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Algorithm for the Use of Biochemical Markers of Bone Turnover in the Diagnosis, Assessment and Follow-Up of Treatment for Osteoporosis

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ABSTRACT

Introduction: Increased biochemical bone turnover markers (BTMs) measured in serum are associated with bone loss, increased fracture risk and poor treatment adherence, but their role in clinical practice is presently unclear. The aim of this consensus group report is to provide

guidance to clinicians on how to use BTMs in patient evaluation in postmenopausal osteoporosis, in fracture risk prediction and in the monitoring of treatment efficacy and adherence to osteoporosis medication.

Methods: A working group with clinical scientists and osteoporosis specialists was invited by the Scientific Advisory Board of European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).

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Results: Serum bone formation marker PINP and resorption marker β CTX-I are the preferred markers for evaluating bone turnover in the clinical setting due to their specificity to bone, performance in clinical studies, wide use and relatively low analytical variability. BTMs cannot be used to diagnose osteoporosis because of low sensitivity and specificity, but can be of value in patient evaluation where high values may indicate the need to investigate some causes of secondary osteoporosis. Assessing serum levels of β CTX-I and PINP can improve fracture prediction slightly, with a gradient of risk of about 1.2 per SD increase in the bone marker in addition to clinical risk factors and bone mineral density. For an individual patient, BTMs are not useful in projecting bone loss or treatment efficacy, but it is recommended that serum PINP and β CTX-I be used to monitor adherence to oral bisphosphonate treatment. Suppression of the BTMs greater than the least significant change or to levels in the lower half of the reference interval in young and healthy premenopausal women is closely related to treatment adherence.

Conclusion: In conclusion, the currently available evidence indicates that the principal

clinical utility of BTMs is for monitoring oral bisphosphonate therapy.

Keywords: Algorithm; Bone; Bone biomarker; CTX; Osteoporosis; P1NP; Rheumatology

INTRODUCTION

Osteoporosis—Diagnosis and Burden of Disease

Osteoporosis is a disease characterized by low bone mineral density (BMD) and deterioration of bone microarchitecture, which leads to increased risk of fragility fracture [1, 2]. Osteoporotic fractures, especially of the hip and spine, commonly result in disability, increased morbidity and mortality [3]. In 2010, the number of fractures in the European Union was estimated at 3.6 million, of which 620,000 were hip fractures [4]. Patients at high fracture risk can be identified by investigating known clinical risk factors, which can be combined using a fracture risk calculator such as FRAX, for the calculation of 10-year probability of major osteoporotic and hip fracture [5]. A

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measurement of BMD using dual-energy X-ray absorptiometry (DXA) provides a good surrogate for bone strength and is used to diagnose osteoporosis, which in postmenopausal women and men aged ≥ 50 years is defined as a BMD value of -2.5 standard deviations (T-score) or below the mean of the young adult woman [6, 7]. The estimation of fracture risk probability in FRAX can be further refined by adding femoral neck BMD to the clinical risk factors in the calculation and is recommended in many clinical guidelines [8].

Measuring Bone Turnover

Bone turnover is necessary to replace damaged bone, for example, containing microcracks, with new and healthy bone and to release calcium into the circulation to maintain calcium homeostasis. Bone resorption comprises the 4–6-week process in which osteoclasts excavate bone to cause resorption pits, from which degraded bone releases calcium into the microenvironment and later the circulation. In a coupled process, bone resorption triggers bone formation by osteoblasts, a process taking

4–5 months, which fills the resorption cavity with an unmineralized osteoid, a connective tissue rich in collagen. Levels of bone turnover markers reflect the activity and number of bone-forming (osteoblasts) and bone-degrading cells (osteoclasts), providing an estimate of bone resorption and bone formation. Bone turnover markers can be measured non-invasively in either blood or urine at a fairly low cost (usually $< \text{€}20$).

