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Original Article

Consensus Statement on the Use of Bone Turnover Markers for Short-Term Monitoring of Osteoporosis Treatment in the Asia-Pacific Region

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Abstract

Osteoporosis is a major health issue. By 2050, a greater than 2-fold increase in patients number with hip fractures will occur in Asia representing 50% of all hip fractures worldwide. For the Asia-Pacific (AP) region, more efforts on controlling osteoporosis and the subsequent fractures are crucial. Bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is commonly used to diagnose osteoporosis and monitor osteoporosis treatment. However, the inconvenience, cost, limited availability of DXA and the delay in detection of BMD changes after treatment initiation support an important role for bone turnover markers (BTMs), as short-term tools to monitor therapy. With regards to low adherence rates of medical treatment of osteoporosis, the experts reached consensus on the use of BTMs for both raising awareness and short-term monitoring of osteoporosis treatment in the AP region. The experts endorse the use of BTMs, especially serum C-terminal telopeptide of type 1 collagen (CTX) and serum procollagen type 1 N propeptide (P1NP), as short-term monitoring tools to help clinicians assess the responses to osteoporosis therapies and appropriately adjust treatment regimens earlier than BMD. Either the absolute values or the degree of change from baseline in BTMs can be used to monitor the potential efficacy of osteoporosis therapies. The use of BTMs can be incorporated in osteoporosis care programs, such as fracture liaison service (FLS), to improve patient adherence and treatment outcomes. Encouraging sufficient reimbursement from health care systems may facilitate widespread use of BTMs in clinical practice in the AP region.

Key Words: Osteoporosis; anabolics; anti-resorptives; bone formation maker; bone resorption maker.

Introduction

The rapid aging of world's population is being recognized as a serious public health burden, especially in the Asia-Pacific (AP) region due to its enormous population base *(1)*. Osteoporosis remains a greatly under-diagnosed and under-treated disease in the AP region, even in high-risk patients with fragility fractures. A 2−3 fold increase in the incidence of hip fractures has been noted in most Asian countries over the past three decades *(2)*. In 2004, the World Health Organization (WHO) estimated that osteoporosis would incur approximately 9 million fractures worldwide, with 2.5 million and 1.6 million in the Western Pacific regions and Southeast Asia, respectively *(1)*. It is projected that by 2050, 50% of hip fractures worldwide will occur in Asia *(1)*. The annual number of hip fractures is expected to increase from 1.12 million in 2018 to 2.56 million in 2050, a 2.28-fold rise *(3)*. Therefore, the threat of bone health hazards in the AP region will grow in coming decades and optimal diagnostic and monitoring strategies must be developed to mitigate this risk *(4)*. On the other hand, low adherence to osteoporotic treatment is not uncommon, such as less than one-third of Taiwanese osteoporotic women and only 10% of Taiwanese osteoporotic men receiving anti-osteoporotic medications between 2009 and 2013 *(5)*. Thus, strategies for improving the adherence can never be over-emphasized in the AP region.

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Fracture liaison service (FLS) in the AP region

The IOF Capture the Fracture® programme facilitates the establishment of Fracture Liaison Services (FLS) with a goal to properly identify and treat patients with fragility fractures, improve quality of post-fracture care, adherence, and prevention of secondary fractures worldwide, including the AP region *(4, 6)*. In 2017, the Asian Federation of Osteoporosis Societies (AFOS) also emphasized the need for managing patients with osteoporosis *(7)*. Meta-analyses and systematic reviews of more than 150 publications on osteoporosis-related fractures demonstrated that compared with care programs without FLS, those with FLS can increase BMD assessment rate, treatment adherence as well as reduce the risk of secondary fractures and mortality *(8)*. FLS has shown a favorable economic impact and cost-effectiveness clinically *(9)*.

These encouraging reports that FLS implementation per IOF Best Practice Standards should be fully supported and endorsed by the AP region *(4)*. Up to October 2018, more than 300 FLS programs have been established worldwide, with 57 sites in the AP region. FLS is increasingly important for secondary fracture prevention in this region, especially in Australia and Taiwan *(4, 10)*.

