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Review Article

# Position Statement on the Use of Bone Turnover Markers for Osteoporosis Treatment

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Current evidences continue to support the clinical application of bone turnover markers (BTMs) in the management of postmenopausal osteoporosis. The limitations of bone mineral density measured by dual energy X-ray absorptiomet especially emphasize the beneficial roles of BTMs, such as serum C-terminal telopeptide of type I collagen and serum procollagen type I N-propeptide, as monitoring tools to assess the responses to treatment. Therefore, the proper application and assessment of BTM in clinical practice is very important. However, their use in Korea is still insufficient. Therefore, the BTM committee has set up by the Korean Society for Bone and Mineral Research have been constituted and provided a position statement which will suggest on the clinical application of BTM for the management of postmenopausal osteoporosis in Korea.

**Key Words:** Bone remodeling · Osteoporosis · Republic of Korea

## INTRODUCTION

Osteoporosis is a major health burden and its impact is expected to rise throughout the world. Osteoporosis is defined as a disease characterized by low bone mass and deteriorated bone quality, which leads to decreased bone strength and subsequent increase in the risk of fracture.[1] Bone mass is mainly expressed by bone mineral density (BMD) and bone quality is composed of microarchitecture, bone turnover rate, mineralization, and microdamage accumulation.[2] The BMD measurement using dual energy X-ray absorptiomet (DXA) is the most commonly used tool for the diagnosis of osteoporosis.[3] Although BMD is used for the determination of treatment strategy and the evaluation of bone loss rate or treatment response, it still does not completely capture the risk of osteoporotic fracture. Moreover, serial BMD measurements as a tool for treatment response require a long in-

terval of more than a year.

Bone turnover, which is the process of removal of old bones by bone resorption and followed by replacement of new bones by bone formation, is continuously occurring.[4] The change of bone turnover rate could affect the bone quality. Bone turnover marker (BTM) is an index reflecting the rate of bone turnover and BTM can be measured with urine and blood non-invasively. Considering the limitations of BMD and the characteristic of BTMs reflecting bone quality, there has been growing interest in the potential role of BTMs in predicting fracture risk and to monitoring the treatment response in clinical practice.

There is emerging evidence on clinical use of BTMs to predict bone loss and fracture risk and to monitor the response to osteoporosis treatment.[5-7] Also, the measurement of BTMs will gives us a better understanding of the pathogenesis of osteoporosis. However, the value of the BTMs can be influenced by several physiological and pathological factors, and, in some cases, by multiple methodologies used for the same analyst. Among various BTMs, serum C-terminal telopeptide of type I collagen (CTX-I) and serum propeptide of type I collagen (PINP) are recently recommended as a monitoring targets for osteoporosis treatment by several osteoporosis guidelines including the International Osteoporosis Foundation (IOF), the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), and the National Osteoporosis Foundation (NOF) and Japan Osteoporosis Society.[8-10]

Despite this current attention in the clinical implication of BTMs for the management of postmenopausal osteoporosis, the use of BTMs is still insufficient in Korea. Therefore, the Korean Society for Bone Mineral Research organized the BTM committee to provide recommendations on their use to clinicians in Korea.

## STANDARDIZATION OF BTMs

### 1. What are available assay methods for measurement of BTMs in Korea?

BTMs are classified as either bone formation markers or bone resorption makers.

#### 1) Bone formation markers

Bone formation markers include osteocalcin, bone specific alkaline phosphatase (BSALP), carboxyterminal propeptide of type I procollagen (PICP), and PINP. BSALP and osteocalcin are released by osteoblasts and play a major role in bone mineralization. PICP and PINP are cleaved from procollagen type I during collagen synthesis. In Korea, osteocalcin and BSALP are most commonly used bone formation markers.[11] Osteocalcin is measured by immunoradiometric assay (DIAsource Immunoassays S.A., Nivelles, Belgium) and an electrochemiluminescence assay (ECLIA; Roche Diagnostics, Mannheim, Germany). BSALP is measured by chemiluminescence assay (Beckman Coulter Inc., Sacramento, CA, USA), enzyme immunoassay (Quidel Corporation, San Diego, CA, USA), and electrophoresis assay (Helena Laboratories, Beaumont, TX, USA). Although PINP has not been widely used yet in Korea, it can be measured by the ECLIA (Roche Diagnostics) and covered by insurance in osteoporotic patients recently.