The most widely used markers are N-terminal collagen type I extension propeptide (PINP), osteocalcin and bone alkaline phosphatase for bone formation and C-terminal cross-linking telopeptide of type I collagen ($\beta\text{CTX-I}$), N-terminal telopeptide of type I collagen (NTX), deoxypyridinoline, hydroxyproline or tartrate-resistant acid phosphatase isoform 5b (TRAP5b) for bone resorption (Table 1) [9]. Post-translational cleavage of type I collagen during bone matrix formation gives rise to PINP, which subsequently leaks out into the circulation and can be measured in serum. Osteocalcin is also produced by osteoblasts during bone formation, is excreted by the kidneys and is one of the most abundant non-collagenous proteins in bone. It

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is also released during bone resorption. Alkaline phosphatase (ALP) is secreted from bone to the circulation when the osteoid is mineralized, but only about half of serum ALP levels are derived from bone, and the other half emanates mainly from the liver. However, there are currently available assays that to a high degree are specific to the circulating bone ALP isoform (BALP).

Each bone marker has distinct features that reflect particular aspects of bone physiology. For example, TRAP5b reflects the number of osteoclasts and is not secreted in urine and can therefore be useful in assessing bone and mineral disorder in chronic kidney disease, whilst measuring β CTX-I in such patients is inappropriate since the bone marker accumulates in serum if renal function is poor. β CTX-I reflects osteoclast activity resulting in bone degradation and is useful in evaluating, e.g., glucocorticoid induced osteoporosis [10], in which β CTX-I increases rapidly and peaks after about a week after glucocorticoids are started. Oral glucocorticoid treatment also inhibits bone formation, as reflected by a rapid and profound decline in serum osteocalcin levels, whereas the decline in PINP is considerably smaller [10].

Most clinical trials have used bone turnover markers to monitor osteoporosis treatment but the use has not been widely adopted in clinical practice [11–14].

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Table 1 Biochemical bone turnover markers

	Measurement medium
<i>Bone formation markers</i>	
Bone alkaline phosphatase	Serum
PICP	Serum
Osteocalcin	Serum, urine
PINP ^a	Serum
<i>Bone resorption markers</i>	
CTX-I ^a	Plasma, serum*, urine
ICTP	Serum
NTX	Serum, urine
Trap5b	Serum

Biochemical bone turnover markers that can be measured in serum are listed. ^aDenotes bone turnover markers recommended by IOF and IFCC

PICP procollagen type 1 C propeptide, *PINP* procollagen type 1N propeptide, *CTX-I* carboxyterminal cross-linking telopeptide of type I collagen, *ICTP* carboxy-terminal cross-linking telopeptide of type I collagen, *NTX* amino-terminal cross-linking telopeptide of type I collagen, *Trap5b* tartrate-resistant acid phosphatase 5b [18]

Factors Affecting Levels of Bone Turnover Markers

Bone resorption markers, including β CTX-I, show diurnal variations, with the highest blood concentration early in the morning and the lowest at around 2 p.m. Both the levels of bone resorption and formation markers are suppressed by feeding, but the effect is much larger for resorption markers (excepted Trap5b), which are suppressed by 20–40%, whilst formation markers are suppressed by < 10% [15, 16]. A fracture normally results in a rapid increase in bone resorption markers, which doubles in weeks, followed by more slowly increasing bone formation markers, which double in serum levels after about 3 months, but remain elevated for up to a year after fracture [17]. Several other factors, including glucocorticoids, menopausal state, age, gender, pregnancy/lactation, aromatase inhibitors,

Table 2 Controllable and uncontrollable sources of pre-analytical variability in biochemical bone turnover markers

	Effect	Recommendation	Importance
<i>Controllable sources</i>			
Circadian rhythm	High BTM concentrations at night and early morning, lowest in the afternoon	Collect serum samples in the morning (7.30–10.00 h)	High
Food intake	Decrease in BTMs, especially bone resorption markers (about 20–40%) after food intake	Collect samples of bone resorption markers after overnight fast	High
Exercise	Intense exercise can decrease bone resorption and increase bone formation markers	Ask patient to refrain from intense exercise the day prior to blood sampling	Low
Alcohol intake	Alcohol consumption decreases BTMs	Ask patient to refrain from excessive alcohol intake the day prior to blood sampling	Low
Seasonal	Higher levels of BTMs in winter	In research, take samples in the same season or adjust for seasonal variation	Low
<i>Medications</i>			
-oral GC	Rapid and dose-dependent decrease in bone formation markers, small effect on bone turnover markers	Consider dose of oral GC	High
-aromatase inhibitors	Increase in BTMs		
<i>Uncontrollable sources</i>			
Age	Postmenopausal women have higher BTMs than premenopausal women	Use age-based reference intervals	High
Bed rest/immobility	Bone resorption markers increase and formation markers decrease	Consider different expected baseline level when evaluating BTMs	High
Ethnicity	Small differences. Lower osteocalcin in African Americans vs. Caucasians	Unclear if different reference intervals are needed for different ethnicities	Low
Fracture	BTMs increase after fracture, with maximum effect 2–12 weeks, but remains elevated up to 52 weeks	Limits evaluation in patients with recent fracture	High
Menopause	BTMs increase at the time of the final menstrual period	Use reference intervals considering menopausal status	Moderate