Monitoring of osteoporosis treatment and unmet needs

Bone mineral density (BMD) assessed by dual energy X-ray absorptiometry (DXA) using the WHO T−score definition of osteoporosis is currently the major criterion for the diagnosis of osteoporosis *(11)* with the advantages of predicting fracture risk, diagnosing osteoporosis, and

monitoring therapeutic response *(11, 12)*. DXA is the most widely validated technique for measuring BMD at the spine, proximal femur, and distal radius that are sites commonly associated with osteoporotic fractures *(11)*. Increases in BMD after treatment are correlated with a reduction of fracture risk. However, the slow change of BMD with treatment requires at least 1 year or longer to assess the efficacy of treatment *(13)*. Other limitations of DXA include inconvenience, cost and limited availability all reflected in the unmet clinical need. Thus, other methods for evaluating treatment efficacy earlier may have clinical benefits.

Although BMD measured by DXA is used to diagnose osteoporosis according to the WHO recommendations *(11)*, there are other skeletal properties, collectively called "bone quality," that also determine bone strength and fracture risk. In addition, some clinical trials have shown that the reduction in fracture risk associated with anti-resorptive therapy may occur independently of changes in BMD *(14)*. Therefore, for complete assessment of bone strength, BMD should be combined with assessments of bone quality. One important contributor of BMD and bone strength is the rate of bone remodeling, which can be assessed by measurement of bone turnover markers (BTMs).

Previous studies have demonstrated that the magnitude of BTM suppression is strongly associated with fracture risk reductions *(15)*. Indeed, for some treatments, changes in BTMs may explain more of the variance in fracture risk reduction than does BMD. BTMs commonly used in both clinical trials and clinical practice are serum C-terminal telopeptide of type I collagen (CTX), a marker of bone resorption, and serum procollagen type 1 amino-terminal propeptide (P1NP), a marker of bone formation *(16)*. Although not consistently seen in all studies, high pretreatment BTMs serum level may reflect a higher bone remodeling rate and subsequent risk of fracture, especially in untreated subjects with low BMD *(15)*. On the contrary, low pretreatment serum P1NP levels were associated with a non-significant decrease in fracture risk during alendronate treatment *(17)*. Several other BTMs are available, including bone remodeling marker osteocalcin (OC); serum bone formation markers such as bone isoenzyme of alkaline phosphatase (BAP) and C-propeptide of type I collagen (P1CP), in case of limited availability of CTX and P1NP *(18, 19)*. Changes of bone resorption markers levels can be detected as early as 1 month after initiating therapy and have been shown to be helpful for monitoring patients in clinical practice *(20)*. CTX and P1NP are recommended as a monitoring targets for osteoporosis treatment by several global osteoporosis guidelines including the International Osteoporosis Foundation (IOF), the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), the National Osteoporosis Foundation (NOF), and the Japan Osteoporosis Society (JOS) *(21–23)*. The AACE/ACE recommends using BTMs for the initial evaluation and follow-up of osteoporosis patients *(21)*. The NOF agrees that BTMs can aid in risk assessment and serve as an additional monitoring tool when treatment is initiated *(22)*. The Taiwanese Osteoporosis Association (TOA) recommends measuring BTMs at 3–6 months after starting anti-osteoporotic medications *(24)*. The utility of BTMs can be applied under several clinical situations, including:

(1) Educate patients who have suboptimal understanding of the need for treatment;
(2) In patients who are scheduled to receive pharmacotherapy;
(3) When a physician aims to select an appropriate treatment for osteoporosis, as well as to evaluate the response to treatment (23).