#### 2) Bone resorption markers

Bone resorption markers include CTX-I, N-terminal telopeptide of collagen type I (NTX-1), free and total pyridinoline (PYD), and free and total deoxyPYD.

In Korea, CTX-I is the most commonly used as a bone resorption marker and has been mainly measured by the ECLIA using β-CrossLaps kit (Roche Diagnostics).

### 2. Patient sample collection procedure standardization

#### 1) Importance of standardized patient sample collection procedure

The primary challenge to the adoption of many BTMs in routine practice has been the poor reproducibility within-subject and between-laboratory. For clinical utility of BTMs, the pre-analytical sources of variability, along with the underlying disease process, must be identified, minimized, and controlled through carefully standardized patient preparation and sample handling procedures.[12,13]

Because serum PINP and CTX-I have recently been recommended as a reference BTM,[14] we focused on the proper sample collection procedures for both CTX-I and PINP in this position statement.

#### 2) Sample collection and processing

Although either serum or plasma sample may be used for the measurements of CTX-I and PINP, ethylenediaminetetraacetic acid plasma has the advantage over the serum as it


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has superior sample stability.[15-17] The same sample type should be used consistently when monitoring a patient. CTX-I exhibits a circadian rhythm in blood. CTX-I level peaks during the early morning hours (2-5 a.m.) and reaches a nadir between 11 a.m. and 2 p.m. The only known modulator having a major effect on this circadian pattern is food intake. Overnight fasting markedly reduced the circadian variation of CTX-I. Therefore, blood samples for CTX-I measurement must be collected following an overnight fast during the morning between 7:30 a.m. and 10:00 a.m.[18-20] Other BTMs have minimal circadian rhythm and are minimally affected by food intake. Sample processing is described previously.[11]

#### 3) Sources of pre-analytical variability: Patient related factors

The patient related factors can be divided into controllable and uncontrollable factors (Table 1). Controllable factors include the menstrual cycle, seasonal variation, and physical activities. The optimal time to collect samples in pre-menopausal women is the early-mid-follicular phase.[21] There is a minor but detectable seasonal variation for CTX-I in older adults and those with severe vitamin D deficit.[22,23] Intensive physical training (e.g., elite soccer players) moderately increases serum CTX-I and slightly decreases PINP. Vigorous exercise should be avoided the day prior to sampling.[24] Uncontrollable factors include age, sex, pregnancy, geography, renal function, and specific diseases and medications.[14]

**Table 1.** Factors determining pre-analytical variability of bone turnover markers

| | |
|---|---|
| Uncontrolled factors | - Age |
| | - Menopausal status |
| | - Gender |
| | - Fracture |
| | - Pregnancy and lactation |
| | - Bed rest/Immobility |
| | - Geography and ethnicity |
| | - Day to day variation |
| | - Drugs (corticosteroids, anticonvulsants, heparin, GnRH agonists, oral contraceptives) |
| | - Diseases (thyrotoxicosis, diabetes, renal impairment, liver disease) |
| Controlled factors | - Circadian rhythm |
| | - Fasting status |
| | - Exercise |
| | - Menstrual cycle |
| | - Season |
| | - Lifestyle factors (smoking, alcohol, diet) |

GnRH, gonadotropin-releasing hormone.