Selected factors affecting the pre-analytical variation in bone turnover markers (BTMs) [9, 22]

GC glucocorticoids

renal insufficiency, immobility and exercise, have an impact on blood-bone turnover markers and should also be considered in their evaluation (Table 2) [18].

Current Recommendations of Use of Bone Turnover Markers in Clinical Guidelines

The use of serum bone formation marker PINP and resorption marker β CTX-I in the investigation of osteoporosis or in monitoring treatment is currently recommended in several guidelines around the world, including those issued by the UK National Osteoporosis Guideline Group (NOGG), by the National Osteoporosis Foundation in the US [19–21] and by the International Osteoporosis Foundation (IOF) [22, 23].

Aim

The aim of this consensus group report is to provide guidance, based on the opinion of the experts of this group, to clinicians on how to use bone turnover markers in patient evaluation, in fracture risk prediction and in monitoring treatment effect and adherence to oral bisphosphonates in postmenopausal osteoporosis. The results of this report are endorsed by the Scientific Board of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).

METHODS

An international working group was gathered to develop recommendations for the use of bone turnover markers in the diagnosis and treatment of osteoporosis. Specialists in internal medicine, endocrinology, rheumatology, rehabilitation, geriatrics, clinical biochemistry and epidemiology were invited to participate by the Scientific Advisory Board of European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). A 1-day in-person meeting was held on 5 February 2019 in Geneva to discuss the existing scientific literature on the

topic and to propose recommendations. After the meeting, members of the writing group (ML, JYR, JK, EM) drafted the first manuscript with the recommendations. The manuscript was then reviewed and commented on by all group participants from the Geneva meeting. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS AND DISCUSSION

Preferred Bone Markers

The IOF and International Federation of Clinical Chemistry and Laboratory Medicine recommend that the bone formation marker PINP and resorption marker β CTX-I be used as reference markers and measured in serum using standardized assays. These markers were chosen based on a number of criteria, including adequate characterization of the marker, specificity to bone, performance in clinical studies, biological and analytical variability, wide availability, potential for standardization of methods, sample handling, stability and medium of measurement (serum vs. urine) [22–24].

The Role of Bone Turnover Markers in the Diagnosis of Osteoporosis and Patient Evaluation

Osteoporosis is operationally defined by BMD using DXA. There is an inverse relationship between BMD and the serum levels of bone turnover markers, but the correlation is weak to moderate [25]. In the TRIO study, only 20% of postmenopausal women, diagnosed with osteoporosis using DXA had serum β CTX-I above the upper normal range for healthy premenopausal women [26]. Therefore, bone turnover markers cannot be used for the diagnosis of osteoporosis. However, abnormal levels of bone turnover markers, particularly when high, can be useful for identifying patients in whom further investigations may be needed to detect secondary causes of osteoporosis (e.g.,

primary hyperparathyroidism, thyrotoxicosis, malabsorption) or other bone diseases (e.g., osteomalacia, Paget's diseases, bone metastases, multiple myeloma) [27].

