Clinica Chimica Acta 498 (2019) 101–107

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Executive summary of the Japan Osteoporosis Society Guide for the Use of Bone Turnover Markers in the Diagnosis and Treatment of Osteoporosis (2018 Edition)

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ARTICLE INFO

Keywords:
Guide
Bone turnover marker (BTM)
Osteoporosis
Diagnosis

ABSTRACT

With the aging of society, the number of osteoporosis-related fractures is increasing. Prevention of osteoporosis and maintenance of the quality of life of osteoporosis patients require early diagnosis, effective treatment, and highly precise treatment monitoring. Although bone biopsy is clinically one of the essential techniques for diagnosis of osteoporosis, it is invasive and difficult to perform in general clinical practice. Bone mineral density measurement is another essential technique available in clinical practice that provides good precision. However, it is not effective for determining the appropriate treatment options or evaluating short-term treatment efficacy. On the other hand, bone turnover markers (BTMs) have gained attention because they provide information that is valuable for both the selection of treatment and short-term monitoring.

BTMs are now positioned to become a tool for clinically assessing bone turnover outcomes. Since the Japan Osteoporosis Society issued its Guidelines for the Use of Bone Turnover Markers in the Diagnosis and Treatment of Osteoporosis in 2012, new drugs, drug formulations, and combination drug therapies have been approved; therefore, we updated the 2012 guidelines in the Guide for the Use of Bone Turnover Markers in the Diagnosis and Treatment of Osteoporosis (2018 Edition).

Abbreviations: ADL, activities of daily living; BAP, bone alkaline phosphatase; BMD, bone mineral density; BTM, bone turnover maker; CKD, chronic kidney disease; CTX, type I collagen cross-linked C-telopeptide; DPD, deoxypyridinoline; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; MSC, minimum significant change; NTX, type I collagen cross-linked N-telopeptide; OC, osteocalcin; P1CP, type I procollagen-C-propeptide; P1NP, type I procollagen-N-propeptide; PTH, parathyroid hormone; PYD, pyridinoline; QOL, quality of life; RANKL, receptor activator of NF-κB ligand; SD, standard deviation; SERM, selective estrogen receptor modulator; TRACP-5b, tartrate-resistant acid phosphatase 5b; ucOC, undercarboxylated osteocalcin; YAM, young adult mean; 1CTP, type I collagen C-telopeptide

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https://doi.org/10.1016/j.cca.2019.08.012
Received 11 July 2019; Received in revised form 14 August 2019; Accepted 14 August 2019
Available online 16 August 2019

Table 1
Types, abbreviations, samples, and assay methods of BTMs (as of April 2018).

Marker	Abbreviation	Sample	Assay	Notes
Bone formation markers				
Osteocalcin[b]	OC	Serum	ECLIA[a] , FEIA[a]	
Bone alkaline phosphatase[c]	BAP	Serum	CLEIA , EIA	
Type I procollagen-C-propeptide[d]	P1CP	Serum	RIA[a]	
Intact type I procollagen-N-propeptide	Intact P1NP	Serum	RIA	Measure trimer only
Total type I procollagen-N-propeptide	total P1NP	Serum	ECLIA	Measure trimer and monomer
Bone resorption markers				
Pyridinoline	PYD	Urine	HPLC[a]	
Deoxypyridinoline	DPD	Urine	EIA, CLEIA, HPLC[a]	
Type I collagen cross-linked N-telopeptide	sNTX	Serum	EIA	CLEIA is approved in Japan
	uNTX	Urine	EIA, CLEIA	
Type I collagen cross-linked C-telopeptide[e]	sCTX	Serum	EIA , ECLIA	
	uCTX	Urine	EIA	
Type I collagen C-telopeptide	1CTP	Serum	RIA[a]	
Tartrate-resistant acid phosphatase 5b	TRACP-5b	Serum	EIA, CLEIA, POCT	POCT is under development
Bone matrix-related markers				
Undercarboxylated osteocalcin	ucOC	Serum	ECLIA	
Pentosidine[f]	–	Plasma	EIA[a]	
		Urine	HPLC[a], EIA[a]	
Homocysteine	–	Plasma	HPLC[a]	

ECLIA: electrochemiluminescence immunoassay, FEIA: fluorescence enzyme immunoassay, EIA: enzyme-linked immunosorbent assay, RIA: radioimmunoassay, HPLC: high-performance liquid. chromatography, CLEIA: chemiluminescent enzyme immunoassay, POCT: point of care testing.