### 3. Interpretation of BTMs concentrations - The role of reference intervals

The reference intervals of BTMs are useful for interpreting the results in patients with osteoporosis. Several prospective studies have reported that the presence of increased BTMs have an additive effect on the increase risk of fracture in women.[7] The very high BTM values (>3 standard deviation above the mean of the reference values) during the initial assessment suggests other metabolic bone disease than osteoporosis. However, sufficient consensus has not been achieved for determining a cut-off point of BTMs that predicts an increased fracture risk or assesses response of treatment. It is necessary to establish reference intervals of BTMs for different geographic areas and ethnicities. Although reference intervals of PINP in Korean population were previously reported [12] median level was not suggested according to menopausal state. Median serum CTX-I level was 0.279 ng/mL (range, 0.036-0.899 ng/mL) in 321 healthy pre-menopausal Korean women.[25] For the other BTMs including osteocalcin and NTX-1, the only data on reference intervals are given by manufactures (Table 2).

## CLINICAL UTILITY OF BTMs

### 1. Can BTMs predict fractures?

#### Elevated levels of BTM can predict more rapid rates of bone loss and higher fracture risk

Several BTMs were introduced as having an additive effect on fracture risk in women with a low BMD.[26] Two large population-based studies found that increased levels of serum BSALP, urinary and serum CTX-I are significantly associated with an increased risk of osteoporotic fracture (hip and vertebra) with a relative risk of 2.3 to 4.8.[5,27] The predictive value of BTMs for the risk of fracture was slightly weakened, but persisted after adjustment for BMD. Additionally, the patients with both increased bone resorption markers and decreased bone formation makers were at higher risk of fracture than the patient with either one of 2 predictors.[7,27-29] These studies suggested that the index of BTMs provides the information on the risk of fracture independently of BMD, therefore, the risk of fracture

**Table 2.** The reference intervals and median value of available bone turnover markers in Korea

| Bone turnover marker | Sample | Assay method | Reference interval | Median |
|---|---|---|---|---|
| Bone formation markers | | | | |
| BSALP[a] | Serum | CLIA | Men: ≤20.1 μg/L<br>Women: premenopausal ≤14.3 μg/L | |
| | Serum | EIA | Men: ≥25 years 15.0-41.3 U/L<br>Women: 25-44 years 11.6-29.6 U/L | |
| Osteocalcin[a] | Serum | RIA | Men: 21-30 years 6.0-20.0 ng/mL<br>Women: 21-30 years 4.0-20.0 ng/mL | |
| | Serum | IRMA | Men: 31-40 years 10.7-34.1 ng/mL<br>Women: 31-40 years 7.7-31.9 ng/mL | |
| | Serum | ECLIA | Men: 30-50 years 14-42 ng/mL<br>Women: premenopausal 11-43 ng/mL | |
| PINP | Serum | ECLIA | Men: 30-39 years 26.1-79.8 μg/L[a]<br>Women: 30-39 years 18.7-83.2 μg/L | 45.0 (37.9-54.2)<br>40.0 (31.4-50.9) |
| Bone resorption markers | | | | |
| CTX-I | Serum, plasma | ECLIA | Men: 30-50 years <0.584 ng/mL[a]<br>Women: premenopausal 0.036-0.899 ng/mL | 0.279 ng/mL |
| NTX-I[a] | Serum | ELISA | Men: 5.4-24.2 nm BCE<br>Women: 6.2-19.0 nm BCE | |
| | Urine | EIA | Men: 3.0-63.0 nmol BCE/mmol·Cr<br>Women: 5.0-65.0 nmol BCE/mmol·Cr | |
| | | CLIA | Men: 21-83 nmol BCE/mmol·Cr<br>Women: premenopausal 17-94 nmol BCE/mmol | |
| DPD[a] | Urine | EIA, CLEIA | Men: 2.3-5.4 nmol BCE/mmol·Cr<br>Women: 3.0-7.4 nmol BCE/mmol·Cr | |