The BTMs and its role in fracture liaison service (FLS)

The FLS focused on the patients with recent fractures, of them including most dominantly untreated or underdiagnosed old fragility fractures *(25)*. Considering the need for convenient and reliable parameters for identifying non-compliant patients with subsequently risk of refracture, BTMs can be an option as an earlier real-time monitoring osteoporosis treatment efficacy in the FLS program. BTMs are useful in assessing bone remodeling before selecting an initial osteoporosis therapy option, to monitor likely adherence and response to osteoporosis therapies within months of starting and to facilitate ongoing treatment decisions *(26)*. However, Silverman et al. reported that providing BTMs data may not improve the persistence to oral bisphosphonate therapy adequately *(27)*. Recently, the IOF and European Calcified Tissue Society (ECTS) Working Group recommended that the medication compliance rate might be addressed by using CTX and P1NP, if a significant decrease is observed the treatment can be continued; but if no change is observed, the physician should reassess the compliance to the treatment and also other potential issues with the drug *(28)*. Indeed, early detection of low adherence and/or low response of treatment may draw the attention of healthcare team, thus decreasing the risk of fractures as well as burden on healthcare cost *(29)*. Short-term monitoring of the treatment response by BTMs might also play a role in selecting a more proper osteoporosis therapy for individual patient with old fragility fracture. However, the BTMs level will fluctuate right after a recent fracture episode. Therefore, BTMs should be carefully used in monitoring treatment response since BTMs can be affected up to as much as 12 months or more after a new fracture, the impact is largest during the first 6 months. Thus, the levels of BTMs in this period for monitoring may be inconclusive. Therefore, the role of BTMs in FLS should be case-sensitive by clinical situation. Currently, lack of

reimbursement under healthcare insurance scheme makes BTMs not systematically incorporated into most FLS programs in different countries among the AP region. Table 1 summarizes detailed recommendations and reimbursement policies by country/region.

The intervals and reference change values of BTMs

CTX and P1NP are the most commonly used markers in many clinical studies, as recommended by the IOF and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) *(26)*. As an example, patients treated with oral and intravenous bisphosphonates have been monitored based on the change of CTX serum level from baseline to 3 months after starting treatment. A decrease of 30% to 60% for CTX was considered as the reference change value in oral bisphosphonate treatment *(28, 30)*. An optimal treatment response with CTX for patients who are not postmenopausal is suggested to be either a decrease of 100 ng/L or to below 280 ng/L *(31)*.

The serum level of P1NP may be also utilized for monitoring the efficacy of both anabolic and anti-resorptive treatments. It has been suggested that the efficacy of oral bisphosphonates and intravenous bisphosphonates could be assessed at 3 months and 6 months after treatment, respectively *(31)*. The reference change value for oral bisphosphonate treatment is considered for those decrease more than 20%−40% for P1NP measured at 3 months after starting therapy compared with baseline *(28, 30)*; another suggested measure of optimal treatment response for patients who are not postmenopausal is either a decrease of 10 μg/L or to below 35 μg/L *(32)*. Furthermore, P1NP may be used for monitoring anabolic therapy with an optimal response being an increase in P1NP of more than 10 μg/L *(33)*. Strong correlations between changes of P1NP levels at 1 and 3 months and increases of spinal BMD at 12 and 18 months following anabolic therapy have been shown in several clinical studies *(33)*. A significant increase of P1NP 1 month after anabolic treatment revealed the strong relationship between early change in P1NP and later change in lumbar spine BMD during teriparatide therapy *(20)*. However, when shifting to anabolics after the treatment with anti-resorptive drug, the P1NP takes a longer time to reach a plateau. In such a situation, it may be appropriate to measure P1NP 6 months after starting treatment. When a baseline value is not available, as often occurs in real-world practice, a threshold may be used instead. For example, 100 ng/L for CTX or 10 μg/L for P1NP. Evidence is insufficient to reach consensus about the use of BTMs for monitoring offset of bisphosphonate action during a drug "holiday" or combination therapy or in patients with a recent fracture (within 6 months).

