound bone density measurement and interpretation, peripheral site(s), any method
- 77078 Computed tomography, bone mineral density study, one or more sites
- 77080 - 77081 Dual energy X-ray absorptiometry (DXA), bone density study, one or more sites
- 84075 - 84080 Phosphatase, alkaline
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M14.671</td>
<td>Charcot's joint, ankle and foot</td>
</tr>
<tr>
<td>M14.679</td>
<td></td>
</tr>
<tr>
<td>M80.00X+</td>
<td>Age-related osteoporosis with or without current pathological fracture</td>
</tr>
<tr>
<td>M81.8</td>
<td></td>
</tr>
<tr>
<td>M87.08</td>
<td>Idiopathic aseptic necrosis of bone, other site [jaw]</td>
</tr>
<tr>
<td></td>
<td>[not covered for evaluating risk of developing bisphosphonate-induces jaw osteonecrosis]</td>
</tr>
<tr>
<td>N18.1</td>
<td>Chronic kidney disease (CKD)</td>
</tr>
<tr>
<td>N18.9</td>
<td></td>
</tr>
<tr>
<td>Q78.0</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>T84.030+</td>
<td>Mechanical loosening of internal prosthetic joint</td>
</tr>
<tr>
<td>T84.039+</td>
<td></td>
</tr>
<tr>
<td>T84.050+</td>
<td>Periprosthetic osteolysis of internal prosthetic joint</td>
</tr>
<tr>
<td>T84.058+</td>
<td></td>
</tr>
<tr>
<td>Z13.820</td>
<td>Encounter for screening for osteoporosis</td>
</tr>
<tr>
<td>Z78.0</td>
<td>Asymptomatic menopausal state</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


randomized controlled trial. JAMA. 2005;293(9):1082-1088.
46. Royal College of Nursing. Women’s health and the menopause. RCN guidance for nurses, midwives and health visitors. London, UK: Royal College of Nursing; revised April 2005.


82. Rosen HN. Use of biochemical markers of bone turnover in osteoporosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2013. (Last reviewed April 2015).


Copyright Aetna Inc. All rights reserved. Clinical Policy Bulletins are developed by Aetna to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Clinical Policy Bulletin contains only a partial, general description of plan or program benefits and does not constitute a contract. Aetna does not provide health care services and, therefore, cannot guarantee any results or outcomes. Participating providers are independent contractors in private practice and are neither employees nor agents of Aetna or its affiliates. Treating providers are solely responsible for medical advice and treatment of members. This Clinical Policy Bulletin may be updated and therefore is subject to change.

Copyright © 2001-2017 Aetna Inc.
There are no amendments for Medicaid.