[a]Described in kit manufacturer's package insert or manufacturer's in-house data.
BSALP, bone specific alkaline phosphatase; PINP, propeptide of type I collagen; CTX-I, C-terminal telopeptide of type I collagen; NTX-I, N-terminal telopeptide of collagen type I; DPD, deoxypyridinoline; CLIA, chemiluminescence assay; EIA, enzyme immunoassay; RIA, radioimmunoassay; IRMA, immunoradiometric assay; ECLIA, electrochemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; CLEIA, chemiluminescence enzyme immunoassay.

can be assessed and supplemented with BTMs if DXA is not available.[28]

Nonetheless, uncertainties over their clinical use still remains, and the routine use of BTMs to assess the fracture risk is not recommended. Despite with the association between BTMs and the risk of fracture, the previous studies have shown inconsistent findings due to their large variability.[30,31] The difference in the predictive value of the various BTMs were noted in many studies and the reasons for this discrepancy are not clear. Another critical flaw is that a common approach to statistically analyze the results of BTMs in the prediction of osteoporotic fracture is odds ratios of fractures per standard deviation of increase in BTMs (e.g., the risk of fracture in patients with higher values is compared with that with lower values).[28] The use of odds ratios is not ideal for clinical decision-making in predicting fractures, so it is not easy to apply the results to the general population.[32]

Therefore, the measurement of absolute risks, such as 10-year probabilities, should be evaluated in a further study with large population. Another possible avenue remains the development of international reference standards and standardization of their measurement that may help minimize or eliminate old problems.[33,34]

## 2. Can BTM monitor therapeutic efficacy?

### BTMs can reflect the therapeutic responses to anti-osteoporosis therapies earlier than BMD

#### 1) Anti-resorptive drugs

Inhibition of bone resorption by anti-resorptive drugs results in a decrease in bone resorption markers followed by a plateau. Changes in BTMs during anti-resorptive therapy depend on the mechanism of action of the drug, degree of inhibition of bone resorption, and the route of administration. This inhibition of bone resorption secondarily causes a decrease in bone formation markers, due to physiologic mechanisms linking osteoclast and osteoblast activity.


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*(1) Bisphosphonate (BP)*

BPs are the most commonly used drugs for treatment of osteoporosis. Bone resorption markers are maximally suppressed after 8 weeks of treatment and bone formation markers are maximally suppressed after 26 weeks of treatment. The oral BPs, such as alendronate, ibandronate, and risedronate, have been compared in the TRIO study [35] to evaluate the clinical utility of BTMs to assess treatment response. Alendronate and ibandronate decreased BTM (CTX-I, NTX-1) more than risedronate. In this study, more than 80% of patients responded to treatment as defined by a decrease more than the least significant change (LSC) for CTX-I (56%) and PINP (38%) after 3 months of treatment. Response can also be defined as a reduction to a level below the median found in healthy young women.[35] BPs administrated intravenously inhibit bone resorption and decrease levels of bone resorption markers faster than BPs administrated orally. Zoledronic acid is given by annual intravenous infusion, thus avoiding concerns about poor absor ption. It results in a reduction in CTX-I by 2 weeks and when it is given for 6 years as in the Horizon Study, the suppression of CTX-I and PINP is maintained.[36]

*(2) Denosumab*

Denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor-κB ligand, is administrated subcutaneously inhibited bone resorption 12 hr after administration.[13] Bone resorption markers (such as CTX-I) decrease within 24 hr of treatment. Denosumab results in a greater inhibition of bone resorption than zoledronic acid.[37] PINP decreases over several months to a lesser extent than the bone resorption markers and remains suppressed with continued dosing for up to 10 years.[38] Once the drug is stopped, the BTM overshoot so that their levels are increased compared to baseline. These elevation of BTMs results are associated with accelerated bone loss, and there are recent reports of multiple vertebral fractures associated with this high BTM.[39]

*(3) Selective estrogen receptor modulator (SERM)*

SERM such as raloxifene have a weaker effect on the change of bone turnover than BPs and denosumab. In 60% to 65% of women with osteopenia, a significant response could be demonstrated using the LSC approach with CTX-I or PINP.[40]

2) Anabolic drugs

The linkage between osteoclasts and osteoblasts can also function in the opposite direction, with anabolic drugs compared to anti-resorptive drugs.