[a] Not covered by health insurance for osteoporosis management.

[b] Differences in reactivity to molecular fragments between IRMA (immunoradiometric assay), which was formerly widely used, and ECLIA and FEIA, which are the current standards, may cause apparent differences of approximately threefold in measured values, and caution is necessary because it is impossible to compare measured values with past data.

[c] EIA, which measures enzyme activity, was formerly widely used, but today CLEIA, which measures the amount of protein, is the standard procedure.

[d] Cannot currently be assayed in Japan because reagent production has been discontinued.

[e] CTX has α and β isomers, but the CTX in both serum and urine is generally the β isomer (βCTX).

[f] For the urinary pentosidine assay, new EIAs have been developed that do not require sample pretreatment of the sort required in the plasma pentosidine assay (enzyme treatment at 55 °C), but since they are research reagents, at this stage their use is limited to some clinical studies.

1. Objective of and background to the preparation of this guide

With the aging of the Japanese population in recent years, the number of osteoporosis patients is increasing, and osteoporosis-induced fractures are also on the rise. Proximal femoral fractures reportedly occur in older patients after a fall or other minor accident, often require hospitalization and surgery, and markedly reduce the patients' ability to engage in activities of daily living (ADL), leading to poorer survival. Measures to prevent osteoporotic fractures are thus an urgent task. Fortunately, the science of osteoporosis has made dramatic progress over the past 30 years, with the advent of numerous therapeutic drugs on the market and continuing improvements in their clinical effectiveness, and the clinical management of osteoporosis has been transformed. In this process, bone turnover markers (BTMs) have become an essential clinical tool for managing treatment [1–5].

The prevention of osteoporosis and its effective treatment not only enable the quality of life (QOL) of osteoporosis patients to be maintained, but also reduce the medical costs associated with fractures. To achieve this effect, the early diagnosis of osteoporosis, the effective treatment of existing osteoporosis and highly precise treatment monitoring, and the assessment of fracture risk are all essential. One currently available clinical test to meet these conditions is bone morphometry based on bone biopsy. Bone morphometry provides indices that can be used to assess bone dynamics, including the degree and speed of bone calcification, the extent and severity of bone resorption, and the degree and speed of bone formation, and it is an essential tool for evaluating bone structure.

However, bone biopsy is an invasive method of investigation, and its repeated performance is difficult in general clinical practice. These indices also only indicate localized bone changes at the biopsy site, and in some cases, it may not necessarily be appropriate to regard them as systemic bone findings.

Bone mineral density (BMD) measurements have recently become the main method used for osteoporosis diagnosis, and their accuracy has improved remarkably. However, in the daily clinical treatment of osteoporosis, dynamic indices are preferable as useful tools for assessing the status of bone turnover to evaluate progression and/or changes after drug administration.

Studies have found that BTMs can accurately express the state of daily bone turnover and are thus more useful as dynamic indices. The use of BTMs thus enables more appropriate drug selection, and they have therefore become positioned as a tool for clinically assessing bone turnover outcomes. In practice, BTMs are essential to osteoporosis treatment and have become clinical tests that provide excellent dynamic indicators, to the point that the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is now taking the lead in efforts toward their harmonization [6,7]. In particular, it is no exaggeration to date the start of the widespread adoption of the testing of BTMs in clinical practice in Japan to 1999, when it was first approved for medical insurance coverage, and the work carried out by the Japan Osteoporosis Society since 2001 to encourage the appropriate use of BTMs and to standardize their measurements [1–3].