Predicting Bone Loss Using Bone Turnover Markers

Declining circulating estradiol levels, particularly during the menopausal transition, gives rise to increased bone turnover due to an increased number of bone remodelling units with a greater increase of osteoclastic activity, causing an imbalance between bone resorption and formation, leading to bone loss. The increased bone turnover is reflected by an increase in bone turnover markers, which is associated with loss of both trabecular and cortical bone [28, 29]. Bone turnover marker levels correlate with bone loss on a group level, and this correlation can be strengthened by sampling blood on several occasions to reduce the between-samples variation. However, the proportion of the variation in BMD change that can be explained by bone turnover markers remains quite small. Thus, predicting an individual's bone loss over time using bone turnover markers has proved challenging and cannot be recommended in a clinical setting [30–32]. Since bone loss from the forearm and hip has been associated with increased risk of fracture, it seems reasonable to assume that bone turnover markers, which are associated with bone loss, can predict fractures [33, 34]. In addition, bone turnover markers may affect fracture risk independently of BMD. Increased bone turnover can be accompanied by a high proportion of newly formed and partly mineralized bone, which is weaker than mineralized bone, and poor trabecular bone microstructure, because of resorption cavities on the trabeculae, trabecular perforations and loss of trabecular connectivity, can have a substantial negative impact on bone strength, not captured with DXA [35, 36].

The Role of Bone Turnover Markers in Fracture Risk Prediction

Most prospective studies investigating the associations between bone turnover markers

and incident fractures in postmenopausal and older women have found that the higher the level of bone turnover markers, the greater the fracture risk [18]. With some exceptions, bone resorption markers and bone alkaline phosphatase are more strongly associated with fractures (all, multiple, spine and hip) than other bone turnover markers [32, 37–39]. Elevated bone turnover markers increase fracture risk independently of BMD in some but not in all studies [18]. The role of serum PINP and β CTX-I in fracture prediction was investigated in a meta-analysis of six prospective cohorts with women and men. The risk of fracture was increased by 23% [hazard ratio 1.23 (95% CI 1.09–1.39)] and 18% [hazard ratio 1.18 (95% CI 1.05–1.34)] per SD increase in serum PINP and β CTX-I, respectively, but these analyses were not adjusted for BMD [40]. In a recent meta-analysis of nine studies of mostly postmenopausal women, bone turnover markers were weakly associated with fracture risk after adjustment for confounders, with a gradients of risk of 1.20 for serum β CTX-I and of 1.28 for serum PINP. It was concluded that PINP and β CTX-I appear to predict fracture risk independently of BMD and clinical risk factors [41], but the availability of knowledge of confounding variables was very variable. Bone turnover markers' ability to predict fractures seems to be stronger over short (within a few years) rather than long time periods [42, 43], which likely limits their value and usefulness in long-term fracture prediction in risk calculators such as FRAX, but makes them more appealing in the prediction of short-term or imminent fracture risk. Based on the relatively weak associations between bone turnover markers and fracture risk, uncertainty about the independent ability to predict fractures, the natural variability in the markers, problems with the assays and the inability to predict fracture over long time periods, the Fracture Risk Assessment Tool (FRAX) Position Development Conference members concluded that bone turnover markers should not be included in the calculation of the 10-year probability of fracture in the FRAX tool [44].

The Use of Bone Turnover Markers in the Monitoring of Osteoporosis Treatment

Bisphosphonates

Bisphosphonates, including alendronate, risedronate, zoledronate and ibandronate, are the most commonly used medications to treat osteoporosis [4]. They reduce bone resorption by inhibiting osteoclasts, increase BMD and lower the risk of spine, hip and non-vertebral fractures [45–47]. With treatment in recommended doses, β CTX-I is reduced rapidly, by approximately 50–80%, reaching maximum suppression after about 2 months, whilst PINP suppression is slightly smaller and reaches its nadir after about 6 months [48].

Several clinical trials have reported a relationship between the reduction of bone turnover markers and the reduction in vertebral and nonvertebral fracture risk following anti-resorptive treatment [18]. For example, changes in bone turnover markers have been shown to explain a considerable proportion, 54–77%, of the nonvertebral fracture risk reduction with risedronate treatment [49]. The 12-month decrease in β CTX-I and PINP with alendronate treatment in the Fracture Intervention Trial was associated with the reduction of spine fractures [50]. However, due to low sensitivity, it has been deemed inappropriate to use bone turnover markers to predict an individual patient's response to treatment [51].

Another complicating factor is that the effect on bone marker suppression varies across the licensed bisphosphonates. For example, in the TRIO study, alendronate and ibandronate treatment given to postmenopausal osteoporotic women caused a greater suppression of β CTX-I and NTX-I levels than risedronate [26].