*(1) Recombinant human parathyroid hormone (PTH) 1-34 (teriparatide)*

Teriparatide is typically characterized as an anabolic agent, but results in increases in both bone formation and resorption markers.[41,42] Bone formation markers increase within a few days of starting treatment,[42] peaking by 3 months. PINP has been proven to be the most responsive BTM to this treatment.

For monitoring of early response to teriparatide therapy, PINP is measured prior to the initiation of teriparatide, and then after 1 to 3 months of therapy. Because patients who were pretreated with alendronate then switched to teriparatide showed PINP response rates of 79% at 1 month and 97% at 3 months, follow up assessment of PINP at 3 months may be more helpful than earlier assessments in this group of patients.[43]

The increase in serum PINP concentration by >10 pg/mL may be predictive of a greater increase in BMD.[43]

*(2) Abaloparatide*

Abaloparatide, recombinant human PTH related peptide (1-34), is a newly licensed anabolic therapy for osteoporosis.[44] It works through the PTH receptor as does with teriparatide. This drug stimulates rapid bone formation and resorption and works in a dose dependent manner in women with postmenopausal osteoporosis, but less than teriparatide, leading to a greater increase in BMD compared with teriparatide.[45] The clinical utility of BTMs for monitoring abaloparatide therapy has not yet been fully reported.

*(3) Romosozumab*

Romosozumab, anti-sclerostin monoclonal antibody, also works in a dose-dependent manner and increases bone formation markers. But, unlike teriparatide, there is an early but transient increase in PINP level and a decrease in serum CTX-I.[46] PINP level begin to increase from 1 week after drug administration and reaches a peak in 1 month, then slowly return to pretreatment values within 6 months. CTX-I initially decreased and remained below the baseline value at 12 month.[46] These BTM changes are associated with a rapid increase in BMD.

## 3. Can BTM monitor compliance?

**In postmenopausal women receiving a treatment, BTMs can be used to monitor the individual compliance**

Monitoring of BTM at an individual level may improve the compliance of patients on anti-osteoporotic treatment.[47] The IOF has proposed that a BTM such as PINP or CTX-I measured within 3 months of starting therapy would help to identify those with poor adherence which occur commonly with osteoporosis therapy, especially oral BPs.[48] The absence of change in the BTMs concentration during anti-osteoporotic therapy might reflect poor compliance (e.g., BP not taken at all, or not taken in the fasting state, or taken with milk), poor adherence, inappropriate technique of teriparatide injection, a medical problem (e.g., recent vertebral fracture), secondary osteoporosis, or real absence of response.

According to recently published Consensus Statement in Asia-Pacific region,[49] in patients who are receiving antiresorptive therapies, serum CTX-I and/or PINP can be used to monitor compliance and drug response with measurements at baseline, 3, 6, and 12 months after starting treatment. In patients who are receiving anabolic therapies, serum PINP can be used to monitor compliance and drug response, with measurements at baseline, 1 to 3, 6, and 12 months after starting treatment.

However, further studies are necessary to define an adequate response through the change in BTM concentration that is associated with a greater reduction in fracture incidence. The reference range of BTMs concentration for the adequate response could be helpful when used as target for anti-osteoporotic treatment.

## 4. Can BTMs be useful for drug holiday?

**Monitoring BTMs during drug holiday can be helpful to decide to resume treatment, but the evidence was insufficient yet**