Since the Japan Osteoporosis Society issued its Guidelines for the Use of Bone Turnover Markers in the Diagnosis and Treatment of Osteoporosis (2012 Edition) [3], more and more new drugs and drug formulations have been introduced into actual clinical care, and the prominence of their effects is transforming osteoporosis management, while combination drug therapies are also in the process of undergoing evaluation. Two issues must now be addressed: what significance should currently be allotted to drug turnover markers, and the fact that the Guidelines were formulated only for the treatment of primary osteoporosis, whereas, in clinical practice today, secondary osteoporosis is also a target of treatment. In addition, although there is yet insufficient evidence to achieve full consensus on many of the matters described outside the framework of the 2012 Guidelines, such as what significance to allot to bone matrix-related markers, in practice these

Table 2
Points to note for BTMs.

- **Samples are normally collected in the early morning in the fasting state**

However, if measurements are made for response evaluation, they do not necessarily have to be made in the early morning in the fasting state, as long as the test conditions before and after treatment are the same[a]

- **The acute phase after a fracture should be avoided**[b]
- **Perform measurements after waiting for the effects of previous treatment to wear off**[c]

However, if the previous treatment was denosumab, markers remain suppressed for 6 months after final administration

- **The effects of lifestyle improvements must be kept in mind when evaluating the effectiveness of drug treatment**[d]
- **Evaluate on the basis of the reference values for the assay device and method concerned**

[a] In principle, morning fasting-state sample collection is used for sCTX.
[b] The effect of the fracture is less pronounced for samples taken within 24 h (mean 6.8 h) after the fracture occurred.
[c] A 6-month drug holiday is preferable for bisphosphonate treatment, with a 1-month drug holiday or longer for other treatments.
[d] Increasing calcium intake by around 1 g reportedly suppresses bone metabolism.

Table 3
Effects of renal function on BTM measurements.

Marker	Affected by renal impairment
Bone formation markers	
OC	+
BAP	−
Intact P1NP	−
total P1NP	+
Bone resorption markers	
PYD	+
DPD	+
NTX	+
CTX	+
TRACP-5b	−
Bone matrix-related markers	
ucOC	+
Pentosidine	+
Homocysteine	+

Renal impairment: CKD Stage 3 or worse.
(+) Affected.
(−) Unaffected.

matters must be dealt with in osteoporosis management.

In response to these needs of the current era, we investigated whether they could be covered as guidelines. We concluded that, although the formulation of guidelines was not feasible at this point, we should aim to formulate a Best Practice Guide with the aim of positioning BTMs as a tool for better osteoporosis management, and as a result, the Guide for the Use of BTMs in the Diagnosis and Treatment of Osteoporosis (2018 Edition) [8] was produced.

2. Types of bone turnover markers

As shown in Table 1, several different types of BTMs are measured in clinical tests [3], and in the 2018 Guide, the Japan Osteoporosis Society Bone Turnover Marker Investigation Committee has classified them into bone formation markers, bone resorption markers, and bone matrix-related markers.

3. Specimen collection and handling

Table 2 shows points to note when measuring BTMs. In the assessment of BTMs to evaluate response to pharmacologic treatment, drugs that affect bone and calcium metabolism should be discontinued at least 1 month before initial assays to reduce their effect on markers. However, the effect of bisphosphonates persists for 6 months after they are taken [3]. If there is a possibility that a new therapeutic drug may be selected for a patient already undergoing pharmacotherapy, BTM assessment should be performed while the current treatment is continued.

If assays are performed repeatedly for the same patient, some BTM levels vary diurnally or from day to day, and specimens should be collected at the same time of day and handled in the same way as for the previous tests. Older patients, particularly women, have a high rate of chronic kidney disease (CKD). Age-related muscle loss also affects serum creatinine and urinary creatinine excretion. Renal impairment and muscle loss both progress with advancing age. Since osteoporosis treatment is predicated on long-term drug therapy, test results for BTMs that are affected by these factors must be interpreted considering this [3]. As shown in Table 3, some BTMs are affected by renal impairment, whereas others are unaffected [9]. Since serum markers do not require urinary creatinine correction, there is no need to consider diminished ADL, sarcopenia, or renal impairment, and the values for each assay can be compared directly, suggesting that they may be useful as BTMs.