A major challenge with oral bisphosphonates is the poor adherence with less than half of patients taking medication 1 year after treatment initiation [52]. Women adhering to oral bisphosphonates have greater reductions in serum bone turnover marker levels and lower fracture risk than women with poor adherence [26]. It has therefore been proposed that bone turnover markers can be used to monitor treatment adherence. For such a task to be successful

and clinically useful, clear definitions of what constitutes an adequate response to treatment must exist. A blood test prior to and after a certain time post-treatment initiation will be required to determine the level of change in the bone turnover markers. Since serum PINP and β CTX-I are responsive to treatment and have low within-subject variability, their use is recommended. A commonly proposed approach to determine if the change in the bone marker is physiologically relevant (and not due to measurement or sampling error) is to compare the observed change with the least significant change (LSC). Assuming that the change is normally distributed, a true change would have to be greater than the LSC, which equals $\sqrt{2} \times 1.96 \times \text{intra-individual coefficient of variation (CV)} = 2.77 \times \text{CV}$. For example, using this approach, serum β CTX-I would need to drop from 350 ng/l to 259 ng/l, assuming an intra-individual CV of 9.4%, which corresponds to an LSC of 26%, in a treated patient to confirm a positive treatment response. In the TRIO study, 3-month bisphosphonate treatment resulted in suppression of PINP and β CTX-I larger than LSC in 75–94% and 68–73%, respectively, of the included women. A detection level, describing the proportion of patients taking oral bisphosphonates that show decreases (larger than LSC) in each of the markers, β CTX-I and PINP, was investigated and was found to be 84% for PINP, 87% for β CTX-I and as high as 94% when measuring both markers [26, 53]. Based on the findings of the TRIO study, the International Osteoporosis Foundation (IOF) and European Calcified Tissue Society (ECTS) Working Group recently issued a recommendation to monitor oral bisphosphonate treatment using a baseline and 3-month measurement of serum β CTX-I and PINP. According to this recommendation, if the decrease is smaller than the LSC, the treating clinician should reassess to identify problems with treatment, which usually relate to poor adherence (Fig. 1) [53].

Another approach that has been proposed is to define the target for treatment as suppression of the bone turnover marker to the lower half of the reference interval in young and healthy premenopausal women [54]. This strategy is

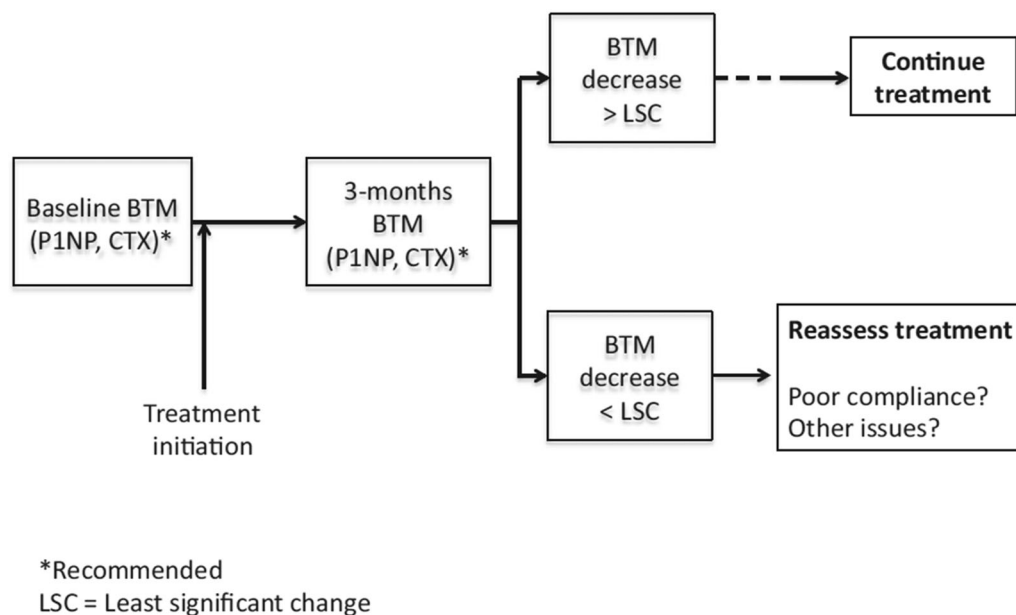


Fig. 1 Algorithm proposed by an IOF-ECTS working group for monitoring bisphosphonate treatment adherence using CTX-I and/or PINP [53]

complicated by the fact that not all women are above this interval prior to receiving treatment. If bone turnover markers have not been measured prior to starting therapy, the reference interval method could still be used, which increases the clinical usefulness of the method. An analysis from the TRIO study revealed that the proportion of responders detected using the reference interval approach was very similar to the one detected using the LSC approach [26].