Reference values for P1NP and CTX for the population have been obtained from studies in Italy, UK, France, Belgium, USA, Saudi Arabia, and Denmark *(32)* with no major differences among these countries *(34)*. In addition, for Asian populations, Nishizawa et al. had found that values for both biomarkers in several Japanese clinical trials are similar to those in Western countries *(35)*. Based on the best available evidence, BTM reference values may be universal without racial or geographic variations. However, it should be noted that the reference interval is very large for both CTX (~100 to ~700 ng/L) and P1NP (~15 to ~70 μg/L), regardless of the countries where the studies conducted *(32, 34, 35)*, depends on the assay adopted. Significant disagreement between the IDS-iSYS and Roche Cobas assays for both reference markers has been reported *(32, 36)*. In review published by Morris et al., different reference intervals were showed between the measurements of 2 methods *(32)*. In a study included 2,308 individuals in a Danish population, the 2 CTX assays with a mean difference of 13 ng/L (LoA: 187−214) and the 2 P1NP assays with a mean difference of −3 μg/L (LoA- 19−14) *(36)*. Therefore, monitoring the change of CTX and P1NP with treatment may be more suitable than using absolute mean values in the clinical practice setting *(35)*.

On the other hand, the suboptimal BTMs response to treatment may indicate either non-compliance or the presence of secondary causes of osteoporosis which may need to be addressed *(37)*, especially in subjects with lower pretreatment level of BTMs. Bone resorption and formation markers seem to be lower in patients with diabetes *(19)*, and are variable in patients with chronic kidney disease (CKD) *(19)* and some other endocrine diseases associated with osteoporosis. Adult patients with congenital hypophosphataemia on long-term phosphate supplementation as treatment may have a high rate of bone resorption, as indicated by elevated CTX *(38, 39)*. Parathyroid hormone (PTH) has been reported to be associated with elevated levels of OC and CTX in postmenopausal women with vitamin D insufficiency *(40)*. Because of inverse the correlation between serum 25-hydroxyvitamin D (25[OH]D) levels and PTH *(41)*. Patients on treatment with active vitamin D may show relatively higher CTX levels. On the contrary, no significant association between serum 25(OH)D and P1NP has been found in healthy population *(42)*. Furthermore, it is important to note that BTMs levels may be significantly elevated even at 6 months following a fracture because of the repair process. IOF-IFCC Bone Marker Standards Working Group recommending the use of BTMs for monitoring the efficacy of osteoporosis treatment should be considered carefully in patients with a recent fracture (43). In summary, when using BTMs for monitoring therapeutic responses in patients with comorbidities or who are using medications which may influence BTMs, they should be cautiously interpreted and alternative assessments should be considered.

The succinct comparisons between 5 frequently used BTMs assays are summarized in Table 2 *(13, 14, 37−42, 44)*, including PINP, CTX, NTX, OC and BAP. IOF-IFCC Bone Marker Standards Working Group recommending when comparing BTM results over time that the same assay platform should be used. Because of CTX is affected by food intake, fasting plasma sample should be used. If patients have abnormal renal or hepatic function, BAP could be

Table 1
Summary of BTM or CTX/P1NP in national guidelines in Asia-Pacific region

Country/Region	Organization/Guideline	Recommendation	CTX/P1NP reimbursed by national healthcare insurance
Australia	The Royal Australian College of General Practitioners/Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men	• The International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine recommend one serum bone formation marker (procollagen type I amino-terminal propeptide, or PINP) and one bone resorption marker (C-terminal telopeptide, or CTX) to be used as reference markers. • These should be 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.	Yes
China	Chinese Society of Osteoporosis and Bone Mineral Research, Chinese Medical Association/Guidelines for primary osteoporosis diagnosis and management(2017)	• Bone turn over markers help clinicians identify the Primary and secondary Osteoporosis condition and predict speed of bone loss, evaluate risk of bone fracture and choose medication as well as enhance patient's compliance. • Recommends PINP and CTX as a standard bone resorption and bone formation markers.	Yes
Hong Kong	The Osteoporosis Society of Hong Kong (OSHK)/2013 OSHK Guideline for Clinical Management of Postmenopausal Osteoporosis in Hong Kong	• Changes in BTMs are much more rapid than the changes in BMD. With most effective anti-resorptive therapies, BTMs decrease rapidly and reach a drug- and dose-dependent plateau within a few months. • Short-term reduction in BTMs have also been shown to correlate with the longer-term BMD response to therapy and reduction in fracture risk. • There is emerging support for their use in monitoring treatment response, especially within the first 3–6 months of initiation of anti-resorptive therapy when BMD changes are too small to be detected clinically.	No
India	Indian Rheumatology Association guidelines for management of glucocorticoid-induced osteoporosis (GIOP)(2011)	• Bone resorption markers (N-telopeptide, C-telopeptide of type I collagen) can be used in addition to a BMD assessment to identify high risk patients for future fracture and monitoring of response to treatment • Bone resorption markers (N-telopeptide, C-telopeptide of type I collagen) along with DXA can be used to monitor treatment response if feasible. Two separate baseline values followed by	No