A diagnosis of osteoporosis may lead to lifestyle improvements, and since major changes in dietary and exercise habits may cause changes in bone metabolism, assays should be performed after lifestyles have stabilized [10]. Serum BTMs assess the state of bone metabolism at the time blood was collected and urinary BTMs at the time of urine collection. Urinary bone resorption markers are normally assessed from urine portions. Because urine portions are corrected by creatinine, there is greater variation between measurements. However, there is no scientific evidence for the inferiority of urinary BTMs compared with serum BTMs [11,12]. The evidence for superiority/inferiority between serum BTMs and between urinary BTMs remains insufficient, but, ideally, markers with a high therapeutic effect/error of measurement ratio should be measured.

4. Reference values and their rationales

In osteoporosis, the degree of bone formation assessed by BTMs may not be consistent with the degree of bone resorption assessed by such markers, reflecting the pathophysiology of this disease. In many cases, the degree of bone resorption is higher than that of bone formation. Accordingly, in patients with a definitive diagnosis, simultaneous bone formation and bone resorption marker measurements prior to intervention can provide a clearer assessment of the status of bone metabolism. As shown in Table 4, the reference values for BTMs in the Japanese population have been set as within the range of ± 1.96 standard deviations (SDs) from the mean values established for healthy men, healthy premenopausal women, and healthy postmenopausal women [3]. For tartrate-resistant acid phosphatase 5b (TRACP-5b), however, the reference value for healthy men is used for men, whereas for women, the young adult mean (YAM; healthy premenopausal women aged 30–44 years) is used. No reference value has yet been determined for undercarboxylated osteocalcin (ucOC), and a cut-off value calculated using the vitamin K deficiency concentration is used for patients who meet the diagnostic criteria for primary osteoporosis, considering fracture risk [13].

5. Health insurance reimbursement and conditions for health insurance coverage

The health insurance reimbursement points (revised in April 2018) for BTM tests are covered by health insurance for the management of

Table 4
BTM reference values.

Bone turnover marker (assay method)		Men	Women (premenopausal)	Women (postmenopausal)	Units
Bone formation markers	OC (ECLIA)	8.4–33.1	7.8–30.8	14.2–54.8	ng/mL
	BAP (CLEIA)	3.7–20.9	2.9–14.5	3.8–22.6	μg/L
	P1CP (RIA)	29–181	32–178	32–178	ng/mL
	Intact P1NP (RIA)	19.0–83.5	14.9–68.8 (age 30–44 y)	27.0–109.3 (age 45–80 y)	μg/L
	total P1NP (ECLIA)	18.1–74.1 (age 30–83 y)	16.8–70.1 (age 30–44 y)	26.4–98.2 (age 45–79 y)	μg/L
Bone resorption markers	PYD (HPLC)	17.7–41.9			pmol/μmol·Cr
	DPD (EIA)	2.0–5.6	2.8–7.6	3.3–13.1	nmol/mmol·Cr
	sNTX (EIA)	9.5–17.7	7.5–16.5	10.7–24.0	nmol BCE/L
	uNTX (EIA)	13.0–66.2	9.3–54.3	14.3–89.0	nmol BCE/mmol·Cr
	sCTX (ECLIA)		0.112–0.738		ng/mL
	uCTX (EIA)		40.3–301.4		μg/mmol·Cr
	1CTP (RIA)	0.5–4.9	0.8–4.8		ng/mL
	TRACP-5b (EIA)	170–590	120–420(YAM)	250–760	mU/dL
Bone matrix-related markers	ucOC (ECLIA)	< 4.5 (cut-off value)			ng/mL
	Pentosidine (EIA)	0.00915–0.0431			μg/L
	Homocysteine (HPLC)	6.3–18.9	5.1–11.7		nmol/mL

Reference values are those given in the kit manufacturer's (or vendor's) package insert or in-house data. Reference values may differ between institutions and must therefore be treated with caution. BAP reference value (activity value, EIA): 7.9–29.0 U/L (premenopausal 30 to 44-year-old women) U/L (premenopausal 30 to 44-year-old women). Cut-off value for 1CTP bone turnover marker < 4.5 ng/mL. The TRACP-5b reference value for women is the YAM value (premenopausal women aged 30–44 years), but the reference value for premenopausal women is 120–440 mU/dL.The value for urinary pentosidine (HPLC) was 42.2 ± 17.7 pmol/mg·Cr at age 63.0 ± 9.4 years (n = 32 women). P1CP cannot currently be assayed in Japan because reagent production has been discontinued. BCE: bone collagen equivalent.