Denosumab

Denosumab is a human monoclonal antibody to RANKL, which is administered subcutaneously. It is the most potent inhibitor of bone resorption, as reflected by a very rapid decrease to nearly undetectable levels of bone resorption marker β CTX-I within a few days of administration [55]. Serum PINP is also suppressed by denosumab treatment, but the decrease is not as marked as for β CTX-I and takes up to 3–6 months to be complete [56]. Biannual injections of denosumab reduce the risk of hip, vertebral and non-vertebral fractures in postmenopausal women [13]. The effect of denosumab is more potent than bisphosphonates in increasing BMD, which continues to rise for up

to 10 years of treatment [57]. However, when treatment is stopped, there is a rebound increase in bone turnover markers well above pre-treatment levels and accelerated bone loss is seen [58]. During this phase the risk of multiple vertebral fractures increases [59, 60]. Pretreatment with bisphosphonates reduces this overshoot in bone turnover markers when denosumab treatment stops, and starting bisphosphonate therapy after denosumab cessation is able to attenuate bone loss, but the optimal regime for bisphosphonate therapy after denosumab cessation has not yet been determined [61]. It is possible that monitoring the bone marker response may aid in the use of bisphosphonate treatment frequency and dosing when denosumab treatment is stopped. Future research is needed to address this hypothesis.

Anabolic Treatment

Treatment of postmenopausal women with the parathyroid hormone analogue teriparatide causes a rapid, within days, response in bone formation markers such as PINP, which reach peak levels after 3 months [62, 63]. This increase

is followed several months later by a considerably smaller rise also in bone resorption markers. The response to teriparatide is dose-dependent and the increase in PINP correlates weakly or moderately with increases in BMD, which are considerably larger at bone sites rich in trabecular bone, such as the lumbar spine, than those seen with bisphosphonate therapy [64, 65]. Teriparatide is more effective than oral risedronate in reducing the risk of vertebral and clinical fractures in postmenopausal with severe osteoporosis [66]. A systematic review of the present evidence concluded that there is insufficient evidence to recommend the use of monitoring bone turnover markers for predicting the effect of teriparatide treatment effect [67].

CONCLUSION

Although the use of bone turnover markers has been extensive in clinical trials, prospective cohort studies, case-control studies and at many clinics included in standard patient evaluation for many years, their value in clinical practice is not entirely clear. Challenges relating to large pre-analytical (diurnal variations, feeding, age, gender, menopausal status, etc.) and analytical variations and use of a multitude of markers in different clinical scenarios have impaired the interpretation of their value and makes recommendations for their use in the individual patient more difficult. Despite these challenges, this working group recommends that the following conclusions can be made, based upon the available evidence:

- The bone formation marker serum PINP and resorption marker serum β CTX-I are the preferred markers for evaluating bone turnover in the clinical setting.
- Bone turnover markers cannot be used to diagnose osteoporosis but can be of value in patient evaluation and can improve the ability to detect some causes of secondary osteoporosis.
- Serum β CTX-I and PINP correlate only moderately with bone loss in postmenopausal women and with osteoporosis medication-

induced gains in BMD. Therefore, the use of bone turnover markers cannot be recommended to monitor osteoporosis treatment effect in individual patients.

- Adding data on serum β CTX-I and PINP levels in postmenopausal women can only improve fracture risk prediction slightly in addition to clinical risk factors and BMD and therefore has limited value.
- Bisphosphonates are the most commonly used osteoporosis medications, but adherence to oral bisphosphonates falls below 50% within the first year of treatment. Monitoring PINP and β CTX-I is effective in monitoring treatment adherence and can be defined as the sufficient suppression of these markers (by more than the LSC or to the lower half of the reference interval for young and healthy premenopausal women).

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