(*continued on next page*)

Table 1 (*Continued*)

Country/Region	Organization/Guideline	Recommendation	CTX/P1NP reimbursed by national healthcare insurance
		repeat measurement at 3 months after starting GC should be done. Bone resorption markers can be repeated every year if needed	
Indonesia	Summary of Indonesian Guidelines for Diagnosis and Management of Osteoporosis	• Indication for bone biochemical markers measurement is to identify patient with osteoporosis risk, rapid bone loss, predict femoral fracture risk, to monitor patient with long-term steroid treatment, to evaluate treatment responses and study the pathogenesis of osteoporosis. • Treatment with anti-resorptive agents will rapidly decrease bone remodeling, thus it can be detected using bone marker tests. • Bone metabolism markers can also be used to evaluate treatment responses, and can detect the changes earlier, within 3–4 months.	No*
Japan	Japan Osteoporosis Society Guidelines for the use of bone metabolic markers in the diagnosis and treatment of osteoporosis (2012 edition)	• These proposed guidelines for the appropriate use of bone metabolic markers take into consideration current health insurance regulations in Japan. • However, in order to achieve a more appropriate use of bone metabolic markers, it is now recognized that periodic repeated measurement for monitoring after treatment is also effective.	Yes
Malaysia	Malaysian Osteoporosis Society/Clinical Practice Guidelines on Management of Osteoporosis	• BTM are useful to identify patients at high risk of future fractures. • It can also be used to evaluate treatment efficacy and compliance to therapy. • They should not be used for the diagnosis of osteoporosis. Changes in level of BTM can be seen within 3–6 months after initiation of drug therapy.	No*
New Zealand	Guidance on the Diagnosis and Management of Osteoporosis in New Zealand	Serum procollagen type I N-terminal propeptide (PINP) measurement: • Bisphosphonates reduce bone turnover, which can be assessed by measuring serum PINP. With effective bisphosphonate therapy, PINP levels will decrease to <35 μg/L. • If PINP levels remain ≥35 μg/L after 6 months of oral bisphosphonate treatment, this indicates suboptimal adherence to the bisphosphonate or poor absorption of the bisphosphonate. Switching to an IV bisphosphonate should be considered. • PINP measurement can be organized through the local laboratory, with no time-of-day restrictions for obtaining blood samples. • PINP levels do not usually need to be assessed in patients treated with IV bisphosphonate.	No

(*continued on next page*)

Table 1 (*Continued*)