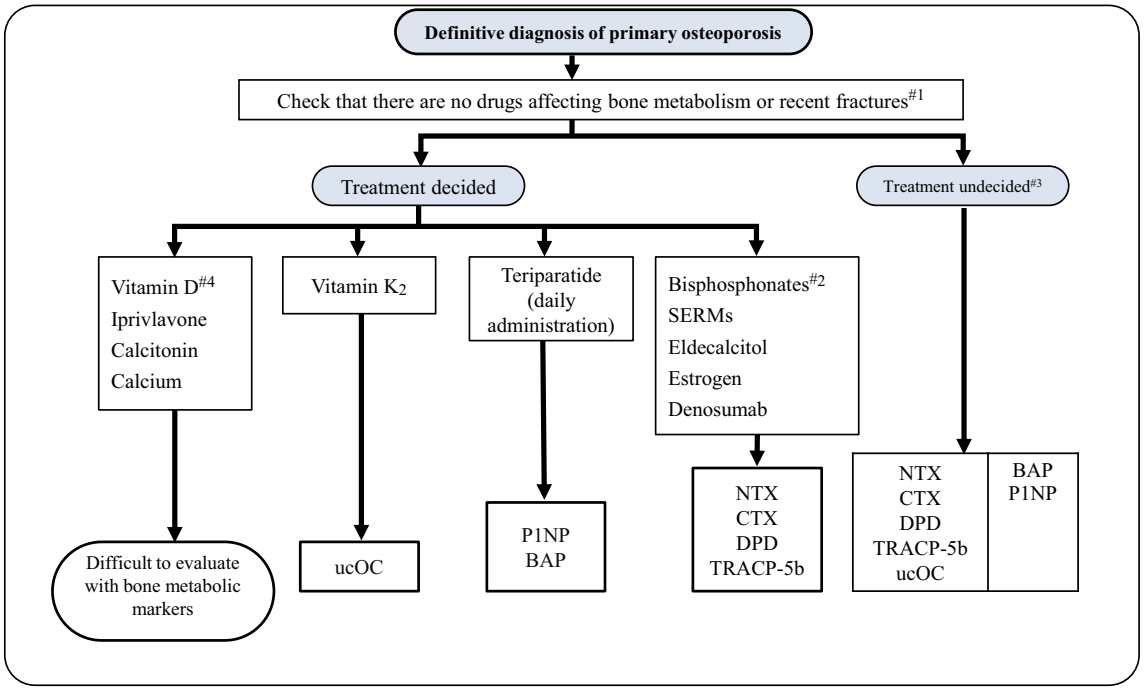

Fig. 1. BTM measurements when osteoporosis is diagnosed.
#1: BTMs are affected for at least 3 months in patients taking bisphosphonates or denosumab, and for 1 month in those taking other osteoporosis treatment drugs. Some consider that they are. affected for 3 months by teriparatide treatment. Fractures have little effect within 24 h after the occurrence of the fracture.
#2: For patients receiving long-term bisphosphonate treatment (3–5 years), measure a bone resorption marker and BAP or P1NP (health insurance restrictions may apply; an explanation for the claim is required).
#3: Measure one each of a bone resorption marker and a bone formation marker.
#4: Excluding eldecalcitol.

osteoporosis, but with certain conditions [14]. Although BTMs may now be measured for osteoporosis management, there are several restrictions on the use of these assays in terms of health insurance coverage. The main reasons for testing BTMs in osteoporosis are to evaluate the status of bone metabolism in patients with a clinical diagnosis of osteoporosis, select therapeutic drugs, and assess response to treatment. Reflecting this situation, bone resorption makers (deoxypyridinoline (DPD), type I collagen cross-linked N-telopeptide (NTX), and TRACP-5b) may be measured either once each before the start of treatment and within 6 months of starting treatment, or once within 6 months of changing the drug treatment strategy, in order to assess the response to treatment. Only one type I collagen cross-linked C-telopeptide (CTX)