BPs are considered as a first-line treatment for osteoporosis. It is effective in reduction of fracture risk over 3 to 5 years of treatment. However, long-term use of BPs is associated with the rare but serious adverse effects such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). Therefore, the concept of a 'drug holiday' from BPs has emerged as being potentially beneficial in avoiding these adverse effects. The effect of BP such as anti-resorption and fracture prevention persist for a long period after cessation of drugs because of long-term deposition of BPs in bones. However, despite BP has long skeletal retention time, fracture risk will increase after discontinuation of it. Therefore, continuous monitoring during drug holiday will be needed for the assessment of fracture risk and to restart treatment if needed. There are limited clinical practice guidelines on BTM monitoring during drug holiday. There are few studies about an assessment of fracture risk using BTMs during drug holiday. A recent retrospective study showed that those in newly developed fracture group during drug holiday was older and had lower BMD than non-fracture group. Other factors associated with fracture such as BTMs, vitamin D level, body mass index, and PTH were not significantly different between 2 groups.[50] Another study presented that BMD by DXA, BTMs (CTX-I, PINP), and fracture-risk assessment tool score may help to guide when to resume treatment during drug holiday.[51] Some researchers suggested that empirical approaches such as monitoring BMD and BTMs are necessary during drug holiday.[52] Several meta-analyses presented that increased bone turnover is a significant determinant of fracture susceptibility.[53-55] In one guideline, they suggested that the increase in bone resorption markers compared to the levels before treatment might be a signal to stop the "holiday".[56] During drug holiday, a significant decrease in BMD or a significant increase in BTMs suggests that the residual effect of BP therapy may be diminishing and that it may be time to resume active therapy.[52,57,58] Roberts and colleagues [51] recommended that if BTMs rise over 30% after drug holiday, treatment should be resumed.

## 5. Could BTMs predict side effects such as ONJ and AFF?

**Although there is still controversy, BTMs can be used carefully as a predictor of long-term side effects of BPs such as ONJ and AFF**

Prolonged BP therapy has been related with rare adverse events such as ONJ and AFF. ONJ is a rare oral disease in which the jaw bone's healing power is impaired because of use of BP or other antiresorptive agents. Patients may be considered to have ONJ if they had current or previous treatment with antiresorptive or antiangiogenic agents and as if there is exposed bone in the jaw that has persisted for more than 8 weeks but without history of radiation therapy or obvious metastatic disease.[59] A number of case reports have suggested that long-term treatment



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with BPs may be related to the occurrence of fractures of the femur below the lesser trochanter, which was regarded as an atypical based on their unusual site and radiographic appearance in patients with osteoporosis.[60] These rare but serious side effects were supposed to be related to the severely suppression of bone turnover. Therefore, several biochemical markers have been used as effective evaluation methods during the bone-remodeling period. In one cross-sectional study, 4 BTMs including serum CTX-I, osteocalcin, PTH, and BSALP were compared between medication-related ONJ patients and control groups. Serum CTX-I, osteocalcin, and BSALP levels were lower and serum PTH level was higher in ONJ patients than in control groups.[59] Another study showed that high CTX-I level was associated with a low risk of ONJ in patients who was treated with BPs and had a tooth extraction.[61] BSALP level over 10 μg/L denoted faster healing and indicated a better prognosis in ONJ patients.[62] Some dentists have suggested CTX-I measurement for the prediction of ONJ. If patients' CTX-I level is lower than 0.100 to 0.150 ng/mL, the risk of ONJ is high, therefore, drug holiday or having surgery after recovery of CTX-I level could be recommended.[63,64] One prospective cross-sectional study suggested that the levels of BTMs including PINP, tartrate-resistant acid phosphatase 5b (TRACP-5b) and undercarboxylated osteocalcin were significantly lower in patients with AFF than in patients with typical osteoporotic femoral fracture. They suggested that severe suppression of bone turnover was associated with the pathogenesis of AFF.[65] Systematic review of case report and case series on AFF presented that bone formation marker was decreased in 14%, normal in 79%, and increased in 7.0% in AFF patients. And bone resorption marker was decreased 18.2%, normal 69.7%, and increased 12.1% in AFF patients.[60]

## 6. How should BTM be used in patient with chronic kidney disease (CKD)?

**The various serum and urine BTMs are affected by renal dysfunction. The measurement of BASLP and PTH is recommended as a BTM in patients with CKD**

Because of urinary and some serum BTMs are excreted into urine by kidney, the serum level of those are affected by renal dysfunction. BSALP, intact PINP, and TRACP-5b are not affected by renal impairment.