Country/Region	Organization/Guideline	Recommendation	CTX/P1NP reimbursed by national healthcare insurance
Philippines	OSPFI & POA/Consensus statements on osteoporosis diagnosis, prevention, and management in the Philippines	• Bone turnover markers should not be used in the diagnosis of osteoporosis. • Biochemical markers of bone turnover in clinical practice can be used for assessing adherence to and effectiveness of therapy.	No*
Singapore	Singapore Ministry of Health/Singapore Ministry of Health: Clinical Practice Guidelines for Osteoporosis	• Alternative method for monitoring therapeutic response is evaluating bone turnover markers at baseline and at 3–6 months intervals. • The use of most effective osteoporosis drugs has been associated with reductions from baseline of between 20% and 40% for bone formation markers such as osteocalcin and bone alkaline phosphatase, and 30–60% for bone resorption markers such as N telopeptide, C telopeptide and deoxypyridinoline. • Not a diagnostic tool for bone fracture prediction but an aid in fracture risk assessment, the prediction of rates of bone loss, as well as in monitoring response to treatment.	No
South Korea	Korean Society for Bone and Mineral Research/Physician's guide for diagnosis & treatment of osteoporosis	http://www.ksbmr.org/image/journal/골다공증%20지침서 2015_final_1002.pdf. (In Korean)	Yes
Taiwan	Taiwanese Guidelines for the Prevention and Treatment of Osteoporosis (2014)	• CTX and P1NP can be utilized as a monitoring tool in osteoporosis treatment, but not diagnostic tool of osteoporosis.	No
Thailand	Thai Osteoporosis Foundation/Thai Osteoporosis Foundation (TOPF) position statements on management of osteoporosis	• Biochemical markers of bone turnover (BTMs) are not recommended for diagnosis of osteoporosis because there are many confounding factors. BTMs can also change several in non-osteoporosis associated conditions. • However, BTMs can be used along with BMD for risk assessment for fracture. BTMs, however, can be useful for follow-up. It is recommended that BTMs should be tested at 3 months and 1 year. These markers can prove to be accurate and efficient in monitoring drug response.	Yes

Abbr: BMD, bone mineral density; BTM, bone turnover markers; CTX, C-terminal telopeptide of type I collagen; DXA, dual energy X-ray absorptiometry; P1NP, procollagen type 1 amino-terminal propeptide.
*The BTMs in Malaysia, Philippines and Indonesia are not reimbursed for outpatients, but may be covered by insurance package for inpatients.

Table 2
Comparison of bone turnover markers (BTMs) assays*

	C-terminal telopeptide of type I collagen (CTX)	N-terminal telopeptide of type I collagen (NTX)	Serum procollagen type 1 amino-terminal propeptide (P1NP)	Osteocalcin (OC)	The bone isoenzyme of alkaline phosphatase (BAP)
Analysis methods	• Automated and manual immunoassays • Multiplex microarray	• Automated and manual immunoassays • Multiplex microarray	• Automated and manual immunoassays • Multiplex microarray • Total or intact fractions	• Automated and manual immunoassays • Multiplex microarray	• Automated and manual immunoassays
Sample type	• Serum • EDTA plasma • Urine	• Serum • EDTA plasma • Urine	• Serum • EDTA plasma	• Serum, • EDTA plasma	• Serum • EDTA plasma
Features	• Affected by food intake • Large circadian variation • Affected by glucose status and renal failure	• Not affected a lot by food intake, but fasting blood sample preferred • Large circadian variation • Affected by renal and hepatic functions • Fewer changes compared to CTX or P1NP	• Not affected by food intake • Small circadian rhythm • Affected by renal failure or metastatic bone disease • Expensive	• Not affected by food intake • Moderate circadian rhythm • Affected by Vit K status and renal function • Large inter-lab variation	• Not affected by food intake • Moderate circadian rhythm • Not affected by renal function • Cheap • Few changes with drug therapy

*References: *(18, 19, 37–42, 44)*.

selected. CTX and NTX have large circadian variations, the sampling time has to be consistent for every testing time point; otherwise P1NP or BAP may be more appropriated for patients who cannot provide samples for measurement at each time point.