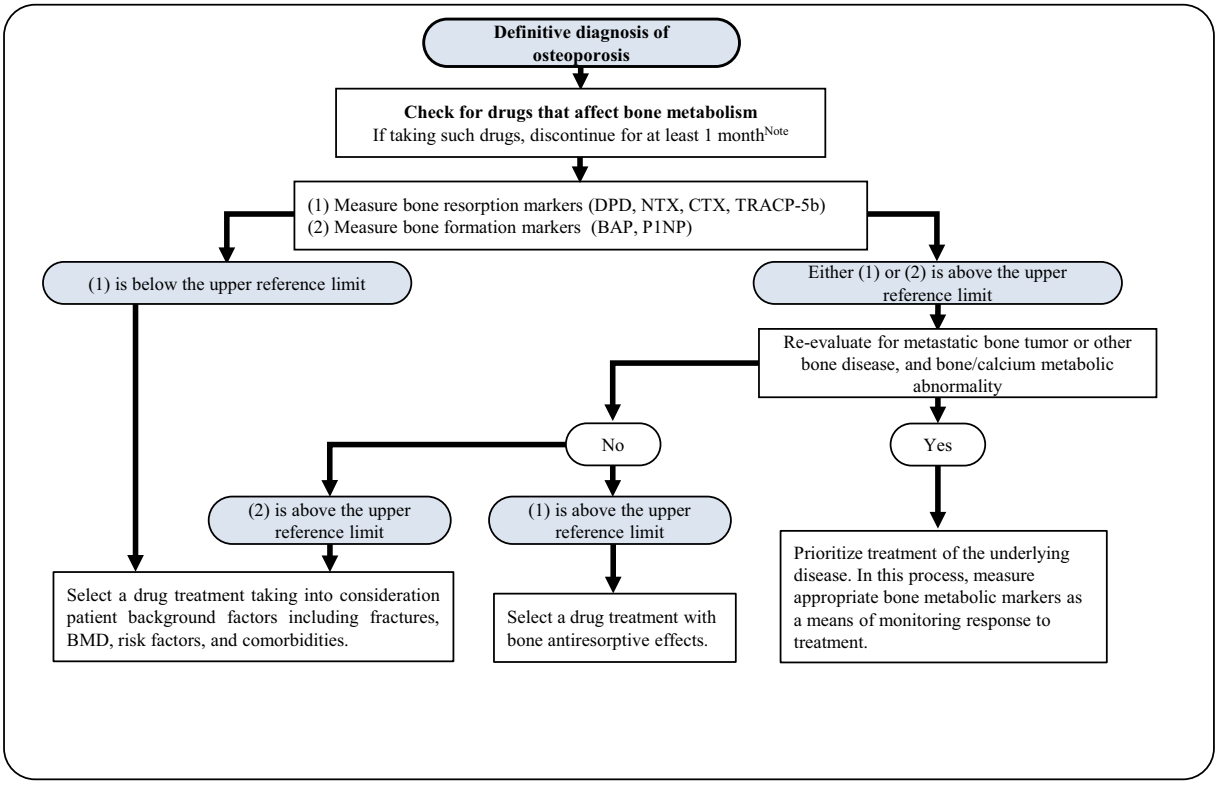

Fig. 2. Bone resorption marker and bone formation marker measurements when selecting a drug treatment for osteoporosis.
Note: Measure after bisphosphonates have been discontinued for at least 3 months.
Female hormones (estradiol, estriol), activated vitamin D_3 (eldecalcitol), bisphosphonates (etidronic acid, alendronic acid, risedronic acid, minodronic acid, ibandronic acid, zoledronic acid), SERMs (raloxifene, bazedoxifine), anti-RANKL antibody (denosumab), and anti-sclerostin antibody (romosozumab) are all known to suppress bone resorption.

assay is covered by health insurance to assess the response to drug therapy that suppresses bone resorption, such as hormone replacement therapy or bisphosphonate therapy, or during treatment of patients with osteoporosis. Caution is therefore required when testing for markers such as DPD, NTX, and TRACP-5b, for which claims can only be submitted once before the start of treatment and once within 6 months of the start of treatment, but not after changing drug treatment strategy. If both serum CTX (sCTX) and urine CTX (uCTX) are measured together, only the main assay may be claimed. TRACP-5b measurement is covered under health insurance for the management of a wide range of disorders, including osteoporosis and other bone metabolic disorders.