### 1) BSALP

Its serum concentration seems to be independent of glomerular filtration rate. Combination of a low PTH (<150 pg/mL) and a low BSALP (<27 IU/L) improved the specificity of diagnosing adynamic bone disease in 103 dialysis patients with bone biopsy. In the newer automated Ostase BSALP assay, the cut-off <20 IU/L is used.[66]

### 2) Osteocalcin

Since osteocalcin is cleared by kidney, its use in CKD patients is limited. The combination of osteocalcin (<41 ng/L) and BSALP (<23 U/L) improved the positive predictive value for diagnosing adynamic bone disease to 77% in a CKD-5 cohort.[66]

### 3) PINP

PINP is present in 2 major forms, an intact trimeric form and a monomeric one. Some assays recognize both forms ('Total PINP'; Roche Elecsys, Mannheim, Germany) while other assays recognize the trimeric form only ('Intact PINP', Orion Diagnostica and IDS iSYS). The proportion of the monomeric form is elevated in patients with CKD, whereas the apparent concentration of intact PINP is unaffected by glomerular filtration rate in kidney disease patients.[67] PINP monomers are not cleared by conventional dialysis sessions and the LSC is of 32% for the intact assay.[68]

### 4) CTX-I

CTX-I is renally excreted and accumulates in CKD patients. CTX-I is cleared by dialysis and therefore pre-dialysis sampling is required for longitudinal monitoring.[66]

### 5) TRACP-5b

TRACP-5b is an enzyme released by osteoclasts to breakdown bone matrix. High serum levels of TRACP-5b therefore reflect increased osteoclastic activity and resorption. Levels of TRACP-5b correlate with PTH and ALP and are unaffected by renal function. However, its use is limited by availability of automated assays.[66]

### 6) The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD-mineral and bone disorder (CKD-MBD)

The KDIGO guidelines recommended that the bone derived markers of collagen synthesis and breakdown, includ-

ing CTX-I, should not be routinely measured in patients with CKD stages 3 to 5D.[69] The primary rationale for this recommendation was that the levels of such markers did not appear to be more effective at predicting clinical outcomes or bone histology than serum PTH or BASLP.[70] However, they suggest that measurements of serum PTH or BASLP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover in patients with CKD G3a-G5D.[69] They also recommend the interval of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, based on rate of progression of CKD (Table 3).[69]

## CONCLUSION

The appropriate use of BTMs in treatment of osteoporosis could be helpful to predict fracture risk and monitor treatment response and patient compliance. But, BTMs have not been used widely in clinical practice due to their poor within-subject and between-lab reproducibility. Researchers are constantly trying to automate and standardize the measurement of bone markers to minimize variability of BTMs. In addition, insurance coverage for BTMs have recently been possible in Korea. Thus, BTMs could be used easily as a dynamic index reflecting bone quality, complementary to BMD. More studies about the efficacy of BTMs are needed in the future.

**Table 3.** The interval of monitoring serum calcium, phosphate, and parathyroid hormone based on rate of progression of chronic kidney disease

| CKD stage | Monitoring of parameters |
|---|---|
| CKD G3a-G3b | Check serum calcium and phosphate, every 6-12 months; and for PTH, based on baseline level and CKD progression |
| CKD G4 | Check serum calcium and phosphate, every 3-6 months; and check PTH, every 6-12 months |
| CKD G5 (including G5D) | Check serum calcium and phosphate, every 1-3 months; and check PTH, every 3-6 months |
| CKD G4-G5D | Check alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH |

CKD, chronic kidney disease; PTH, parathyroid hormone; CKD G5D, chronic kidney disease stage 5 receiving dialysis.