After reviewing recent publications and discussing data in a meeting organized by TOA and held during the Annual Meeting of TOA on October 20, 2018, Taipei, the experts suggested an updated consensus for using BTMs for short-term monitoring of anti-osteoporosis treatment in the Asia-Pacific region. Compared with other BTMs, serum CTX and P1NP levels appear to be more robust in reflecting rates of bone remodeling. In patients who are receiving anti-resorptive therapies, serum CTX and/or P1NP can be used to monitor compliance and drug response, with measurements at baseline, 3 months, 6 months, and 12 months after starting treatment. In patients who are receiving anabolic therapies, serum P1NP can be used to monitor compliance and drug response, with measurements at baseline, 1−3 months, 6 months, and 12 months after starting treatment. We also support the adoption of the National Bone Health Alliance (NBHA) recommendations for standardized sample handling and patient preparation for CTX and P1NP measurements to minimize controllable pre-analytical variability (45). The clinical characteristics of applying CTX or P1NP in clinical practice are shown in Table 3.

Summaries of Consensus Statement

- Endorse the use of BTMs, especially CTX and P1NP, as short-term monitoring tools for osteoporosis treatment, consistent with recommendations of the AACE/ACE, IOF, IFCC, JOS, NOF, TOA, and associated organizations.
- BTMs can be used to differentiate patients with relatively higher or lower bone turnover rates and thereafter, helping clinicians to choose an appropriate anti-osteoporosis treatment regimen.
- BTMs can reflect the therapeutic responses to anti-osteoporosis therapies earlier than BMD and are therefore of help both in selecting osteoporosis treatment and in assessing its responses to therapies.
- Absolute values or the degree of change from baseline for BTMs can be used to monitor the efficacy of osteoporosis therapies clinically.
- CTX and/or P1NP can be used to evaluate patient adherence and drug responses to anti-resorptive agents, with measurements suggested at baseline, 3 months, 6 months, and 12 months after starting treatment.
- P1NP can be used to evaluate patient adherence and drug responses to anabolic agents, with measurements at baseline, 1−3 months, 6 months, and 12 months after starting anabolic treatment.
- Encourage reimbursement of BTMs by different health insurance programs in the Asia-Pacific to improve patient adherence and treatment outcomes.
- Recommend appropriate use of BTMs as a short-term monitoring tool for improving the use of therapeutic regimens in osteoporosis care programs, such as fracture liaison service (FLS).

In conclusion, the use of BTMs can be incorporated in treatment algorithms of osteoporosis care programs to improve patient adherence and treatment outcomes. Encouraging sufficient reimbursement from health care systems may facilitate more widespread use of BTMs in clinical practice in the AP region.

Table 3
The clinical characteristics of serum C-terminal telopeptide of type I collagen (CTX) and N-terminal propeptide of type I procollagen (P1NP) in short-term monitoring osteoporosis treatment

	CTX	P1NP
Monitoring Medication	• Anti-resorptives	• Anti-resorptives • Anabolics
Testing frequency (Length of follow up)	• Baseline • 3 months after 1st treatment • Follow up at 6th month and 12th month	• Baseline • 1 to 3 months after 1st treatment* • Follow up at 6th month and 12th month
Threshold of efficacy (change from baseline)	• >30% or 100 ng/L	• >20% or 10 μg/L
Possible interference	• Circadian variation • Food intake • Glucose status • Affected by renal failure	• Little affected by food intake • Affected by renal failure

Abbr: BTM, bone turnover marker.
*This doesn't include the scenario that using BTMs for monitoring anabolics right after the treatment with anti-resorptive drug or offset of bisphosphonate action during a drug "holiday" or combination therapy.

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Author contributions

Conceived and designed the idea and meeting: CHW, YFC, and RSY. Consensus meeting in person: CHW, YFC, CHC, CW, TM, LBMA, JSH, CLC, GTL and RSY. Review the pre-consensus draft: CHW, YFC, CHC, CW, TM, LBMA, KST, EML, DCC, KS, JKL, STT, WX, WY, YSC, PE, CC, JSH, CLC, GTL and RSY. Prepared the tables: CHW. Wrote the paper: CHW, YFC and RSY. Critically reviewed the manuscript: EML, IR, AM, PE, KS and SLF.

Additional information

Competing financial interests: All authors declare that they have no both competing financial and non-financial interests related to the current study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jocd.2019.03.004.

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