6. BTM measurements when choosing an osteoporosis treatment drug

As shown in Fig. 1, the measured values of BTMs, particularly the bone resorption markers DPD, NTX, CTX, and TRACP-5b, provide one piece of evidence for the selection of therapeutic drugs, and the recommended choices of drugs for patients with values above the upper reference limit include female hormones (estradiol, estriol), activated vitamin D_3 (eldecalcitol, an active vitamin D_3 derivative), bisphosphonates (etidronic acid, alendronic acid, risedronic acid, minodronic acid, ibandronic acid, zoledronic acid), selective estrogen receptor modulators (SERMs) (raloxifene, bazedoxifine), anti-receptor activator of NF-κB ligand (RANKL) antibody (denosumab), and anti-sclerostin antibody (romosozumab), all of which suppress bone resorption [3,15–20]. However, drug selection should be based not only on BMD and previous fractures, but on an overall evaluation including other factors such as bone metabolic marker values, patient characteristics, symptoms and comorbidities, contraindications for drugs, and previous treatments(see Fig. 2). Because measured values of the bone matrix-related marker ucOC reflect vitamin K deficiency, this information is useful when selecting vitamin K_2 drugs and as an adjunct when evaluating their efficacy [3].

7. Use of BTMs for response evaluation after the start of osteoporosis treatment (bone anti-resorptive drugs)

As shown in Fig. 3 and Table 5, the effectiveness of drug therapy is difficult to predict based on bone metabolic marker baseline values alone, and measurements are repeated at a certain time after the start of treatment to evaluate changes compared with baseline and monitor the response to treatment. It can only be concluded that a change in bone metabolism has occurred because of drug therapy if this has resulted in significant changes in BTM values compared with baseline. DPD, NTX, CTX, TRACP-5b, bone alkaline phosphatase (BAP), and type I procollagen-N-propeptide (P1NP) can all be used to assess the effects of female hormones, active vitamin D_3, bisphosphonates, SERMs, anti-RANKL antibody, and anti-sclerostin antibody in individual patients [3,15–19].

P1NP can also be used to evaluate response to bone formation-promoting parathyroid hormone (PTH) drugs (genetically recombinant teriparatide, administered by daily subcutaneous injection) and anti-RANKL antibody [21]. Other therapeutic drugs are more difficult to evaluate by BTM measurements.