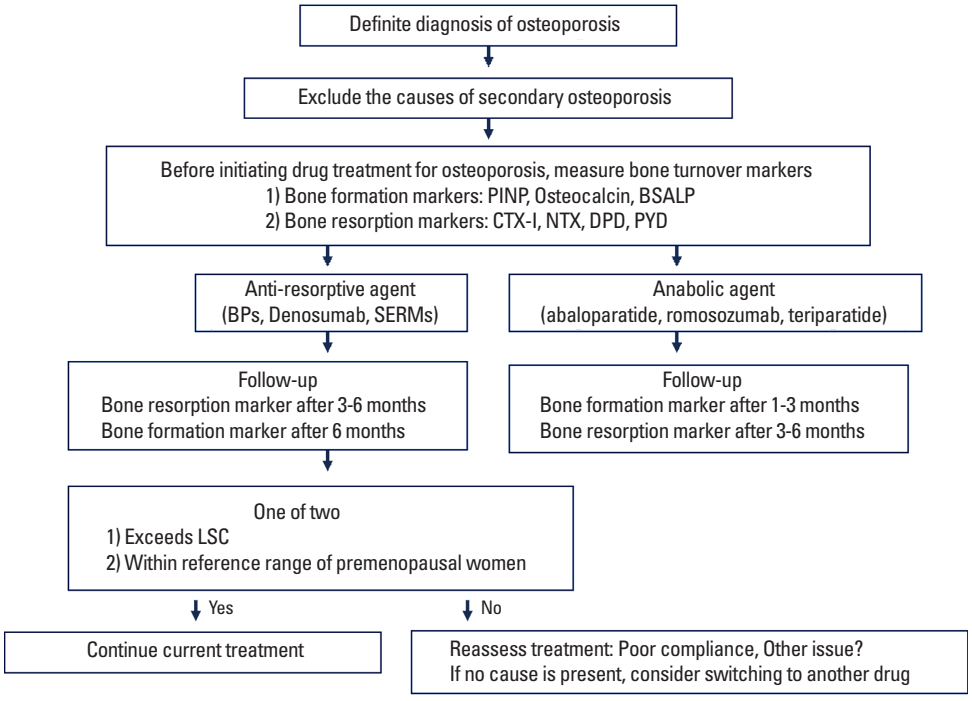


**Fig. 1.** The algorithm of bone turnover marker use in osteoporosis treatment. PINP, propeptide of type I collagen; BSALP, bone specific alkaline phosphatase; CTX-1, C-terminal telopeptide of type I collagen; NTX-1, N-terminal telopeptide of collagen type I; DPD, deoxypyridinoline; PYD, pyridinoline; BP, bisphosphonate; SERM, selective estrogen receptor modulator; LSC, least significant changes.


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## SUMMARIES OF CONSENSUS STATEMENT (Fig. 1)

- Consider using BTMs in the initial evaluation and follow-up of patients with osteoporosis.
- Elevated levels of BTMs can predict more rapid rates of bone loss and higher fracture risk.
- BTMs can reflect the therapeutic responses to anti-osteoporosis therapies earlier than BMD and help in selecting osteoporosis treatment and in assessing response to therapies.
- CTX-I and/or PINP can be used to evaluate patient adherence and response to anti-resorptive drugs with measurement at baseline, 3 to 6 months after starting treatment.
- PINP can be used to evaluate patient adherence and responses to anabolic agents with measurement at baseline, 1 to 3 months after starting treatment.
- For patients taking anti-resorptive agents, target range for successful treatment is to have levels of BTMs in the reference range for premenopausal women. Also, relative change of BTMs from baselines above LSC can be also used.
- Monitoring BTMs during drug holiday can be helpful to decide to resume treatment, but the evidence was insufficient yet.
- Although there is still controversy, BTMs can be used carefully as a predictor of long-term side effects of BPs such as ONJ and AFF.
- The various serum and urine BTMs are affected by renal dysfunction. The measurement of BASLP and PTH is recommended as a BTM in patients with CKD.

## DECLARATIONS

### Ethics approval and consent to participate

Not applicable.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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