One criterion for response evaluation is whether the minimum

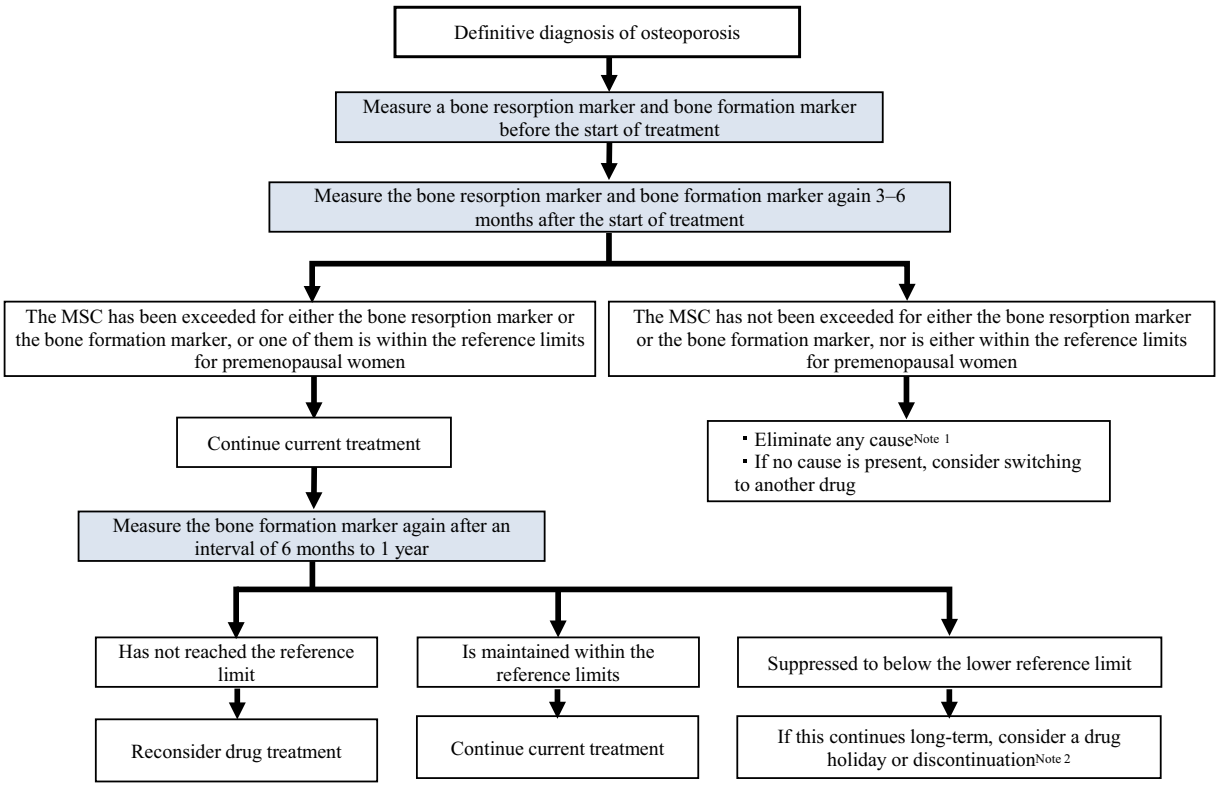

Fig. 3. Use of BTMs for response evaluation after the start of osteoporosis treatment (bone anti-resorptive drugs).
Note 1: See Table 5.
Note 2: Committee opinion.

Table 5
Possible reasons why BTMs may not change significantly after drug treatment.

1 **Reasons for measurement variations and sample handling**
· Measurement conducted at a different time of day than at the start of treatment
· Measurement error due to a long time between measurements
(e.g. seasonal variation, change in the patient's condition, etc.)
· Too short an interval between measurements
· Change in the test center performing the assays
2 **Treatment regimen issues**
· Timing with food (bisphosphonates)
· Poor compliance with the treatment regimen
3 **Comorbidity with another disease causing secondary osteoporosis**
4 **Existence of a recent fracture**

significant changes (MSCs) shown in Table 6 are exceeded [3]. These MSCs are twice the mean morning day-to-day variation seen in pre-menopausal women. It should also be kept in mind that, depending on the drug administered, there are some drugs for which significant changes in DPD, NTX, CTX, TRACP-5b, BAP, and P1NP are not readily apparent [3].

Table 6
Minimum significant changes (MSCs) in bone metabolism markers.

Marker	Assay	MSC(%) (twice the mean day-to-day variation)[a]
Bone formation marker		
BAP	CLEIA	9.0
Intact P1NP	RIA	12.1
total P1NP	ECLIA	14.4
Bone resorption marker		
DPD	EIA	23.5
sNTX	EIA	16.3
uNTX	EIA	27.3
sCTX	EIA	23.2
sCTX	ECLIA	27.0[a]
uCTX	EIA	23.5
TRACP-5b	EIA	12.4
Bone matrix-related marker		
ucOC	ECLIA	32.2

MSC: The minimum significant change is calculated as twice the day-to-day variation derived by the committee (Rationale: Blood and urine samples were collected from 10 volunteer premenopausal women five times during a 14-day period, the samples were frozen until assay, and the measurements were all performed in a single batch at a commercial clinical laboratory in Japan.)
[a] The LSC is the minimum significant change given in the kit manufacturer's package insert.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

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